Protocol NMTRC 008

NCT01802567

A Feasibility Trial using Molecular-Guided Therapy for the Treatment of Patients with Relapsed and Refractory Childhood Cancer

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INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol amendment and agree that it contains all the necessary details for performing the study.

I will provide copies of the amended protocol and of the preclinical and clinical information on the test article, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test article and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. I will submit the protocol modifications and/or any informed consent form (ICF) modifications to the Sponsor and the IRB/IEC, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) [current International Conference of Harmonization (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the Scotland revision (2000) and notes of clarification added in 2002 and 2004.

Investigator's Signature _____ Date _____

Investigator's Printed Name _____

Investigational Site Name _____

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PROTOCOL SYNOPSIS

PROTOCOL TITLE	A Feasibility Trial using Molecular-guided therapy for the treatment of patients with relapsed and refractory childhood cancers
PROTOCOL NUMBER	NMTRC 008
PHASE OF DEVELOPMENT	Feasibility

OBJECTIVES	**Primary**
	Determine feasibility of using tumor samples to assess genomic mRNA expression arrays and DNA Mutation Panels using predictive modeling to make real-time treatment decisions for children with relapsed/refractory cancers.
	
	Secondary
	• To continue to evaluate the safety of allowing a molecular tumor board to determine individualized treatment plans
	• To determine the activity of treatments chosen based on:
	  • Overall response rate (ORR)
	  • Progression free survival (PFS)
	• (Voluntary) To explore the relationship between tumor phenotype/genotype and response by permitting use of tumor tissue in a correlative biologic study
	• To compare PFS interval to PFS intervals of previous chemotherapy regimens since relapse for each subject.

STUDY DESIGN	A prospective open label, multicenter study to evaluate efficacy of molecularly guided therapy in patients with relapsed or refractory childhood cancers A total of 48 evaluable subjects with childhood cancer that are refractory to or have relapsed on conventional therapy will be treated with molecular guided therapy. Subjects will be evaluated in 3 strata: • Stratum 1: 16 subjects with refractory/relapsed neuroblastoma • Stratum 2: 16 subjects with relapsed or refractory brain tumors Stratum 3: 16 subjects with refractory or relapsed rare tumors Guided therapy will allow the use of any therapeutic combination (up to 4 agents) provided it includes medications contained in the study report. All subjects will be followed for survival, disease response, progression and safety. All subjects will be treated according to the discretion of the treating oncologist and study committee (minimum 3 oncologists and one pharmacist). Extent of disease will be measured and assessed for changes throughout the course of the study.

ELIGIBILITY	**Inclusion Criteria** 1. Subjects must have histologically proven neuroblastoma, brain tumor, or rare tumor and confirmation of refractory or recurrent disease with histologic confirmation at diagnosis or at the time of recurrence/progression 2. Subjects must be age >12 months at enrollment 3. Subjects must be age ≤ 21 years at initial diagnosis 4. Subjects must have measurable disease as demonstrated by residual abnormal tissue at a primary or metastatic site measuring more than 1 cm in any dimension by standardized imaging (CT or MRI); tumor must be accessible for biopsy. Subjects with bone marrow only disease expected to be >75% tumor are eligible to enroll. 5. Current disease state must be one for which there is currently no known curative therapy 6. Lansky or Karnofsky Score must be more than 50 7. Subjects without bone marrow metastases must have an ANC > 750/μl. 8. Adequate liver function must be demonstrated, defined as: a. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age AND b. ALT (SGPT) < 10 x upper limit of normal (ULN) for age 9. A negative serum pregnancy test is required for female participants of child bearing potential (≥13 years of age or after onset of menses) 10. Both male and female post-pubertal study subjects need to agree to use one of the more effective birth control methods during treatment and for six months after treatment is stopped. These methods include total abstinence (no sex), oral contraceptives ("the pill"), an intrauterine device (IUD), levonorgestrol implants (Norplant), or medroxyprogesterone acetate injections (Depo-provera shots). If one of these cannot be used, contraceptive foam with a condom is recommended. 11. Informed Consent: All subjects and/or legal guardians must sign informed written consent. Assent, when appropriate, will be obtained according to institutional guidelines **Exclusion Criteria** 1. Subjects who have received any cytotoxic chemotherapy within the last 7 days prior to enrollment and 14 days prior to study treatment start date. 2. Subjects who have received any radiotherapy to the primary sample site within the last 14 days (radiation may be included in treatment decision after biopsy). 3. Subjects receiving anti-tumor therapy for their disease or any investigational drug concurrently.

	4. Subjects with serious infection or a life-threatening illness (unrelated to tumor) that is > Grade 2 (NCI CTCAE V4.0), or active, serious infections requiring parenteral antibiotic therapy. 5. Subjects with any other medical condition, including malabsorption syndromes, mental illness or substance abuse, deemed by the Investigator to be likely to interfere with the interpretation of the results or which would interfere with a subject's ability to sign or the legal guardian's ability to sign the informed consent, and subject's ability to cooperate and participate in the study **Additional criteria:** Subjects willing to participate in the correlative biologic studies will sign an additional consent form to provide tumor tissue.
ESTIMATED NUMBER OF PATIENTS/GEOGRAPHIC REGIONS	48 evaluable (53-59 total) relapsed/refractory pediatric cancer patients- 16 neuroblastoma tumors, 16 brain tumors, and 16 rare tumors. Patients will enroll at Arnold Palmer Children's Hospital (MD Anderson Cancer Center Orlando) ,St. Louis University/Cardinal Glennon Children's Medical Center, Helen DeVos Children's Hospital, Levine Children's Hospital, Connecticut Children's Medical Center, Mercy Children's Hospital, Rady Children's Hospital of San Diego, Medical University of South Carolina, Monroe Carrell Jr. Children's Hospital at Vanderbilt, Phoenix Children's Hospital, Primary Children's Hospital, Kapiolani Medical Center for Women and Children, and at Dell Children's Hospital.
LENGTH OF STUDY	Accrual to this study is estimated to be approximately 2 years.
STUDY ASSESSMENTS	Refer to Table of Assessments for timing of study procedures.
CRITERIA FOR EVALUATION	Feasibility Measures: Primary objective The definition of feasibility for this study will include: **"Enrollment onto study, RNA expression profile completed, DNA Mutation Panel completed, genomic analysis and report generation, tumor board held with treatment decision, treatment review completed and start of treatment by 21 days post biopsy/surgical resection date, and then completion of 1 cycle of therapy."** Safety Measures: Secondary objectives • Safety analysis will be conducted on all subjects who have received at least one dose of therapy, and will include the frequency of all reported adverse events and laboratory abnormalities as well as frequency of dose interruptions, dose reductions and treatment discontinuation.

	Efficacy Measures: Secondary objectives • Response: ♦ To determine the overall response rate (ORR) by the presence of radiologically assessable disease by cross-sectional CT or MRI imaging and/or by MIBG or PET scans. ♦ Duration of response, defined as the period of time from when measurement criteria are met for complete response (CR) or partial response (PR), whichever is first recorded, until the first date that recurrent or progressive disease (PD) is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started) ♦ The assessment of response will include the initial measurable targets and will be performed after cycle 2, then after every other cycle. • A subject will be defined as a responder if CR/PR is observed at any time of the treatment • Clinical response will be seen if stable disease and decrease in tumor markers by ≥ 50% or CR of bone marrow. • Time to progression, defined as the period from the start of the treatment until the criteria for progression are met taking as reference the screening measurements
STATISTICS/SAMPLE SIZE ESTIMATE	48 evaluable subjects

TABLE OF PROCEDURES AND ASSESSMENTS

Procedure	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22 (if applicable)	Subsequent Cycles Day 1	Off Therapy/ 30 Day Follow-up
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X
Vital signs	X	X		X		X	X
Height	X						
Weight	X	X				X	X
Karnofsky or Lansky play score	X	X		X		X	X
CBC w/diff,	X	X	X	X	X	X	X
Serum chemistry *	X	X		X		X	X
Adverse events	X	X	X	X	X	X	X
Urine catecholamines (NB only) or other tumor marker (as available)	X	X				X	X
surgical resection &/or diagnostic biopsy	X						
MRI or CT	X	Radiologic measurements will be performed every 8 weeks or every other cycle (whichever occurs first)					
MIBG/PET (NB only)	X						
Bone Marrow (NB or any subject suspected to have BM disease) ^	X	Should be repeated every 8 weeks or every other cycle (whichever occurs first) if positive at study entry					
B-HCG	X						
EKG (as indicated)	X						

* Total bilirubin, BUN, creatinine, electrolytes, AST, ALT, LDH, Tumor Specific Marker (if available)

^Standard of Care Bone Marrow. (Separate consent required for additional research samples. Collect per section 9.3.1.3)

1 Background

1.1 Study Disease

Relapsed or refractory neuroblastoma, brain tumors, and rare childhood tumors.

1.2 Rationale

Lethality of Relapsed/Refractory Pediatric Cancers is an Unmet Clinical Need.

Neuroblastoma
Neuroblastoma is the most common extracranial solid tumor in children, with 700 new diagnoses projected for 2011. It accounts for 7% to 10% of childhood cancers [1, 2]. Whereas the prognosis for infants with neuroblastoma is generally good, currently only 30% of children diagnosed after 12-15 months of age survive despite aggressive multimodal therapies [3, 4]. Even with high-dose chemotherapy (HDC) followed by hematopoietic stem cell transplantation (HSCT) and maintenance therapy with retinoic acid the 5-year event-free survival remains below 50% [5, 6]. Long-term survival of patients who are treated with conventional therapies following relapse is <5%. As such, neuroblastoma accounts for 15% of all pediatric cancer deaths in the United States [7]. Consequently, the evaluation of new drugs is strongly needed in this disease.
Recent evidence has established the genetic heterogeneity of the disease and revealed the existence of several major molecular subsets that collectively may provide prognostic value for future disease management [8] [9]. While the poor prognosis for older neuroblastoma patients underscores the need for new treatment strategies, the elucidation of specific biologic subsets of neuroblastoma suggests a way to improve disease management. The current standard-of-care treatments for relapsed neuroblastoma include a variety of Phase II or Phase I studies that generally have only modest response rates (10%-35%) [4]. Even in responding patients, tumors often go on to further rapid relapses and novel strategies to treat this patient population are urgently needed. There are currently few treatment options from which pediatric oncologists can select with any degree of confidence to improve the management of multiply recurrent neuroblastoma patients. The current strategy is to add salvage therapies based on the anecdotal experience of the treating physician, which often leads to drug-related toxicity but may or may not extend life. The identification of agents that target specific molecular pathways associated with the development and/or progression of neoplastic diseases holds promise. Improved approaches that identify in a more rational (data-driven) fashion combinations of existing agents that are likely to be effective should result in a survival benefit in the clinical setting, while avoiding the toxicity associated with agents that are unlikely to be beneficial. [10].

CNS Tumors
CNS tumors are the most common solid tumors in children, with 3000-40
00 new diagnoses each year. CNS tumors account for approximately 25-30% of all childhood cancers. Though many of these CNS tumors are quite treatable, the 5-year survival for pediatric CNS tumors is only 71%[11]. Patients who have relapsed and refractory CNS tumors are those most likely to succumb to their disease, in spite of aggressive chemotherapy and radiation, often followed by HSCT[12, 13]. Therefore, new treatment strategies are needed for control of CNS tumors.

There is a growing focus on treating CNS tumors based on the biology of the disease[14, 15] rather than with "one size fits all" therapy. Risk stratification in CNS tumors based on biology is increasingly understood to be a priority. For example, medulloblastoma has been broken into 4 biologic categories with different genetic mutations and different clinical outcomes[16-18]. Similar to neuroblastoma, these differences in the biology and clinical outcome of patients with medulloblastoma suggest new strategies to improve disease management. The current standard-of-care treatments for relapsed CNS tumors include Phase I and Phase II therapies that often have few, if any, responding patients[19, 20]. Again reflecting the challenges in neuroblastoma, responding patients with high grade CNS tumors often experience multiple relapses and are in dire need of novel treatment strategies. Improved approaches that can inform treatment regimens based on the biology of the disease could result in a survival benefit in this challenging patient population.

Rare Cancers

Although improvements in the past 40 years have led to markedly improved survival rates of approximately 80% overall for pediatric cancers, patients with relapsed, rare and advanced stage tumors still have a very poor prognosis. Soft tissue sarcomas account for ~ 7% of pediatric cancers, with 850-900 new cases annually in the United States [21]. Rhabdomyosarcoma, the most common soft tissue sarcoma in children and adolescents, affects nearly 350 children in the United States each year [21]. Patients with metastatic rhabdomyosarcoma have a poor prognosis with an overall survival rate of ~30% [22]. The non-rhabdomyosarcoma soft tissue sarcomas affect ~500 children each year. Patients with metastatic non-rhabdomyosarcoma soft tissue sarcomas have long-term survival < 20% [23]. Malignant bone tumors (mainly Ewing's Sarcoma and Osteosarcoma) account for 6% of childhood cancers, with ~400 cases of osteosarcoma and 200 cases of Ewing's Sarcoma diagnosed annually [21]. Patients with localized osteosarcoma, who have a poor response to pre-operative chemotherapy have a survival rate of around 50%, while patients with metastatic osteosarcoma or Ewing's sarcoma disease at presentation, have a survival of < 20% [24, 25]. Renal Cancers account for ~6% of pediatric cancer diagnoses, with 95% of cases being Wilms Tumor, which has a very favorable prognosis [21]. However, rare and high risk renal tumors such as metastatic anaplastic Wilms tumor, clear cell sarcoma of the kidney, renal cell carcinoma, and malignant rhabdoid tumor have an inferior outcome, with survival of < 20% [26, 27]. For all these patients survival remains poor, despite use of dose-intensified multi-agent chemotherapy and stem cell transplantation. Therefore, new approaches such as targeted therapies are warranted.

Molecular Networks as the Drug Target.

It is now firmly established that cancer results from perturbations in the molecular networks within cellular systems that disturb the normal homeostatic state [28-30]. Fluctuations in these networks can result from genetic or epigenetic cellular events and/or changes in the molecular constitution of the tumor microenvironment, which collectively dictate the phenotype of the biological system. The molecular networks engaged during tumor development and/or progression are complex. Molecular networks have evolved to provide the ultimate level of cellular plasticity, allowing cells to adapt to or exploit extracellular cues within the local milieu [31]. The complexity of a tumor system is further exaggerated by the inherent genomic instability seen in many neoplasms, which leads to an accelerated micro-evolutionary process that results in further cellular and tumor sub-system heterogeneity [32, 33]. This variability combined with the adaptability of many molecular pathways provides a somewhat predictable and highly probable path to resistance for any given agent that targets a subset of cellular systems within a tumor's

molecular and genetic repertoire [34]. A fundamental challenge in the area of targeted cancer treatment is how to identify optimal therapeutic combinations that can treat heterogeneous tumors that are both highly adaptive and that exhibit significant inter- and intra-patient variation [28, 35-37]. Our proposal outlines an approach by which we can utilize our expanding knowledge of molecular networks and the mechanisms of action of a growing pharmacopeia [38, 39] in conjunction with standardized biomarker assessments to deliver targeted combinations of effective therapies to neuroblastoma patients.

Practice and Promise of Biomarkers for Patient Treatment Planning.
A panel of individual biomarkers has recently been identified that can be used in the clinical setting to identify neuroblastoma patients most likely to respond to a specific therapy. For example, activation of the ALK gene through sequence variation mutations has been identified in a subset of neuroblastoma patients, and small-molecule inhibition of the ALK-encoded receptor tyrosine kinase caused cytotoxicity in affected neuroblastoma cell lines [40]. Such studies, in conjunction with a large body of in vitro and in vivo data, have further demonstrated that the efficacy of specific treatment modalities is dependent upon the molecular constitution of the tumor, and that the observed variations in tumor response to current therapies is attributable in large part to disease heterogeneity at the molecular level.

While individual biomarkers may be predictive of responses to specific therapies, especially in the context of front-line treatment, a different approach to the management of patients with refractory disease is needed in order to identify effective treatments from the catalog of available agents. Advances in informatics and molecular technologies, coupled with our expanding knowledge of molecular networks and mechanism of action of the existing pharmacopeia, provide a great opportunity in translational medicine to develop a model that more accurately predicts tumor response. The studies outlined in this proposal are a step in the development of personalized oncology, in which each patient is truly treated individually based upon the systematic molecular analysis of their disease. Our project is focused on testing the merits of a specific data-driven predictive method through which any number of drugs in our current knowledge base has a chance of being recommended, of these only the FDA approved drugs listed in Appendix III will be used. Although this novel approach to personalized therapeutics brings with it to the concern that toxicities that may arise from novel combinations of agents, it is strongly felt by the investigators that the logical interpretation of molecular data by a committee of highly qualified physicians and pharmacists in order to identify drug candidates for consideration in the treatment of a patient population with few alternative options is a worthwhile endeavor. The systematic biomarker-driven approach outlined in this proposal, by tailoring a combination of drugs targeting the specific molecular composition of a tumor—irrespective of tumor classification or anatomical origin— provides a feasible alternative to the conventional approach that targets specific organs or tissues without consideration of the underlying tumor biology.

Validation of Gene Expression as a Predictive Biomarker.
The determination of gene transcript abundance through gene expression profiling has been frequently exploited in biomarker research. The mRNA analyte provides an estimation of the dynamic molecular events within a biological specimen. Moreover, various technologies that permit gene expression profiling have provided a systematic and high-throughput means to assess multiple mRNA transcripts simultaneously within a biological sample on a genomic scale, and have created an abundance of empirical datasets across cohorts of moderately characterized biological specimens [41]. Within the field of cancer research, gene expression profiles derived

from human tumor specimens have been used to identify molecular subtypes associated with tumor cell behavior, patient outcome and response to a wide range of therapies [42]. For example, gene expression signatures have been utilized to create a connectivity map in which the genomic consequences of drug exposure can be aligned with de-regulated genes within a tumor specimen to identify compounds that may reverse the tumorigenic genotype [43]. Screening of a large number of potential therapeutic agents in a panel of cancer cell lines with a baseline gene expression profile has permitted the association between a gene expression signature and predicted response to various drugs [44, 45]. Thus, a wealth of publicly available genomic datasets and predictive methodologies coupled with increasing evidence demonstrating the utility of gene expression signatures as a valid biomarker argues for increased efforts towards implementing a more systematic approach to molecular-based theranostics in the prospective clinical setting. We propose to integrate the results of different predictive methodologies based upon the consistent input of tumor-derived gene expression data, to provide consolidated information to the treating physician regarding treatment options with predicted efficacy. The predictive methods under evaluation include the rudimentary analysis of expression of target genes, as well as the more sophisticated analysis of molecular network topology and signature based methods based upon empirical datasets. Throughout the project, we will seek to establish the potential predictive value of standardized gene expression data and the described methodologies for predicting efficacious agents for refractory or relapsed neuroblastoma patients and determine which, if any, of these individual predictive methodologies holds the most promise for further development as a diagnostic standard. Additionally, while beyond the scope of this specific proposal, the tumor resource created will also be used to assess the potential predictive value of emerging molecular technologies that assess other molecular aberrations associated with differential therapeutic response (such as single nucleotide polymorphisms, DNA sequencing, gene amplifications/deletions, gene promoter methylation, protein modifications, etc [28, 30].

Pivotal Pilot Study Highlights Feasibility of Predictive Methodologies.
In conjunction with community hospitals and physician groups in West Michigan, the Van Andel Research Institute under the direction of Dr. Webb recently completed a proof-of-feasibility study in which a heterogeneous group of fifty late stage cancer patients were enrolled to determine the feasibility and potential impact of providing physician's with molecular-based therapy predictions and to provide an early assessment of the first generation predictive methodologies. In this feasibility study, clinical investigators worked closely with Dr. Webb to coordinate a multi-disciplinary team that included individuals from adult and pediatric oncology, surgery, interventional and non-interventional radiology, pathology, pharmacy, clinical research, statistics, bioinformatics, and clinical and basic science laboratories.

Table 1 shows a sample of patients enrolled in this first pilot study, and highlights the patients whose physicians utilized the personalized report providing an early indication of the potential value of the information provided. In brief, 50 patients were consented to the study in which surgical tumor specimens excised as part of a standard of care diagnostic procedure were processed in a real-time fashion to obtain a gene expression profile from each qualified tumor specimen. Consistent with current practices, a series of essential quality control (QC) standards were implemented to ensure assay validity which included criteria regarding the proportion of viable tumor cells within surgical specimens, RNA quality, cDNA synthesis and amplification, GeneChip hybridization, data normalization and analysis. After obtaining a gene expression profile on the tumor specimen, researchers utilized the XB-BIS system to generate a standardize report for physicians to utilize in determining patient drug regimen. It is important to note that our

current procedures permit a < 3 week turnaround from receipt of an individual tumor sample to the generation of a standardized report predicting drug efficacy. Our ability to provide real time feedback in less than 3 weeks is critical to permit the consideration of the predicted therapies in the care of the individual patient, and is concomitant with the wash out period between the patient's prior treatment and administration of a new regimen.

Diagnosis	Gender	Age at Enrollment	Specimen Type	Report Generated	Report Information Used	Clinical Benefit Observed
Neuroblastoma	F	5	Bone Marrow Aspirate	Yes	Yes	Yes
Hodgkin Lymphoma	F	19	Peripheral Blood	Yes	No	
Synovial Sarcoma	F	16	Surgical	Yes	No	
Clear Cell Sarcoma of the Kidney	M	5	Surgical	Yes	Yes	Yes
Osteosarcoma	M	17	Surgical	Yes	No	
Lung Cancer	M	67	Pleural Fluid	No		
Osteosarcoma	F	17	Surgical	No		
Wilms' Tumor	M	3	Surgical	No		
Gastric Cancer	F	50	Ascites Fluid	Yes	Yes	No
Gastric Cancer	F	50	Ascites Fluid	Yes	Yes	No
Malignant Melanoma	M	56	Surgical	Yes	Yes	No
Colon Cancer	M	49	Needle Biopsy	Yes		
Ewing's Sarcoma	F	22	Surgical	Yes	Yes	No
Lung Cancer	M	70		No		
Colon Cancer	M	54	Surgical	Yes	Yes	No
Esophageal Cancer	M	48	Needle Biopsy	No		
Inflammatory Myofibroblastic Tumor	M	12	Needle Biopsy	Yes	Yes	No
Breast Cancer	F	61	Surgical	No		
Mantle Cell Lymphoma	M	62	Needle Biopsy	Yes	No	
Rhabdomyosarcoma	F	14	Surgical	Yes	No	
Malignant Melanoma	M	29	Surgical	Yes	No	
ALL	F	14	Bone Marrow Aspirate	Yes	Yes	Yes
Ewing's Sarcoma	M	15	Surgical	Yes	Yes	No
Gastro Esophageal Junction Cancer	M	62	Pleural Fluid	No		
Malignant Melanoma	F	50	Surgical	No		
Breast Cancer	F	35	Surgical	No		
Non Small Cell Lung Cancer	F	57	Surgical	Yes	Yes	No
Lung Cancer	M	65	Surgical	Yes		
Breast Cancer	F	63	Surgical	Yes	Yes	No
Pancreatic Cancer	M	58	Needle Biopsy	Yes	Yes	Yes
Osteosarcoma	F	10	Surgical	Yes	Yes	No
Colon Cancer	M	32		No		
Malignant Melanoma	M	56	Surgical	Yes	No	
Colon Cancer	F	48	Needle Biopsy	Yes	No	
Merkel Cell Carcinoma	M	49	Surgical	Yes	Yes	No
Lymphangioma	M	6	Surgical	Yes	No	
Small Bowel Cancer	F	69	Needle Biopsy	Yes	Yes	No
Hepatoblastoma	M	4	Surgical	Yes	Yes	Yes
Breast Cancer	F	60	Needle Biopsy	Yes		
Renal Cell	F	66	Needle Biopsy	No		
Colon Cancer	F	45	Surgical	Yes	Yes	No
Pancreatic Cancer	M	69	Needle Biopsy	Yes	No	
Osteosarcoma	F	16	Surgical	Yes		
Non Small Cell Lung Cancer	F	50	Surgical	Yes	Yes	No
Plasmacytoma	M	62	Surgical	Yes		
Ovarian	F	50	Surgical	Yes	Yes	Yes
Non Small Cell Lung Cancer	F	63	Surgical	Yes	Yes	Yes
Renal Cell	M	52	Surgical	Yes	Yes	Yes
Non Small Cell Lung Cancer	M	63	Surgical	Yes	Yes	Yes
Lymphoma	M	80	Surgical	Yes	Yes	No

Table I: Sample of patient feasibility assessments.

While this first 50-patient study was designed to determine the feasibility of the overall approach in different tumor types and to establish the necessary logistical workflow between the multiple disciplines, some anecdotal signs of tumor response and physician-reported patient benefit were observed (Table 1). As the Table illustrates, useful data was generated on 39/50 patients. Of these, 24 out of the 34 cases utilized the report information. Treatment decisions were based on the reported data for 24 patients, and 9 patients experienced tumor responses (37.5% response

rate) determined through objective assessment of tumor burden (radiological imaging and/or biomarker endpoints, manuscript in preparation). While these findings remain anecdotal due to the uncontrolled nature of the study, they provide significant impetus to move ahead with the disease focused trial design outlined in this proposal. Moreover, these preliminary studies have demonstrated the feasibility of the approach in the real time prospective clinical setting.

Use of Transcriptional Analysis to Assess Gene Target Expression.
In the proof-of-feasibility study, the specific predictive methodologies were being developed and refined throughout, and led to the standardized methods outlined in this proposal. The most rudimentary method of transcriptional analysis relates to assessment of target gene expression. In some cases, the over-expression of a specific drug target at the transcriptional level is associated with efficacy of an inhibitor against the corresponding protein target; for example over-expression of *Her2* indicates use of trastuzumab in breast cancer [46]. Despite concerns over the discordance between transcript expression and protein target activity (which is partially addressed through development of our network topology method described below), the simple assessment of target transcript abundance showed early promise in the pilot study. For example, a complete response was observed in a female adolescent with acute lymphoblastic leukemia (ALL) following the administration of a multi-kinase inhibitor that was selected based upon a significant over-expression of one of the drugs known targets (*Flt-3)* at the transcriptional level (z-score >+10). Thus, while we now also incorporate a more sophisticated analytical method to infer target activation status based upon analysis of network topology (see below) and will also be testing the utility of well published signature-based methods for selecting drug candidates[43-45, 47, 48] simple target gene expression remains a rational method for identification of drug candidates. The knowledge base utilizes the existing pharmacopeia's postulated molecular mechanisms of action and contains molecular entities that are targeted by drugs, many of which are approved for human use. This includes several targets of particular relevance to neuroblastoma including VEGFA-VEGFR, TRK, mTOR, ALK, HDAC etc [8]. The transcriptional status of each of these targets is reported using the standardized z-score where the relative level of each target within an individual's tumor is determined through a comparison with a whole body reference set.

Novel Molecular Network Topology Analysis to Improve Utility of Targeted Pharmacopeia.
A novel method developed in partnership with GeneGo over the past few years relates to the analysis of molecular network topology [49]. As stated above, the expression of a target gene does not necessarily equate to activation of the target protein. Nonetheless, we investigated the possibility of utilizing known protein-protein and protein-small molecule interactions within GeneGo's MetaCore™ database (over 200,000 interactions) in conjunction with transcriptional data to infer key network targets that if modulated with a targeted agent, may disrupt the disease system(s) identified within each patient's tumor. As with all methodologies in this proposal, tumor-derived transcriptional data (normalized to a reference set of normal whole body samples) provides the consistent input to the algorithm. This specific methodology was applied retrospectively to the data generated during the first 50-patient feasibility study and anecdotally corroborated the potential of this systematic approach for identifying key target hubs within perturbed molecular networks. For example, in the leukemic cells of the pediatric patient with ALL described above, *Flt-3* was identified as a likely input point to an integrated transcriptional network. This patient responded well to a targeted therapy that inhibits multiple kinases including Flt-3. In an adult patient with metastatic non-small cell lung carcinoma, analysis of network topology highlighted *Egfr* as a likely input to a highly connected transcriptional network, and subsequent treatment with erlotinib showed some efficacy (patient exhibited a partial response).

This methodology has also been tested more systematically against specific public domain datasets. For example, Dr. Webb's group applied the methodology to a public dataset derived from the transcriptional profiling of skin from psoriasis patients. They were quickly able to identify several key targets and some associated targeted agents using this approach, many of which have been validated in the psoriasis literature. Collectively, we believe that the approach to the identification and subsequent analysis of neuroblastoma networks outlined in this proposal provides an exciting tool for systematically selecting network-based targeted regimens for the treatment of refractory or relapsed neuroblastoma patients. The systematic and automated approach described in this proposal is readily applicable to uncovering high quality therapeutic targets, and holds great promise for developing network-based combinational treatment strategies for a wide range of diseases especially for diseases such as neuroblastoma which have a low survival rate and are in need of new therapies. [2, 30].

Methods to be used in generating this reports are; Drug Target Expression Algorithm, Network Target Activity (Systems Biology Method, GeneGo); Drug Response Signatures Algorithm (Connectivity Map), and Drug Sensitivity Signatures Algorithm (PGSEA). These are furthered explained in section 3.

Reference Set: Whole body bank of normal tissue gene expression levels are used as the reference set for the normalization calculations. Whole body reference is chosen to provide a wide variance of gene expression for comparison in order to better identify signal from tumor tissue. This reference set will also help to decrease risk for toxicity as it will not identify targets that are highly expressed in normal tissues.

Normalization Calculations

A z-score is calculated using the mean gene expression level from the reference set to the same gene's expression level from the patient's tumor. A z-score is a quantitative measure of the number of standard deviations above or below the mean of the observed value (patient's gene) in comparison to the same observed value (the same gene in the reference set). Positive z-scores reflect the number of standard deviations that the observation being evaluated is above the mean (over-expressed) and conversely negative z-scores represent the number of standard deviations that the observation being evaluated is below the mean (under-expressed).

Drug Knowledgebase

The drug knowledgebase is comprised of publically available, peer-reviewed and clinically relevant pharmacological data. Numerous sources contribute to the knowledgebase including GeneGo, DailyMed, DrugBank, UpToDate, Entrez Gene, Entrez Pubmed, PharmaGKB, MedTrust Online and MedTrack.

Preclinical Model for Neuroblastoma Patients

Neuroblastoma cells can be isolated from either tumor biopsies or the bone marrow of patients using flow cytometry panel (GD2, CD81, CD9, CD56, CD34, CD45) or ficoll gradient isolation [50]. The bone marrow cells have been sorted and mRNA isolated for expression arrays. The patient cells have been cultured in our lab resulting in both adherent neuroblastoma cells and neurospheres. These cells have been grown for drug testing in vitro and injected into mice for *in vivo* tumor formation. This will be an important correlative study to continue to use in comparison to clinical response in patients.

Analysis of OncInsight's Drug Prediction Compared to Empirical Drug Sensitivity of SK-N-AS and SH-SY5Y Neuroblastoma Cell Lines

Total RNA preparations from each of SK-N-AS and SH-SY5Y from Dr. Khan's laboratory were analyzed using Affymetrix's HG-U133 Plus 2 platform. Raw MAS5 data was converted using Intervention Insight's whole body expression data, a collection of 45 different adult tissues supplied by Asterand. Dr. Khan's laboratory supplied Intervention Insights with CEL file data from Affymetrix's HG-U133 Plus 2 platform generated in their laboratory to be used as a comparator of cross-laboratory expression data. An Intervention Insights, OncInsights report of predicted drugs was prepared exactly as described elsewhere in the protocol.

Fifty-six compounds were tested at high and low concentrations in a cell growth assay for each of SK-N-AS and SH-SY5Y (determined as percent growth at 24 hrs post drug treatment)[51]. Of the fifty-six compounds tested, the OncInsights system could select up to eighteen drugs. Of the eighteen drugs selectable, nine were selected (50%, selected either as sensitive or insensitive). Seven drugs were selected in the analysis of SK-N-AS and nine drugs were selected in the analysis of SH-SY5Y. Thirty two overlaps were comparable [SK-N-AS high concentration (7); SK-N-AS low concentration (7); SH-SY5Y high concentration (9) and SH-SY5Y low concentration (9)]. For SK-N-AS, 79% agreement was observed and 21% disagreement was observed. For SH-SY5Y, 61% agreement was observed and 39% disagreement was observed. Combined, OncInsights accurately predicted growth sensitivities for SK-N-AS and SH-SY5Y 63% of the time.

Analysis of OncInsight's Drug Prediction Compared to PPTP drug sensitivity.

The National Cancer Institute (NCI) has established the Pediatric Preclinical Testing Program (PPTP) for testing drugs against in vitro and in vivo childhood cancer models to aid in the prioritization of drugs considered for early phase pediatric clinical trials. Drugs tested in xenograft models and predicted to be effective were evaluated using the OncInsights report as a comparison.

AZD2171 Response in Rhabdoid Kidney Tumor

FGFR2 overexpression has been identified to affect a variety of bone, skin and cancer pathologies[52]. In this PPTP xenograft sample of a rhabdoid kidney tumor (KT-16), a complete response was shown when treating the tumor with AZD2171 (Recentin®). The mRNA from the xenograft KT-16 was analyzed using Affymetrix's HG-U133 Plus 2 platform and converted using Intervention Insight's whole body expression data. The OncInsights platform using the Drug Target Expression Method identified AZD2171 as a potential therapeutic option, based on the overexpression of FGFR2 (Z=3.978) from this mouse xenograft.

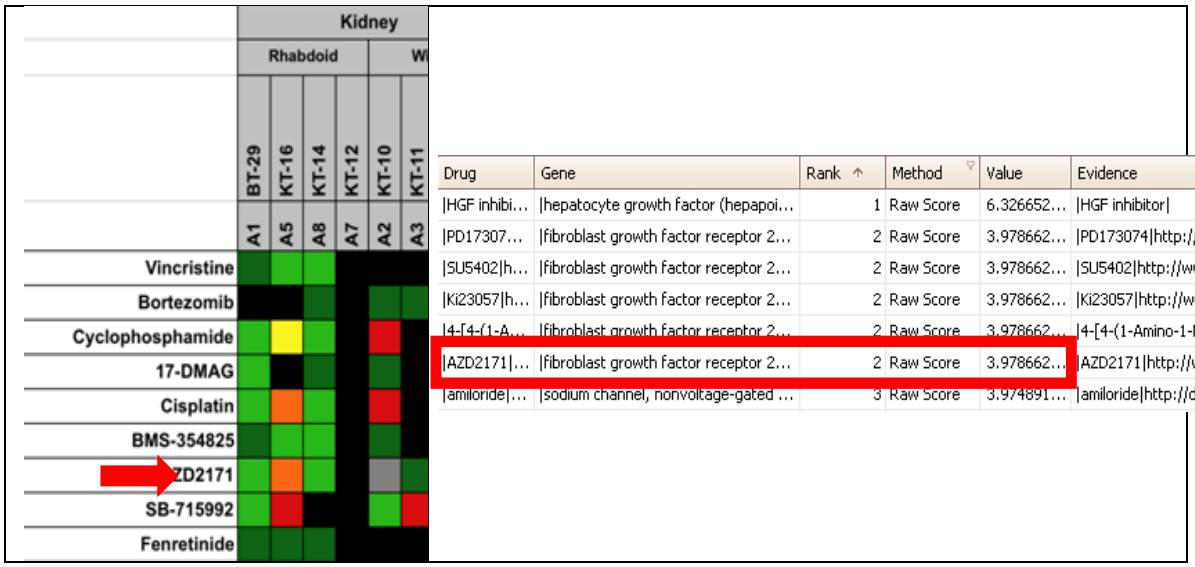

Figure 1: (Left) A complete response (orange square) to the experimental agent, AZD2171, is shown in the PPTP Rhabdoid Kidney xenograft, KT-16. (Right). The Drug Target Expression Method identifies ADZ2171 as a potential therapy based on overexpression of FGFR2.

Dasatinib Response in B-Cell ALL

Several recent papers have demonstrated the effectiveness of dasatinib in the treatment of patients with ALL[53-55]. In this PPTP mouse xenograft of B-cell ALL (ALL-4), treatment with dasatinib resulted in a complete response. The mRNA from the xenograft ALL-4 was analyzed using Affymetrix's HG-U133 Plus 2 platform and converted using Intervention Insight's whole body expression data. The OncInsights platform showed that three of the seven targets of dasatinib were found to be activated in this tumor using the network-based Transcription Factor Activity Method.

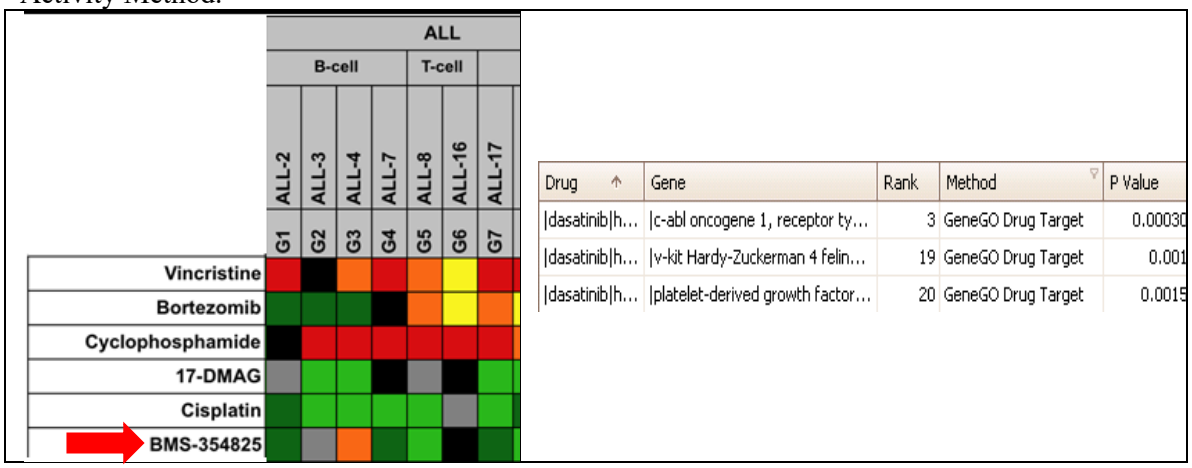

Figure 2: (Left) Dasatinib (BMS-354825) was shown to produce a complete response (orange square) in this mouse xenograft of B-cell ALL (ALL-4). Of the seven targets of dasatinib, three were found to be activated using our Transcription Factor Activity Method.

DNA mutation panel and use of Ion Torrent
Spectrum Health Molecular Diagnostics offers a CLIA certified targeted next generation sequencing test utilizing multiplex PCR with ion semiconductor sequencing (The Ion AmpliSeq™ Cancer Hotspot Panel v2) designed to amplify 207 amplicons covering approximately 2,800 COSMIC mutations from 50 oncogenes and tumor suppressor genes. This includes the 739 COSMIC mutations from 46 genes in the first Ion AmpliSeq™ Cancer Panel along with added hotspot mutations from significant cancer genes. The test can provide important individual information regarding tumor development and progression, and a more reliable prediction of personalized cancer therapies. This Cancer Gene Mutation Panel is designed to target 739 mutations in the following 46 key cancer genes: ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL, EZH2, GNA11, GNAQ, and IDH2. This mutation panel is designed to detect targeted mutations only. The 46 genes are not sequenced in their entirety. Mutations outside the targeted regions will not be detected. The limit of detection is 5% at 500X coverage.

This is a test currently available at centers such as Baylor College of Medicine as the "Cancer Gene Mutation Panel - Targeted Mutation Detection by Next Generation Sequencing". While it is currently available for patients, our study will examine the safety and predictive value for tumor boards of this test in pediatrics.

A Pilot Trial Testing the Feasibility of using Molecular-Guided Therapy in Patients with Refractory or Recurrent Neuroblastoma.

The primary objective of this pilot study was to evaluate the feasibility of using predictive modeling based on genome-wide mRNA expression profiles of neuroblastoma tumor biopsies to make real-time treatment decisions. Feasibility was defined as the completion of the following in a two week time period: tumor biopsy, quality RNA extraction, mRNA U133 2+ Affymetrix gene chip hybridization, analysis utilizing a series of predictive methodologies, report generation, tumor board review with formulated treatment plan, and medical monitor review. Subjects were not treated on this study. There were 5 subjects enrolled between April-June 2010 with multiply relapsed or refractory neuroblastoma. Subjects had received between 2-13 previous relapsed therapies and were between 2-6.5 years post diagnosis. All subjects had soft tissue disease which was able to be biopsied. All biopsies were adequate by pathology evaluation (>75% viable tumor) and RNA quality (>6.5 RIN). Gene chips were completed in 3-7 days, report generation was 1-5 days, tumor board was 1-3 days, medical monitor sign off was 1 day. The total time was 10-12 days for all subjects. The tumor board which consisted of 4-10 pediatric oncologists from sites across the US and a pediatric oncology pharmacist was able to create individualized therapy regimens for all subjects. Correlative biology specimens were obtained and grown in culture. Mice xenografts of 3/5 subjects were established. Cultures and xenografts are able to be used for validation studies of predicted drug sensitivity. In conclusion it is feasible to obtain real-time genomic profiling for molecularly guided therapy for use in treatment decision making.

A Feasibility Trial using Molecular-Guided Therapy in Patients with Refractory or Recurrent Neuroblastoma.

The primary objective of this feasibility study was to evaluate the feasibility and safety of using predictive modeling based on genome-wide mRNA expression profiles of neuroblastoma tumor biopsies to make real-time treatment decisions. Feasibility was defined as "enrollment onto study, quality mRNA obtained, gene chip completed, tumor board held, medical monitor review and approval, start of treatment by 21 days post biopsy/surgical resection date, and completion of 1 cycle of therapy." There are 11 subjects enrolled to date with multiply relapsed or refractory neuroblastoma. Subjects were between 1-7 years post diagnosis. All subjects had soft tissue disease which was able to be biopsied. All biopsies were adequate by pathology evaluation (>75% viable tumor) and RNA quality (>6.5 RIN). 2 subjects were deemed ineligible due to tumor type after biopsy. Gene chips were completed in 3-8 days (95% CI: 3.8 – 6.8), report generation took 0-3 days (95% CI: 0.0 – 1.5), tumor board took 1-6 days (95% CI: 1.6 – 4.2), medical monitor sign off took 1-2 days (95% CI: 0.8 – 1.4). The total time from date of biopsy to tumor board was 6-11 days (95% CI: 7.5 – 10.2) for all subjects and 7-20 days to treatment (95% CI: 8.9 – 16.1). The tumor board which consisted of 4-15 pediatric oncologists from sites across the US and a pediatric oncology pharmacist was able to create individualized therapy regimens for all subjects. Correlative biology specimens were obtained and grown in culture. Mice xenograft establishment is ongoing. Cultures and xenografts are able to be used for validation studies of predicted drug sensitivity. In conclusion it is feasible to obtain real-time genomic profiling for molecularly guided therapy for use in treatment decision making.

The study endpoint showing that 9/14 patients were feasible to enroll, biopsy, genomic analysis, tumor board review and patient treatment was met. All regimens were found to be safe by the medical monitor proving that the molecular tumor board was able to make safe decisions similar to hospital tumor boards making treatment decisions without molecular information on the patients. It was felt that the pharmacy review for evaluating drug-drug interactions and deciding on laboratory and safety testing was an important part of the tumor board (this is not usually present at hospital tumor boards) and will continue to be incorporated in this and future trials. All patients tolerated therapy well and were treated without any adverse events >grade 2 related to study drugs.

Neuroblastoma Gene Target Analysis Platform Reproducibility

Activities

Five core needle biopsies were processed for the reproducibility study: MGT 2, 3, 4, 7, and 8. One of these, MGT 4, was subsequently found to be a neuroendocrine carcinoma. Since five such samples are required, completion of the reproducibility study requires one additional patient.

Background and Goal

The Neuroblastoma Gene Target Analysis Platform (IDE # G100111) includes a process that, based on core needle biopsies of a neuroblastoma solid tumor, provides genome-wide expression profiles, comparative gene expression profiles based on a reference collection of normal tissues, and a set of drug therapies, each of which has a score (Figure 1). We proposed to study reproducibility of the IDE by applying it to triplicate samples obtained by dissecting each of five solid tumors. The primary goal of the reproducibility study is to evaluate the variation among sets of drug therapies associated with the same tumor. Secondary goals are 1) to compare the variation among sets of drug therapies from the same tumor with variation between tumors from distinct patients and 2) to evaluate variation associated with earlier steps in the process, in particular, expression profiles and comparative expression profiles (Figure 1).

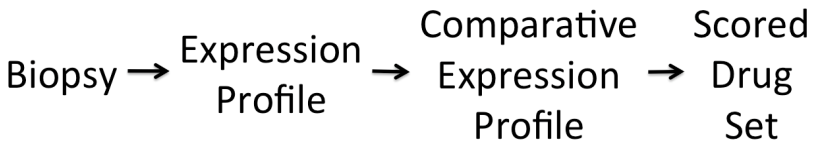

Figure 1. The IDE identifies drug therapies based on a solid tumor biopsy. Expression profiles and comparative expression profiles are intermediate results.

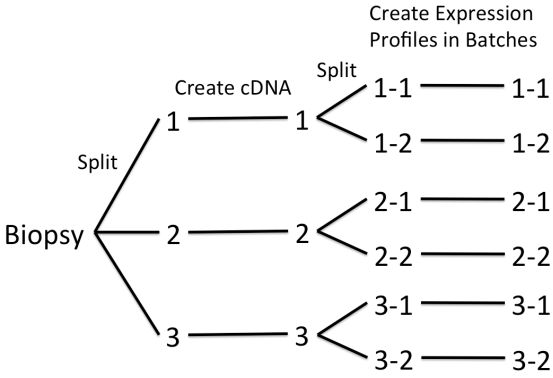

Figure 2. Reproducibility study design. Triplicate patient biopsies allow us to quantify variation within biopsies and to evaluate it in the context of the variation between biopsies. Each of the three biopsy sections is processed to obtain cDNA. cDNA samples are split and processed in two batches, allowing us to evaluate variation associated with processing batch.

Design

The design employed (Figure 2) was a hierarchical component that allows us to quantify variation within biopsies and to evaluate it within the context of the variation between biopsies as well as a cross-classification by GeneChip batch that allows us to evaluate batch effects.

Methods

Affymetrix GeneChip oligonucleotide array technology is used to obtain gene expression profiles, $\{E_g | g \in G\}$, where G is the set of probe sets on the GeneChip. The OncInsights service calculates comparative expression profiles, $\{Z_g\}$, from the sample mean and sample standard deviation, $\{(\bar{E}_g^R, s_g^R)\}$, of a Reference collection of normal tissue expression profiles using $Z_g = \frac{E_g - \bar{E}_g^R}{s_g^R}$.

The OncInsights service uses comparative expression profiles to obtain a set of drug therapies, D_{pr}, for each patient, p, and replicate biopsy, r, as well as scores, $\{S_{prd}\}$, for each drug, d in D_{pr}. The reproducibility of the identification of a drug, $d \in D_{pr}$, is defined as the proportion of other drug sets associated with the same patient that identify the drug

$$F_{prd} = \frac{1}{|R_p| - 1} \sum_{r' \in R_p, r' \neq r} H(d \in D_{pr'})$$

where H is an indicator function that equals 1 when its argument is true and 0 otherwise, R_p is the set of replicates, and $|R_p|$ is the size of R_p (3, the number of replicates). $F_{dpr} = 1$ when drug d is identified on all replicate lists and $F_{prd} = 0$ when it is not identified on any other list. We consider the average reproducibility associated with each patient, $\bar{F}_p$, that is, the average of F_{prd} over replicates and drugs,

$$\bar{F}_p = \sum_r \frac{1}{|D_{pr}|} \sum_{d \in D_{pr}} F_{prd}$$

as well as the average reproducibility of drugs scoring above a threshold, $\bar{F}(S)$, that is, the average of F_{dpr} over patients, replicate drug lists, and drugs, conditional upon the drug achieving a minimum score

$$\bar{F}(S) = \frac{1}{|P|} \sum_p \sum_r \frac{1}{|d: S_{prd} > S|} \sum_{d: S_{dpr} > S} F_{prd}$$

We note that a method that uniformly identifies every drug would not be an acceptable method yet would exhibit perfect reproducibility. We therefore evaluate the variation among drug lists associated with the same patient in the context of the variation among drug lists from different patients. Methods developed by Gower, Anderson, and their coworkers [56-58] and the Jaccard distance allow us to use the framework familiar from univariate ANOVA. More precisely, these methods allow us to test the null hypothesis that the variation among sets lists associated with different patients can be accounted for by the variation among drug sets associated with the same patient as well as to partition the variation into components so that their magnitudes can be compared.

Results

Expression profiles

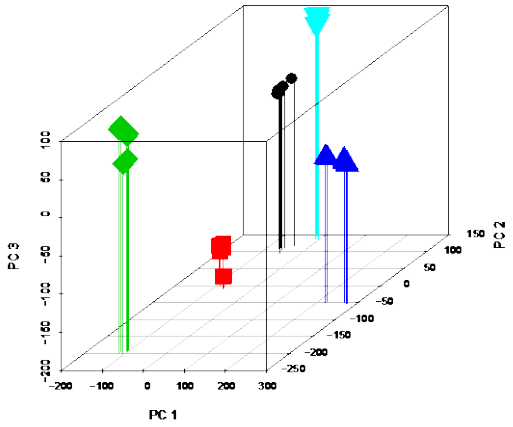

Figure 3 Principal Component Analysis. The first three principal component scores, PC1-PC3, illustrate the observation that the variation associated with the six samples for each biopsy (all of which have the same symbol and color) is small relative to the variation between biopsies.

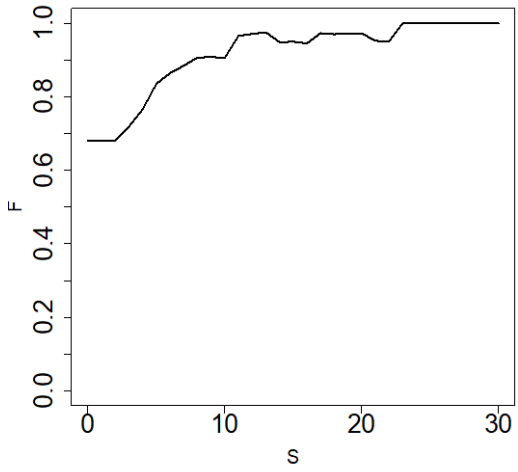

Figure 4. Reproducibility as a function of the threshold score. The reproducibility averaged over patients, replicates, and drugs is 0.68 (the intercept with the horizontal axis). As the threshold score increases the reproducibility increases to 1.

Distance-based nonparametric multivariate analysis of variance [57, 58] allowed us to reject the null hypothesis that variation between biopsies can be accounted for by the variation within biopsies (p=0.001). That the variation among expression profiles associated with the same biopsy is small compared with the variation between expression profiles associated with different biopsies is apparent from Principal Component Analysis (Figure 3).

Sets of drug therapies

Similarly, the variation among drug sets associated with the same biopsy is small compared with the variation among drug lists associated with different biopsies (p=0.001). The reproducibility averaged over patients, replicates, and drugs is 0.68. As the threshold score increases the reproducibility increases to 1 (Figure 4).

Conclusion

Collectively, the early preclinical and current clinical data suggests that this integrated approach is highly feasible and safe in neuroblastoma and that it is reproducible among repeat samples within patients. It is also clear that an investigation of this approach in other targeted patient populations is warranted. Brain tumors, and rare solid tumors are logical diseases in which to evaluate this approach, based upon the analogous need to develop a more rational-based approach to therapeutic selection in these difficult to treat tumors. Furthermore, the ongoing collaborative efforts between the co-investigators of this proposal in identifying novel molecular-based treatments for pediatric cancers and provides further justification to develop this analysis further to include DNA mutation analysis in tumor board decision making.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Determine feasibility of using tumor samples to assess genomic mRNA expression arrays and DNA mutation panels using predictive modeling to make real-time treatment decisions for children with relapsed/refractory cancers.

2.2 Secondary Objectives

- To continue to determine the safety of allowing a molecular tumor board to determine individualized treatment plans
- To determine the activity of treatments chosen based on:
  - Overall response rate (ORR)
  - Progression free survival (PFS)
- To explore the relationship between tumor phenotype and response by permitting use of tumor tissue in a correlative biologic study
- To compare PFS interval to PFS intervals of previous chemotherapy regimens since relapse for each subject.

3 STUDY DESIGN

This is an open label, multicenter prospective feasibility study in patients with refractory or recurrent childhood cancers.

3.1 Subject Enrollment and Sample Procurement and Data Processing

Eligible subjects will be enrolled onto this study at each site following a registration process that includes receipt of a signed subject consent form and a copy of the required baseline laboratory tests. Subjects will undergo a scheduled surgical resection and/or diagnostic biopsy procedure. Common sample identifiers will be provided by the NMTRC Lead Study Coordinator to the participating site and will be used by all parties throughout the project to ensure sample, data and report alignment between participating organizations. At the time of tissue resection or biopsy, two fresh tumor samples will be committed for this specific research study (referred to as "Primary Samples"), and prepared immediately per Appendix II and section 9.3. Primary Samples will be sent to Clinical Reference Laboratory (CRL) and Spectrum Health Molecular Diagnostics. Samples will be reviewed by local pathology to confirm >75% tumor and >75% tumor cell viability which is required for microarray analysis. In the absence of an adequate tumor specimen from the enrolled subject, this would represent a non-feasible outcome for this subject on the study. Tumor samples will also be sent for research purposes (referred to as "Secondary Samples.") A portion of the tumor tissue biopsy will be shipped overnight to the Neuroblastoma Translational Research Laboratory on dry ice.
Upon arrival of the tumor specimens at the Clinical Reference Laboratory (CRL), Spectrum Health, the Neuroblastoma Translational Research Laboratory, and TGen, the samples will be logged and immediately processed according to details in Section 9.

3.2 RNA Microarray Analysis

Cells or tumor samples will have RNA isolated and amplified for hybridization to an Affymetrix U133 Plus 2.0 GeneChip®. This step will be performed by molecular technologists in conjunction with the Clinical Reference Laboratory (CLIA certified lab) in Lenexa, KS. The RNA extraction, amplification, hybridization, and scanning procedures adhere to strict standard operating procedures to ensure that results are highly accurate and reproducible. The operation includes stringent controls over quality including measurements of RNA quality to minimize the chance that inaccurate data will be utilized in the study. By default, a failure in an individual step will result in a re-run of that specific step if suitable material remains. A second failure will result in exclusion of the subject from the study unless an additional fresh surgical specimen can be obtained. Standard metrics include the 260/280 ratio and the Agilent 2100 bioanalyzer (Pico Chips) which provides a measure RNA degradation as an RNA integrity number (RIN). To pass QC, the 260/280 ratio must exceed 1.8 and the RIN number must be greater than 6.5 which indicates substantially intact RNA. In the isolation, purification, amplification, and labeling processes, a sole individual will handle all samples to limit operator errors. Positive mutation findings from the Ion Torrent Panel will be verified using Sanger Sequencing. While all attempts will be made to have this data available to the tumor board, due to the potential length of time to process Sanger Sequencing samples, these results may not be available until after the tumor board has met and the patient has started protocol treatment. If Sanger Sequencing results differ from Ion Torrent results and the subject has already started protocol treatment, this information will be communicated to the treating site Principal Investigator who will then communicate this information to the patient and a mutual decision about continued treatment will be made.

3.3 DNA Mutation Panel

Ion Torrent Deep Amplicon Sequencing of Tumor Samples: Deoxyribonucleic acid will be extracted from tumor tissues and quantitated using the Qubit2 fluorometer (Invitrogen). Ten nanograms of DNA will be used for multiplex PCR of a panel covering 739 mutations in 46 cancer-related genes (Ion AmpliSeq Cancer Panel, Life Technologies). Subsequent processing of samples will be performed according to the manufacturer's protocol. Library constructions of the amplicons and subsequent enrichment of the sequencing beads will be performed using the OneTouch system. Sequencing will be done on the 314 chip with 10 megabases capacity using the Ion Torrent Personal Genome Machine (Life Technologies) as per the manufacturer's protocol. Data analysis, including alignment to the hg19 human reference genome and base calling, is done using built-in software. De-identified Data will be sent to the NMTRC via secure e-mail for creation of the DNA Mutation Panel Drug Prediction Report.

3.4 Data Analysis and Predictive Methodologies

Each subject will be assigned a unique anonymous identifier by the Data Manager at the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), which will be used to track the "Subject" derived "Samples" and performed "Experiments". At each entity level, pertinent data can be associated; for example, primary and secondary clinical endpoints can ultimately be associated with the Subject and the histopathological assessment of the donated Sample, and experimental parameters with each Experiment. For the proposed work it should be adequate to exchange sample information in tables that provide for easy identification of the subject identifier. In addition, the normalized Affymetrix GeneChip data will be associated with the Experiment for further analysis as described below. Upon exchange of the normalized GeneChip data and all associated experimental parameters, an additional QC check will be

performed to ensure all critical experimental steps passed the required threshold of acceptance. While quality control parameters are checked by the CLIA certified laboratory, a secondary assessment provides an additional level of quality assurance. If no failures are noted upon this review, a complete analysis of the molecular data will proceed.

3.4.1 Intervention Insights OncInsights mRNA Expression Service

The following describes the Intervention Insights OncInsights service which utilizes data generated from the RNA Microarray analysis (as described in section 3.2 above).

A consistent step for the OncInsights methodologies outlined in this proposal is the conversion of normalized probe set intensities to a relative measure of transcript abundance. While many studies use an arbitrary fold change threshold relative to a reference sample as a means to determine significant changes in gene expression, we prefer to utilize a standardized z-score method (described below in Signal Pre-Preprocessing and Z-Score Calculation) to determine statistically significant differences in each neuroblastoma sample relative to a whole body reference. This method assigns a z-score to each probe set based upon the number of standard deviations from the normal sample population mean. This provides a good assessment of transcript "differences" relative to a whole body reference set which may not necessarily be associated with large fold changes in transcript expression. Having established a consistent data input of relative transcript abundance in each subjects tumor specimen, the following analytical methods will be applied to the standardized data to predict drug efficacy.

Predicted Therapeutic Compounds: At this time, there are currently greater than 300 drugs within the OncInsights system each with a published and defined molecular target. For the purposes of this protocol, the tumor board will only use the drugs listed in Appendix III.

Drug Knowledgebase
The drug knowledgebase is comprised of publically available, peer-reviewed and clinically relevant pharmacological data. Numerous sources contribute to the knowledgebase including GeneGo, DailyMed, DrugBank, UpToDate, Entrez Gene, Entrez Pubmed, PharmaGKB, MedTrust Online and MedTrack.

Whole Body Reference Set: A whole body bank of forty-five normal tissue gene expression levels are used as the reference set for the normalization calculations. A whole body reference was chosen to provide a wider variance of tissue specific gene expression for comparison in order to best identify expression differences from tumor tissue. The reference also helps to decrease toxicity risk by not identify targets that are highly expressed in normal tissues.

Signal Pre-Processing, Z-Score Calculation and Sibling Probeset Logic
Signal Pre-Processing. Signal data from the Affymetrix U133 2.0 Plus GeneChip is normalized using Affymetrix's MAS5.0 Normalization Algorithm. Using Affymetrix Annotation version 32 (released August 2011), probesets which map to more than one gene (potential cross-hybridizing) are removed from the analysis. Probesets marked "present" by Affymetrix P/M/A algorithm are included in the OncInsights method calculations. In addition and to include down regulated genes, probesets marked "absent" or "marginal" are included in the OncInsights method based on the following logic: probesets with a tumor signal value less than the mean reference signal value and the reference probeset is marked "present" by Affymetrix P/M/A logic 50% or more of the

time in the whole body reference set. All probesets which pass the pre-processing thresholds as described above are evaluated for inclusion in the OncInsights report.

Z-Score Calculation. The z-score is calculated for all included probesets using the whole body reference mean and whole body reference standard deviation as follows:

$$z = \frac{x - \mu}{\sigma}$$

Where x is the signal intensity, μ is the mean probeset intensity from the reference standard and σ is the standard deviation of the mean of the reference. Interpretation of the z-score is straightforward and has no special case. Positive z-scores represent the number of standard deviations that the observation being evaluated is above the mean; conversely negative z-scores represent the number of standard deviations below the mean. Observations with high, positive z-scores are said to be "up-regulated" or "over-expressed" whereas observations with low, negative z-scores are said to be "down-regulated" or "under-expressed". Finally, it is important to note that the z-score represents the individual z-score relative to the same probeset in the normal reference group and not its z-score among all other probesets within the total expression data.

Sibling Probeset Logic. Within the Affymetric Annotation file, numerous probesets map to the same Entrez Gene, these probesets are called siblings. To merge multiple probeset measurements (converted to Z-score), the OncInsights systems using an industry accepted logic as follows:

A probeset maps to a single Entrez Gene, the z-score value is assigned to the Entrez Gene.

Two probesets map to a single Entrez Gene, the maximum observed z-score value is assigned to the Entrez Gene.

Three or more probesets map to a single gene, the median observed z-score vaule is assigned to the Entrex Gene,

Upon conclusion of these methods, the OncInsights system has a list of genes with their associated z-score value. These genes and their measured z-score values are used in all subsequent OncInsights methods except the Drug Response Signatures Algorithm which uses only probeset values as described below.

BioMarker Based Rules (Sensitive and Insensitive Rules)
The method employs predefined and published rules maintained in the drug knowledgebase in which a drug effect has been associated with an expression of a genomic marker. This method not only predicts drugs which would be suited to treat a specific condition (sensitive), it also flags drugs which are predicted to be insensitive given a subject's tumor biomarker expression (insensitive). Genes with z-score values within the rule range (positive or negative z-score values) trigger display of the therapeutic compound. As an example, one rule within the BioMarker Based Algorithm refers to AR, androgen receptor, and bicalutamide. When tumor AR z-score is ≥ +3.0 (three standard deviations above the reference mean) the rule is trigger and bicalutamide is included in the OncInsights report. This is an example of a therapeutic compound that is "sensitive" when "over-expressed". Other rules trigger "sensitive" when "under-expressed" as when tumor ERCC1, excision repair cross-complementing repair deficiency, z-score ≤ -3.0 (three standard deviations below the reference mean) triggers carboplatin as

"sensitive". While simple and practical in nature, one concern with this methodology is that over-expression of a drug target can represent a means by which tumors develop resistance to a targeted agent [35]. In addition, BioMarker Based Rules can trigger "insensitive" when gene expression is "over-expressed" or "under-expressed". Currently there are 30 sensitive rules and 12 insensitive rules within the BioMarker Based Rules knowledgebase. Each rule is confirmed against two or more publically available sources in which the therapeutic agent (drug) has an effect on the gene target.

Drug Target Expression Algorithm

Genes with z-scores ≥ +3 (three standard deviations above the reference mean) are submitted to the method and therapeutic compounds which meet the rule requirement are selected and displayed in the OncInsights report. This is analogous to the current approaches of detecting *Her2* and *Egfr* gene amplification or over-expression prior to treatment with the appropriate targeted inhibitors [59, 60]. For this approach, we utilize public domain knowledge of the existing pharmacopeia and their molecular mechanisms of action [38, 39]. For example, one rule within the Drug Target Expression Algorithm refers to ESR1, estrogen receptor 1, and tamoxifen. When tumor ESR1 z-score expression is ≥ +3.0 the rule is triggered and tamoxifen is included in the OncInsights report. Currently, 163 rules are contained within the Drug Target Expression Algorithm rule set. Each rule is confirmed against two or more publically available sources in which the therapeutic agent (drug) has an inhibitory effect on the gene target.

Network Target Activity (Systems Biology Method, GeneGo)

A major consideration for the future of predictive therapeutics is the identification of active (or inactive) molecular networks within a tumor to permit network-directed therapeutic strategies [28, 30, 61]. In partnership with GeneGo (www.genego.com), we have developed a systems wide biology method based upon network topology for predicting drug target status and contribution within tumor-specific networks [62]. The method looks at biological pathways by constructing a shortest path network within a list of the subject's genes which are above a predefined threshold (z-score ≥ +2). Using these genes, a global network representing known geneomic pathways is constructed using knowledge contained in GeneGo's master database of publically available, peer-reviewed literature describing protein-protein interactions. These two networks are then compared to determine which genes may represent significant pathways with respect to the subject's tumor biology. Genes are "scored" using the comparison of the two networks. The method is designed to uncover regulatory proteins (kinases, transcription factors) which may not be affected at the differential gene expression level, but drive down stream transcription activity through transcription factors. Statistically, this method evaluates the enrichment in transcriptional targets compared to the global protein network and evaluates whether there is a higher proportion of possible transcriptional targets in the gene set of interest than would be expected in a random collection of genes. This algorithm yields a robust analysis of tertiary expression of targets and downstream effects of regulation.

Drug Response Signatures Algorithm (Connectivity Map)

The method uses a publically available data set called The Connectivity Map developed at the Broad Institute [43, 48] and recently commercialized by private equity. In the original description of the method, Lamb et al were able to successfully predict cell lines that were responsive to estrogen receptor inhibitors [43]. Subsequently, the general approach has been applied to several datasets to hypothesize potential drug efficacy in the background of different disease contexts [42, 49]. It was developed to elicit gene expression signatures from human cells associated with drug exposure to identify a functional (disease state) connection. The top 500

genes ranked by z-score with a z-score ≥ 1.5 and the bottom 500 genes ranked by z-score with a z-score ≤ -1.5 are submitted to the OncInsights Drug Response Signature algorithm. The connectivity score is calculated from a nonparametric, rank-based pattern-matching strategy based on the Kolmogorov-Smirnov statistic with p-values estimated by permutation testing (n=50,000 tests) as described previously [63, 64]. Upon completion of the analysis, drugs with p-values ≥ 0.05 (negative enrichment scores) are included in the report. A negative enrichment score implies that genes that are down-regulated by the drug are up-regulated in the tumor sample and vice versa. The implication is that the drug reverses the gene expression changes associated with the disease and thus may act to reverse the disease.

Drug Sensitivity Signatures Algorithm (PGSEA)
The Drug Sensitivity Signatures algorithm reproduces the published implementation of the Parametric Gene Set Enrichment Analysis (PGSEA) using the NCI-60 cell line sensitivity signatures [44, 45]. A PGSEA drug signature maps over-expressed genes (determined pre-drug treatment) to drug sensitivity as measured by the half maximal inhibitory concentration (IC50) of the cell line studied. The drug signature is a collection of Entrez Gene IDs that were found to be over-expressed in drug sensitive cells. Based on this evidence, if a tumor's gene signature of over-expression is similar to a sensitive cell's gene signature of over-expression the drug may also be effective for the tumor cells. To evaluate potential sensitivity to a signature, a one sample t-test is applied to evaluate if the mean of the z-score values is significantly greater than zero. The analysis only tests for a difference in the positive z-score direction. A negative z-score trend even if it is significant is discarded. This approach is consistent with well published methods for inferring drug sensitivity utilizing the NCI 60 cell line dataset [45, 51].

OncInsights Version.
The study will use OncInsights version 1.4.7.0

3.4.2 DNA Mutation Panel Analysis

The following describes a process which utilizes data generated from the DNA Mutation Panel analysis (as described in section 3.3 above).

DNA Mutation Panel Drug Prediction
The data from the Spectrum Health Ion Torrent Cancer Panel will be provided to the NMTRC.. A knowledge database created from published research literature linking mutations with targeted drugs in cancers will provide a report for the tumor board showing the mutations and predicted therapeutics from the list provided in Appendix III.

An in-house software application is implemented that produces reproducible, rules-based lists linking gene mutations with potential drug therapies. An electronic rule-capture interface is used to import a spreadsheet database, that contains genes, measurement types, and values for those measurements, and any other additional columns. Rules (for each gene) are assigned to the application by the investigators, without modifying the core software code. All conditions follow the basic form "<measurement> <verb> <value>". These verbs include <, <=, >, >=, equals, is present, is not present. Every rule may have any number of modifiers that effectively serve as sub-rules that associate the rule with other potential drug treatment for the parent rule.

Report:
The process of report generation begins with gene specific input with accompanying aberration data. If gene matches gene in the database then aberration is checked. This will generate a rule in table-format stating a direct relationship, indicate/do not indicate drug. If an aberration is not exactly matched it will trigger an inferred relationship, indicate/do not indicate drug. The generated report includes a PubMed ID for each rule, which will be included as both supplementary data and an outbound hyperlink. The software enables only authorized investigators to access the underlying system configuration. Users of this application are able to access the data only through the GUI "front-end", thereby locking the data relationships for the duration of an investigational trial. This software takes into account the following:

1. 100% reproducible output given the same input.
2. Simple yet sophisticated rules management.
3. Cross reference data with several open source data sets.
4. Generation of a clinically understandable, actionable report.

Positive mutation findings from the Ion Torrent Panel will be verified using Sanger Sequencing. While all attempts will be made to have this data available to the tumor board, due to the potential length of time to process Sanger Sequencing samples, these results may not be available until after the tumor board has met and the patient has started protocol treatment. If Sanger Sequencing results differ from Ion Torrent results and the subject has already started protocol treatment, this information will be communicated to the treating site Principal Investigator who will then communicate this information to the patient and a mutual decision about continued treatment will be made.

3.5 Treatment Protocol Decision

3.5.1 Decision Making Rules for Treatment Regimens

Treatments protocols will be generated from the tumor board meeting which will consists of three pediatric oncologists (minimum) and one pharmacist utilizing the information contained in a report generated on the basis of genomic analysis of the gene expression profile of the subject's tumor. Specific treatment details will consist of a regimen chosen from a guided list of agents implicated in critical molecular signaling pathways and/or from signature-based predictions of drug efficacy summarized in the guided therapy reports. All agents are listed in the current pharmacopoeia for human use, but will differ amongst individual subjects.

3.5.1.1 Decision rules for the committee will include:

1. All drugs with predicted efficacy will be reported to the tumor board with an associated predicted efficacy score and rank. At this time, FDA approved drugs predicted by one of the different predictive methodologies under evaluation will be included (Drug Target Expression, Biomarker-Based Rules Algorithm, Systems Biology Methods, Connectivity Map, Gene Set Enrichment Analysis, or DNA mutation panel). For these panels the analytical methods are independently applied to the standardized and normalized (relative to whole body reference set) gene expression data derived from the profiling of each subject's tumor. Each method is associated with an objective statistical threshold that must be exceeded in order for a specific drug to be predicted and reported for consideration. Multiple lines of evidence (e.g. multiple methods predicting the same drug, multiple targets for the same drug) will be considered during the review process.

Molecular-based predictions of drug efficacy will be supplemented with evidence gathered from automated searching of the literature, clinical trials and the internet.
2. Drugs must be FDA approved with established standard and safe dosing schedules (see drug dosing below Section 3.5.1.2). Those without known pediatric dosing will be excluded.
3. Potential drug choices will be analyzed with regards to safety, mechanism, availability and cost. Focus will be on low-toxicity, targeted therapies.
4. Drug combinations will be allowed, up to a maximum of 4 agents. Literature searches will be conducted to assemble data on previously established and tested regimens. These regimens will be given priority.
5. A pharmacist will analyze potential drug interactions between the guided agents and the subject's routine medications and supplements. For drug interactions and known toxicities the following databases will be used: MicroMedex LexiComp, E-facts, Natural Medicines Database.

Subjects' history and previously received treatments will be reviewed. Drugs which a subject has failed will be given low priority and used only if there is a rationale for synergy in combination therapy.

3.5.1.2 Recommended priorities for determining drug dosing to be used in individualized treatment plans include the following:

1. For a given proposed individualized combination of drugs the first priority to establish doses will be to identify the same combination of drugs in a peer-reviewed journal article or presented as a reviewed abstract, or which is part of an ongoing peer-reviewed clinical trial registered with clinical trials.gov.
2. When a proposed individualized combination of drugs has not previously been reported, the process to establish doses will be to then identify individual members of the proposed combination that have been used in combination with other cytotoxic agents similar to those being considered for combination therapy. The source of information will be a peer-reviewed journal article or presented as a reviewed abstract, or which is part of an ongoing peer-reviewed clinical trial registered with clinical trials.gov.
3. When a proposed individualized combination of drugs have no available combination data, dosing guidelines will start with the MTD determined from a phase I/II pediatric study. Reference information will be based upon either a peer-reviewed journal article or presented as a reviewed abstract, or which is part of an ongoing peer-reviewed clinical trial registered with clinical trials.gov. Doses will be reduced to compensate for potential additive toxicities of combination agents (refer to protocol section 3.5.1.1 #5 that describes pharmacy programs that are used to evaluate potential interactions and combination dosing for all medications).

Please note that many of the drugs that will be considered for proposed individualized combination therapy in this protocol are not considered cytotoxic agents and therefore will not have previously been specifically tested as part of conventional antineoplastic protocols. Examples of these medications may include anti-seizure or anti-cholesterol agents. These non-cytotoxic agents will be used at standard doses based on recommendations of an experienced pediatric pharmacist (refer to protocol section 3.5.1.1 #5 that describes pharmacy programs that are used to evaluate potential interactions and combination dosing for all medications). The final treatment regimen will be subjected to a 12 hour in depth review and evaluation for safety and

then be signed off by one of the protocol pharmacists. The treatment memo will then be discussed with the subject and their parents (if the subject is < 18 years of age).

3.6 Safety Evaluations

The principal investigator and the study chairs will evaluate reported serious adverse events and other toxicities in real time. Study chair and PI meetings will occur at least monthly. The principal investigator will meet with the clinical research team at frequent and regularly scheduled intervals to determine treatment modifications and treatment based toxicities. Toxicity data must be submitted to the disease specific Study Chair at the end of each cycle of therapy.

Any safety concern or new information that might affect either the safety or the ethical conduct of this trial will be immediately forwarded to the study chairs in written form. The study chairs will be responsible for informing the IRB and DSMB. If trends in toxicities are noted or stopping rules are met, the PI will temporarily suspend enrollment while reviewing the episodes with the IRB and DSMB. The DSMB will convene every 6 months for evaluation of all safety data.

Study will be on hold for safety monitoring by DSMB review when:

1. Any deaths deemed related to the study drug by the treating PI while on study or occurring less than 30 days after medications ended or 2 serious adverse events possibly related to protocol within 60 days.
2. Any other reason that the NMTRC feels it is in the best safety interest of the subjects.

Subjects will be required to either come off study or be dose reduced per treating physician standard of care if one of the following toxicities related to treatment regimen occurs. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Non-Hematologic toxicity:

· ≥Grade 3 non-hematological toxicity not resolved to <Grade 2 or baseline within 2 weeks excluding nausea, vomiting, anorexia, hypertension, electrolyte abnormalities corrected with oral supplementation

· Any Grade 4 non-hematological toxicity.

Hematologic toxicity:

· Grade 4 neutropenia lasting ≥14 days;

· Grade 4 neutropenia with Grade 4 infection

3.7 Efficacy Evaluations

At the times indicated in Section 5 and the Table of Procedures and Assessments, scans will be obtained to evaluate response data for subjects enrolled in this study. Efficacy will be assessed according to criteria outlined in Section 7 (Efficacy Assessments) to evaluate the activity and potential benefit of the chosen treatments protocol in this subject population.

3.8 Biological Studies

Subjects will have an opportunity to participate in correlative biological studies on a voluntary basis. This study will be used to correlate in vivo and in vitro predictive drug responses. This study may be able to contribute to our knowledge of molecular determinants of response to therapy and/or development of biomarkers to help guide future therapy.

4 SUBJECT SELECTION

4.1 Inclusion Criteria

1. Subjects must have histologically proven neuroblastoma, brain tumor, or rare tumor and confirmation of refractory or recurrent disease with histologic confirmation at diagnosis or at the time of recurrence/progression
2. Subjects must be age >12 months at enrollment.
3. Subjects must be age ≤ 21 years at initial diagnosis.
4. Subjects must have measurable disease as demonstrated by residual abnormal tissue at a primary or metastatic site measuring more than 1 cm in any dimension by standardized imaging (CT or MRI); tumor must be accessible for biopsy. Patients with bone marrow only disease expected to be >75% tumor are eligible to enroll.
5. Current disease state must be one for which there is currently no known curative therapy
6. Lansky or Karnofsky Score must be more than 50
7. Subjects without bone marrow metastases must have an ANC > 750/µl
8. Adequate liver function must be demonstrated, defined as:
    a. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age AND
    b. ALT (SGPT) < 10 x upper limit of normal (ULN) for age
9. A negative serum pregnancy test is required for female participants of child bearing potential (≥13 years of age or after onset of menses)
10. Both male and female post-pubertal study subjects need to agree to use one of the more effective birth control methods during treatment and for six months after treatment is stopped. These methods include total abstinence (no sex), oral contraceptives ("the pill"), an intrauterine device (IUD), levonorgestrol implants (Norplant), or medroxyprogesterone acetate injections (Depo-provera shots). If one of these cannot be used, contraceptive foam with a condom is recommended.
11. Informed Consent: All subjects and/or legal guardians must sign informed written consent. Assent, when appropriate, will be obtained according to institutional guidelines. Voluntary consent for optional biology studies will be included.

4.2 Exclusion Criteria

1. Subjects who have received any cytotoxic chemotherapy within the last 7 days prior to enrollment and 14 days prior to study treatment start date.
2. Subjects who have received any radiotherapy to the primary sample site within the last 14 days (radiation may be included in treatment decision after biopsy).
3. Subjects receiving anti-tumor therapy for their disease or any investigational drug concurrently
4. Subjects with serious infection or a life-threatening illness (unrelated to tumor) that is > Grade 2 (NCI CTCAE V4.0), or active, serious infections requiring parenteral antibiotic therapy.
5. Subjects with any other medical condition, including malabsorption syndromes, mental illness or substance abuse, deemed by the Investigator to be likely to interfere with the interpretation of the results or which would interfere with a subject's ability to sign or the legal guardian's ability to sign the informed consent, and subject's ability to cooperate and participate in the study

5 STUDY PROCEDURES AND ASSESSMENTS

5.1 Enrollment of Subjects

All subjects (or subjects' legal representatives) must provide written informed consent before any study specific assessments may be performed. The NMTRC will keep a "possible enrollment list" for all sites combined. Subjects will be allowed to enroll in the order that they are added to that list. Prior to consent of the subject, the NMTRC research coordinator will be contacted (via e-mail) to place subject on this possible enrollment list. The NMTRC coordinator will then reply with study space availability. If a spot is not available at that time, the site will be contacted as soon as a spot does open up (based on the subjects order on the list). If a spot is available at the time, the potential subject will undergo consent and completion of all required screening procedures and certification of all inclusion and exclusion criteria by the Investigator. If the subject fits all enrollment criteria, the site will again contact the coordinator at the NMTRC for official enrollment confirmation and unique subject identifier assignment. In addition, a study enrollment form will be e-mailed or faxed to the coordinator at the NMTRC. A subject may NOT be enrolled on trial until official approval from the NMTRC is received. When a spot becomes available, the first subject from the list will be contacted and will have 5 working days with which to enroll in the study. If this subject does not enroll by that time then the subject forfeits his/her spot and the next subject will be offered that spot.

5.2 Screening

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded.

The following screening procedures must be performed within 21 days (14 days preferred) prior to date of biopsy. Studies must be done *after* last previous treatment for malignancy:

1. Signed informed consent form. All subjects (or subjects' legal representatives) must provide written informed consent before any study specific assessments may be performed. Signed informed consent form for voluntary participation in correlative biologic analysis.
2. Complete medical and surgical history, including documentation of the histologic evidence of malignancy and prior treatments for cancer. Include all other pertinent medical conditions and a careful history of all prior medical treatments;
3. Demographics;
4. Physical examination (including height and weight), noting all abnormalities and sites of palpable neoplastic disease;
5. Vital signs, including temperature, pulse rate, and blood pressure;
6. Karnofsky Performance status/Lansky Play status (Appendix I);
7. CBC with differential;
8. Serum electrolytes (sodium, potassium, chloride, bicarbonate), blood urea nitrogen (BUN), creatinine, albumin, Bilirubin, LDH, ALT, and AST;
9. Serum pregnancy test for female subjects of child bearing potential (onset of menses or ≥13 years of age);
10. CT or MRI of measurable disease sites
11. Solid tumor biopsy for "Primary Sample" with remaining tumor tissue used in correlative biologic studies handled per section 9.3 and submitted per Appendix II.

    For subjects that cannot provide a solid tumor biopsy; a bone marrow core biopsy sample will replace the solid tumor sample as the "Primary Sample." Bone Marrow must have adequate tumor (defined as >75% tumor) in order to qualify as "Primary Sample."
12. Concomitant medications/therapies including documentation of steroid use and dose;
13. Confirmation of inclusion and exclusion requirements;

Following completion of all required screening procedures and certification of all inclusion and exclusion criteria by the Investigator, the coordinator at the NMTRC will be contacted (via e-mail or phone call), at which time the subject will be enrolled in the trial and a unique subject number assigned.

The following screening procedures must be performed within 21 days of enrollment (14 days preferred). These procedures must be done prior to the first dose of study drug, but are not required to be done before biopsy.

1. Neuroblastoma subjects: MIBG scan (not required if subject's disease is previously determined to be non-avid). PET may be considered as alternative for MIBG. Other imaging appropriate for tumor type may also be considered.
2. Any subject that is suspected to have possible bone marrow disease and for all neuroblastoma subjects: Bone marrow aspirate and biopsy. Additional bone marrow for correlative biologic studies will be handled per section 9.3 and submitted as per Appendix II.
3. Baseline EKG (as indicated)
4. Neuroblastoma subjects: Urine for Vanillylmandelic Acid (VMA) & Homovanillic Acid (HVA)
5. Specific Tumor Marker for defined disease (if available)
6. Completion (by study staff) of pre study case report forms
7. Any additional labs or testing required by the tumor board

5.3 Study Procedures/Study Interventions

5.3.1 Study Visits- Cycle 1 Day 1

Subjects will return to the enrolling clinic at Day 1 of cycle 1 for evaluations. The following evaluations will be conducted prior to starting study drug:

1. Physical examination (including body weight);
2. Karnofsky Performance status/Lansky Play status-Appendix I;
3. Vital signs, including weight, temperature, pulse rate, and blood pressure (sitting);
4. CBC with differential;
5. Serum electrolytes, BUN, creatinine, Bilirubin, ALT, AST, LDH;
6. Neuroblastoma subjects: Urine for Vanillylmandelic Acid (VMA) & Homovanillic Acid (HVA) (may have been done within 3 days of treatment start/day 1)
7. Specific Tumor Marker for defined disease (if available) (may have been done within 3 days of treatment start/day 1)
8. Review and recording of concomitant medications;
9. Monitoring of AEs and review of concurrent illnesses
10. Completion (by study staff) of Case Report Forms.
11. Any additional labs or testing required by the tumor board

5.3.2 Study Visits- Cycle 1 Day 8 (± 3 days)

Subjects will return to the enrolling clinic at Day 8 of cycle 1 for evaluations. The following evaluations will be conducted at those time points:

1. Physical examination;
2. CBC with differential;
3. Monitoring of AEs and review of concurrent illnesses
4. Review and recording of concomitant medications;
5. Completion (by study staff) of Case Report Forms.
6. Any additional labs or testing required by the tumor board

5.3.3 Study Visits- Cycle 1 Day 15 (± 3 days)

Subjects will return to the enrolling clinic at Day 15 of cycle 1 for evaluations. The following evaluations will be conducted at those time points:

1. Physical exam;
2. Karnofsky Performance status/Lansky Play status-Appendix I;
3. Vital signs, including temperature, pulse rate, and blood pressure (sitting);
4. CBC with differential;
5. Serum electrolytes, BUN, creatinine, Bilirubin, ALT, AST, LDH;
6. Review and recording of concomitant medications;
7. Monitoring of AEs and review of concurrent illnesses
8. Completion (by study staff) of Case Report Forms.
9. Any additional labs or testing required by the tumor board

5.3.4 Study Visits- Cycle 1 Day 22 (± 3 days)- for 28 day cycles only

Subjects will return to the enrolling clinic at Day 22 of cycle 1 for evaluations. The following evaluations will be conducted at those time points:

1. Physical examination;
2. CBC with differential;
3. Monitoring of AEs and review of concurrent illnesses
4. Review and recording of concomitant medications;
5. Completion (by study staff) of Case Report Forms.
6. Any additional labs or testing required by the tumor board

5.3.5 Completion of Protocol Defined Therapy

Subjects who receive one total cycle of treatment (21 or 28 days) will be considered as having completed the protocol defined therapy for feasibility. Additional treatment cycles may be delivered in a maintenance setting if there are no safety concerns, there is no disease progression, and/or there is an indication of clinical benefit. Maintenance monitoring will be conducted as described for Subsequent Cycles.

5.3.6 Subsequent Cycles (Maintenance Protocol Treatment Cycles) (+/- 3 days to start Day 1 of Cycle treatment)

Drug administration will be according to guidelines in previous cycles with dose modifications if needed per Section 6.1.1. The following evaluations will be performed on day 1 of each cycle as indicated. Evaluations will be performed within 5 days prior to dosing unless otherwise indicated. Subsequent cycles (cycles 2 and beyond) may be given at the subject's home institution. If subjects are to receive subsequent cycles at a home institution, this will occur only at COG (Children's Oncology Group) member hospitals or those specifically approved by FDA.

1. Physical examination;
2. Karnofsky Performance status/Lansky Play status-Appendix I;
3. Vital signs, including weight, BSA, temperature, pulse rate, and blood pressure (sitting); (must be done on Day 1)
4. CBC with differential;
5. Serum electrolytes, BUN, creatinine, Bilirubin, ALT, AST, LDH;
6. Neuroblastoma subjects: Urine for Vanillylmandelic Acid (VMA) & Homovanillic Acid (HVA)
7. Specific Tumor Marker for defined disease (if available)
8. Review and recording of concomitant medications;
9. Monitoring of AEs and review of concurrent illnesses (must be done on Day 1)
10. Completion (by study staff) of Case Report Forms.
11. Any additional labs or testing required by the tumor board

5.3.7 Reevaluation During Subsequent (Maintenance) Cycles

Subjects will be assessed for disease at the end of cycle 2 and every other cycle or every 8 weeks, whichever occurs first, with the following (timing should be during the last week of the cycle):

1. CT or MRI of measurable disease sites (same as study done at study entry);
2. Neuroblastoma subjects only: MIBG scan or PET scan same as/if done at baseline evaluation.
3. Neuroblastoma subjects and any other subject with suspected bone marrow disease with positive bone marrow diease at study entry: Bone marrow aspirate and biopsy; Monitoring of AEs and review of concurrent illnesses
4. Review and recording of concomitant medications;
5. Any additional labs or testing required by the tumor board
6. Additional imagining or studies may be done at any time if clinically indicated by symptoms, exam, or tumor markers.

5.3.8 Off Therapy/30 Day Follow-Up Visit

Subjects will be seen at either the study clinic or their home institution within 30 (+7) days after the last dose of treatment. Last dose of treatment is defined as the last day that the subject receives the combination of tumor board recommended treatments. The following evaluations will be conducted:

1. Physical examination (including body weight), focusing on an update of all previous abnormalities, any new abnormalities;
2. Vital signs, including temperature, pulse rate, blood pressure (sitting);
3. Karnofsky Performance status/Lansky Play status (Appendix I);
4. CBC with differential;
5. Serum electrolytes, BUN, creatinine, Bilirubin, LDH, ALT, AST;
6. Neuroblastoma subjects: Urine for Vanillylmandelic Acid (VMA) & Homovanillic Acid (HVA)
7. Specific tumor Marker for defined disease (if available)
8. Review and recording of concomitant medications;
9. Monitoring of AEs and review of concurrent illnesses
10. Completion (by study staff) of Case Report Forms

Any subject with a suspected study drug-related toxicity at the follow-up visit must be followed until all current drug-related adverse events have resolved to baseline or ≤ Grade 2 or stabilization of the event. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the CRF, as well as in the subject's source documentation.

6 Protocol Drugs

Specific treatment details will consist of a regimen chosen from a guided list of agents implicated in critical molecular signaling pathways and/or from signature-based predictions of drug efficacy summarized from the guided therapy report. All agents are listed in the current pharmacopoeia for human use, but will differ amongst individual subjects. The treatment regimen will consist of FDA approved drugs that have known dosing per Section 3.5.1.2. The treatment regimens will be discussed with families and will include review of known side effects per Pharmacopeia Library (Appendix III) (information obtained from package insert and from MicroMedex LexiComp, E-facts, and Natural Medicines Database), serious adverse effects of possible new drug combinations, and any additional clinical monitoring that may be recommended by the tumor board. The family will be given the option to proceed with therapy and if the family decides to proceed with the tumor board's treatment decision they will be asked to sign a treatment specific memo.

Drugs will be prescribed by the enrolling institution per treating hospital protocol and administered per FDA guidelines and tumor board recommendations.

6.1.1 Treatment modifications

Dosing delays and modifications will be at the discretion of the treating Principal Investigator and their institutional pharmacist and based upon the selected therapy, subject response and practiced dosing regimens. Decisions will be made on the basis of clinical expertise of the physicians and pharmacists and with the subject's welfare being the principal concern. Informational websites such as drug bank (Micromedex, Lexicomp, E-facts, Natural Medicines Database) will be utilized to identify potential adverse events associated with individual treatments. The study pharmacist will be available to consult on decisions made with respect to changes and modification made due to potential drug related adverse events.

6.2 Concomitant Medications and Treatments

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care. All concomitant medications and treatments will be documented on the appropriate case report form.

The following medications are not permitted during the trial:

- Any cytotoxic chemotherapy
- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy, targeted therapies, anti-angiogenic therapies, or monoclonal antibody therapy

The following medications/treatments may be administered as follows:

- Any radiotherapy administered with palliative intent/pain control or recommended by tumor board as part of therapeutic regimen for best patient care.
- Prophylactic filgrastim, pegfilgrastim or oprelvekin; these hematopoietic growth factors may be administered according to ASCO, ASH, or institutional guidelines to treat an established cytopenia
- Erythropoietin, blood products, anti-emetics, steroids, and transfusions may be administered at the discretion of the Investigator based on established criteria.

7 Efficacy Assessments

7.1 Tumor Assessments/Scans

Tumor assessments/imaging studies must be obtained at baseline, at the end of cycle 2 and again after every other cycle (or every 8 weeks, whichever occurs first). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

All radiological images must be available for source verification. Images may be submitted for extramural review for final assessment of antitumor activity.

Subjects who come off study should have a final end of study disease-specific assessment done when possible.

7.2 Scan Submission:

All required study scans (CT's, MRI's, MIBG's and PET's) will be de-identified and sent to the NMTRC. All study required de-identified scans will be uploaded to HIPAA compliant database (if available) or sent on disc to:

Alyssa VanderWerff
NMTRC
Clinical Program Coordinator
100 Michigan Avenue NE MC 272
Grand Rapids, MI 49503
Tel: (616) 267-0327
E-Mail: Alyssa.VanderWerff@ helendevoschildrens.org

7.3 Response Criteria

Overall response rate (ORR) in subjects with radiologically assessable disease will be determined by CT or MRI by cross-sectional imaging, MIBG/PET scans, and/or bone marrow assessment.

Response Assessment: Each subject will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described below.

Response Criteria for Subjects with Solid Tumors: This study will use the (RECIST) Response Evaluation Criteria measurements in Solid Tumor from the NCI (Therasse, et al, 2000) modified for pediatrics.

- Measurable disease: The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm
- Serial measurements of lesions are to be done with CT or MRI, using the same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.
- Quantification of Disease Burden The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement. For this evaluation, all scans will undergo central review.

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry.
- **Stable Disease (SD):** Neither sufficient decrease to qualify for PR or sufficient increase to qualify for PD from study entry.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the longest diameters of all target lesions compared to study entry, the appearance of unequivocal new lesions, or laboratory evidence of clinical progression (e.g., spread to bone marrow or increasing catecholamines).

Response Criteria for Subjects with Bone Marrow Disease:

- Those subjects with morphologic evidence of neuroblastoma by routine H and E staining (NSE staining only is not evaluable) will be evaluable to assess bone marrow response.
- **Complete response:** No tumor cells detectable by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least three weeks apart after study entry.
- **Progressive disease**: Tumor seen on morphology on two consecutive bone marrows done at least three weeks apart in subjects who had NO tumor in bone marrow at study entry. (Note: Subject may be declared as progressive disease in bone marrow after only one diagnostic bone marrow at the discretion of the treating physician after discussion with the study chair.)
- **Stable disease**: Persistence of an amount of tumor in the bone marrow by morphology that does not meet criteria for either complete response or progressive disease.

Response Criteria for Subjects with MIBG or PET Positive Lesions

- Subjects who have a positive MIBG or PET scan at the start of therapy will be evaluable for MIBG or PET response. All MIBG's and PET scans will be performed at the research institution and then centrally reviewed.
- **Complete response** = complete resolution of all positive lesions
- **Partial response** = resolution of at least one positive lesion, with persistence of other MIBG positive lesions.
- **Stable disease** = no change in scan in number of positive lesions (includes subjects who have same number of positive lesions but decreased intensity)
- **Progressive disease** = Development of new positive lesions

Duration of response:

Duration of response is defined as the period of time from when measurement criteria are met for complete response (CR) or partial response (PR), whichever is first recorded, until the first date that recurrent or progressive disease (PD) is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The assessment of response will include the initial measurable targets and will be performed after the first and second cycle, then after every other cycle (or 8 weeks, whichever occurs first). Serial results of bone marrow aspirates, biopsies and urinary catecholamines will be reviewed for responding subjects to confirm response or lack of progression.

Clinical Response

A subject will be defined as having a clinical response if they have stable disease or better and a decrease in their tumor markers by ≥ 50%. Clinical response will also be defined as a subject that has a complete clearing of a previously positive bone marrow while on study.

Progression Free Survival

Time to progression, defined as the period from the first day of administration of study drug until the criteria for progression are met taking as reference the screening measurements, will be assessed.

8 Sample Size Justification

Feasibility

Since this is primarily a feasibility trial, the definition of feasibility for this study will include:

"Enrollment onto study, RNA expression profile completed, DNA Mutation Panel completed, genomic analysis and report generation, tumor board held with treatment decision, treatment review completed and start of treatment by 21 days post biopsy/surgical resection date, and then completion of 1 cycle of therapy."

Our preliminary results for 5 subjects indicates that we have a sample collection success rate of 5/5 (100%) subjects, a genetic report profile success rate of 5/5 (100%) within the 7-10 day time window as well as a treatment agreement success rate of 5/5 (100%) within the 5 day time window. The average time (+/-SD) for completion of the genetic profile was 6.6 days (+/-1.7 days) with a median of 7 days. The average time (+/-SD) for time to Treatment was 3.2 days (+/-0.8 days) with a median of 3 days. Data preliminary to date for each of these three feasibility markers are very consistent with our anticipated performance standards.

Our initial feasibility trial continues to show that it is feasible and safe to use RNA expression analysis for tumor boards creating treatment decisions for patients without curative options. This study will ask the feasibility of adding a DNA mutation panel and expansion to other non-curative pediatric cancers as well.

Assumptions: The feasibility outcome is a binary measure for each of the three clinical strata with a lower success null value of 50% which would require reconsideration of the full process and an upper success value of 75% for the alternative which would be deemed worthy of further consideration for an efficacy trial at the next phase. A binomial distribution was used for the testing process with a combination of Type I error levels (10%) and Power (75%). The basic design overall is a MiniMax approach which minimizes the overall sample size. **The MiniMax design with an interim look will require an overall sample size of n = 16. Each of the three clinical strata will use a two stage decision rule.**

The Two-Stage Stopping Rule for each of the three strata is as follows:

Stage 1: Stop and accept the null hypothesis if the observed feasibility rate is less than or equal to 5/9. Otherwise, continue to stage 2.

The probability of stopping for futility is 0.746 when Ho is true and 0.166 when Ha is true.

Stage 2: Stop and accept the null hypothesis if the observed feasibility rate is less than or equal to 10/16. Otherwise, stop and reject the null hypothesis.

9 Laboratory Evaluations

9.1 Specimens to be Collected, Schedule and Amount

Required samples will be collected at the start of study. Recommended/Secondary (volunteer/optional) samples will also be collected at the start of study. Additionally, optional bone marrow samples will be collected every 6-8 weeks per Study Procedure Table.

9.2 Tumor collection and correlative biology studies.

Viable, fresh tumor >0.2grams from tumor biopsy should be placed in neurobasal tissue culture media using sterile technique for, cell line and xenograft generation. Viable, fresh tumor >0.2grams will also be placed in kit for RNA for CRL laboratory and >0.2grams will be fresh frozen to be shipped to the Neuroblastoma Translational Research Laboratory for RNA analysis and to TGen for RNA and DNA sequencing analysis along with 4-6ml blood sample in a PAXgene tube. Samples should be labeled with subjects study number. If excess tissue is available, then snap frozen tumor tissue approximately 5mm in size should be wrapped in foil, snap frozen in liquid nitrogen and stored at -80ºC. Tissue samples will be coded. Fixed tissue remaining from diagnostic evaluation may be used. Bone marrow samples will also be sent to the Neuroblastoma Translational Research Laboratory for tumor cell isolation and culture and Spectrum Health to be sorted by flow cytometry using the immunophenotyping six-color, ganglioside GD2, analysis using monoclonal antibodies to membrane antigen expression of ganglioside $GD2^{FITC\ dye}$, $CD81^{FITCdye}$, the absence of $CD45^{PerCPdye}$leukocytic antigen, and the presence of $CD56^{APC}$ NCAM antigen, CD9, and/or CD34. Cells or tumor samples will have RNA isolated and run on an Affymetrix U133+ Array chip. Data will be analyzed for comparison of bone marrow tumor and solid tumor expression profiles.

At the Neuroblastoma Translational Research Laboratory tumor cells will be grown to 70% confluency in neurobasal media with EGF and FGF. Cell lines will be maintained in culture for biology studies. These will include determining the growth curves and responsiveness of cells derived from these tumors to a variety of agents identified on the report *in vitro* (both the chosen regimen as well as alternate options). Cells will be injected into the inguinal fat pad of NOD SCID mice for generation of subject xenografts. These mice will be used for correlative drug testing experiments based on predictive models. Evaluation of mechanism of action of new drug combinations will be evaluated in mice models through immunohistochemical staining and western blotting of tumor preps. These models will allow us the opportunity to evaluate alternate drug combinations that might have been superior to the chosen regimen.

9.3 Detailed Procedure For Sending Subject Samples:

At screening, subjects will have biopsy samples sent. The main sample for study report will be referred to as the "Primary Sample."

The "Primary Sample" will be a current solid tumor biopsy or core bone marrow biopsy (with >75% tumor).

If a solid tumor sample cannot be obtained and the subject's bone marrow is <75% tumor then they will be ineligible for study.

In addition to the "Primary Sample", if subjects have signed the additional consent for optional sample collection, they will also have these secondary samples sent as follows.

9.3.1 Sample Procurement and Shipping at Screening:

De-identified subject tumor samples will be sent on all subjects as following:

Label all tubes with subject's unique identifier, date/time of sample collection, and contents (i.e. solid tumor, bone marrow, blood).

9.3.1.1 Send the following Required Primary Samples for All Tumor Types (along with appropriate forms)

1. **Sample 1**

   Required- Solid Tumor or Bone Marrow Core Biopsy (only if solid tumor is not available)- You will be provided a kit for tumor collection. This kit will include instructions, collection tubes containing RNA later (place tumor biopsy here within 20 minutes of harvest), and shipping instructions. Follow collection instructions (also listed in Appendix II) and ship overnight at ambient temperature to:

   Clinical Reference Laboratory
   Attn: Molecular
   11711 W. 83rd Terrace
   Lenexa, KS 66214
   Phone: 913-492-3652

2. Sample 2- Required Tumor Sample for DNA Mutation Panel:

Add tumor or needle core biopsy to cryo-vial, snap freeze and ship on at least 1kg of dry ice to:

Spectrum Health Molecular Diagnostics
145 Michigan St Ne Ste 6201
Lemmen-Holton Cancer Pavilion
Grand Rapids, Michigan
49503-2566
Ph: 616-486-6264

9.3.1.2 **Send the following** Recommended secondary tumor **samples** along with appropriate forms listed **in order of priority** (please work your way down the list of tumor samples until you either run out of available sample or have completed all samples. Once this occurs move on to Bone Marrow samples:

You will be provided a kit for tumor collection (fresh snap frozen and in culture media). This kit will include instructions, collection tools, shipping box, and shipping instructions. Follow collection instructions and ship as directed overnight.

3. Sample 3:

With sterile technique and within 20 minutes add tumor sample or needle core biopsy to T25 flask containing cell growth media (provided), seal with parafilm, and overnight at ambient temperature to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

4. Sample 4:

Add tumor or needle core biopsy to cryo-vial, snap freeze and ship on at least 1kg of dry ice to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

5. **Sample 5:**

Add tumor or needle core biopsy to cryo-vial, snap freeze and ship on at least 1kg of dry ice to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

6. **Sample 6:**

Add tumor or needle core biopsy to RNA Later and ship overnight at ambient temperature to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

7. **Sample 7:**

Add tumor or needle core biopsy to cryo-vial, snap freeze and ship on at least 1kg of dry ice to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

9.3.1.3 For all Tumor Types: Send the following Recommended secondary blood **samples listed in order of** priority (along with appropriate forms):

Blood- Send 4-6 ml of blood in tubes (tubes and instructions will be provided).

1. **Sample 8:**

Send blood in EDTA tube (ambient) to:

DORRANCE CLINICAL LABORATORY at TGen
445 N 5th Street, Suite 400
Phoenix, AZ 85004
Phone: 602-343-8796
Lab Fax: 602-343-8545

2. **Sample 9:**
Send PAX DNA Gene tubes (ambient) to:

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

9.3.1.4 **For Neuroblastoma Subjects or Any subject with suspected bone marrow disease Only- Send the following Recommended secondary bone marrow samples listed in order of priority** (along with appropriate forms):

Bone Marrow Aspirate- Send 4cc of bilateral bone marrow in green top (sodium heparin) tube(s) priority overnight at room temperature to:

1. **Sample 10:**
Send bone marrow aspirate ambient to:

Pam Kidd, MD
Spectrum Health Flow Cytometry Lab
145 Michigan St Ne Ste 6201
Lemmen-Holton Cancer Pavilion
Grand Rapids, Michigan
49503-2566
Ph: 616-486- 6270

2. **Sample 11:**
Send bone marrow aspirate ambient to:
(Please alert site 2-3 days prior to procedure. Contact site to confirm shipment as well.)

Ping Zhao
Neuroblastoma Translational Research Laboratory
Coopers Landing
1345 Monroe Ave
Grand Rapids, MI 49503
Ping.zhao@helendevoschildrens.org

Notes: If all samples are collected, you will be collecting 11 samples and mailing **6** packages. The samples above are listed in decreasing priority (1-11)

* Sample 1 to CRL (ambient)
** Sample 2 to Spectrum Health Molecular Diagnostics (frozen)
***Sample 3, 6, 9, & 11 to VIA (ambient).
****Samples 4, 5 & 7 to VIA (frozen).
***** Sample 8 to TGen (ambient)
****** Sample 10 to Spectrum Health Flow (ambient)

******* Keep all collection tubes at 4 degrees until ready to use.

Please contact Ping Zhao if you have any trouble with the preparation or packaging of the samples. Ping.zhao@helendevoschildrens.org

9.3.2 For Neuroblastoma Subjects or Any subject with suspected bone marrow disease Only- Sample Procurement and Shipping at the end of Cycle 2 and every two cycles after that:

Send the following **Recommended** samples to **Spectrum Health** (Priority if limited samples- **First):**

1. **Bone Marrow Aspirate**- Send 2cc of bilateral bone marrow in green top (sodium heparin) tube(s) priority overnight at room temperature to:

   Flow Cytometry Lab of Spectrum Health
   Attn: Pam Kidd, MD
   Lemmen-Holton Cancer Pavilion
   145 Michigan Street NE Suite 6201
   Grand Rapids, MI 49503
   Ph: 616-486- 6270

   Send the following Recommended samples (along with appropriate forms) to the Neuroblastoma Translational Research Laboratory (Priority if limited samples- Second)

2. **Bone Marrow Aspirate-** Send 4cc of bilateral bone marrow in green top (sodium heparin) tube(s) priority overnight at room temperature to:

   Ping Zhao
   Neuroblastoma Translational Research Laboratory
   Coopers Landing
   1345 Monroe Ave
   Grand Rapids, MI 49503
   Ping.zhao@helendevoschildrens.org

9.4 Correlative Biology Studies

At the Neuroblastoma Translational Research Laboratory tumor cells (from either biopsy or bone marrow samples) will be grown to 70% confluency in neurobasal media with EGF and FGF. Cell lines will be maintained in culture for these and future biology studies. These will include studies such as determining the growth curves and responsiveness of cells derived from these tumors to a variety of agents identified on the report in vitro (both the chosen regimen as well as alternate options). Cells will be injected into the inguinal fat pad of NOD SCID mice for generation of subject xenografts. These mice will be used for correlative drug testing experiments based on predictive models. Evaluation of mechanism of action of new drug combinations will be evaluated in mice models through immunohistochemical staining, western blotting, and RNA expression profiling of tumor preps. These models will allow us the opportunity validate predictive modeling in a laboratory model.

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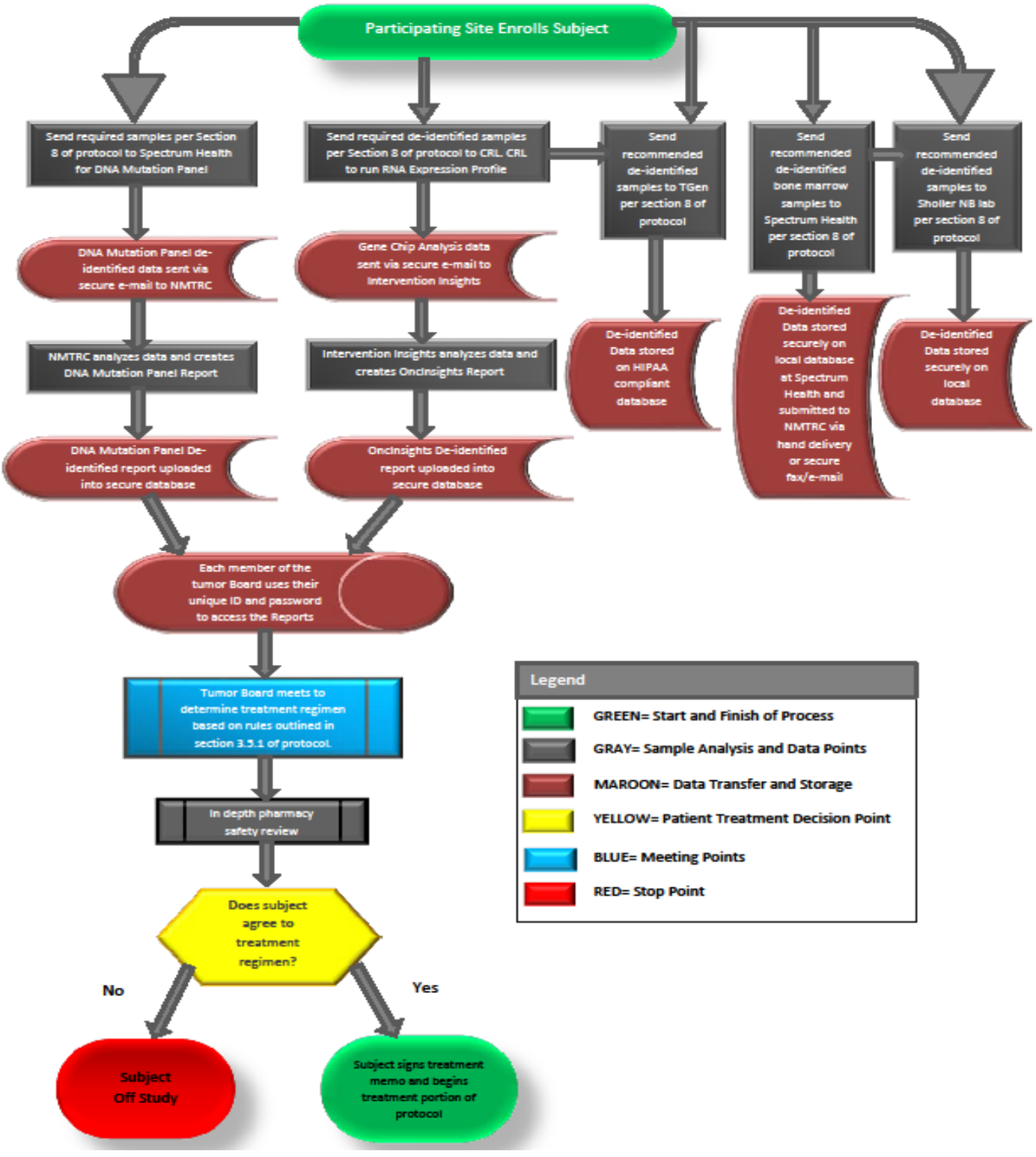
Samples will be sent to the Translational Genomics Institute (TGen) for DNA and RNA sequencing. Isolation of DNA and RNA from subject samples will be performed for use in genomic studies. Nucleic acids will be extracted from blood, bone Marrow or tumor tissues. Analysis for mutations or Single Nucleotide Variants (SNVs) in tumors, using germ line DNA as control, will be conducted using blood and fresh or frozen tumor tissue. Comparative Genomics Hybridization, whole genome sequencing of tumor and germline DNA, messenger RNA sequencing and expression analysis and epigenentic studies including whole methylome analysis using next generation sequencing may be performed.

Bone marrow samples will also be sent to Spectrum Health to be sorted by flow cytometry using the immunophenotyping six-color, ganglioside GD2, analysis using monoclonal antibodies to membrane antigen expression of ganglioside GD2FITC dye, CD81FITCdye, the absence of CD45PerCPdyeleukocytic antigen, and the presence of CD56APC NCAM antigen, CD9, and/or CD34. Cells or tumor samples will have RNA isolated and run on an Affymetrix U133+ Array chip. Data will be analyzed for comparison of bone marrow tumor and solid tumor expression profiles.

9.5 Storage

Blood and tumor samples collected for any studies performed in this protocol, and any other components from the processed cells, may be stored indefinitely to research scientific questions related to cancer and/or study drugs. The subject retains the right to have the sample material destroyed at any time by contacting the principal investigator.

9.6 Plan for Communication of Samples and Data



9.7 Plan for Communication of Collaborating Sites

Communication between centers will be critical in this trial. Prior to consent of the subject, the NMTRC research coordinator will be contacted (via e-mail). If a spot is available at the time, the potential subject will undergo consent and completion of all required screening procedures and certification of all inclusion and exclusion criteria by the Investigator. If the subject fits all enrollment criteria, the site will again contact the coordinator at the NMTRC who will notify the Clinical Reference Laboratory, Spectrum Health, Neuroblastoma Translational Research Laboratory , TGen, and Intervention Insights in preparation for collection and processing of tissue sample. The research coordinator at NMTRC will organize the convening of members of the tumor board for discussion of the current case once the full report is available. In addition, a study enrollment form will be faxed to the coordinator at NMTRC, a unique subject identifier will be assigned and the enrollment form will be sent back to the participating site. The NMTRC will contact all sites via e-mail if the study enrollment is on hold or closed at any time.

Subject samples will be collected at each institution and follow the flow chart above. Once the reports are generated they will be sent to NMTRC/Dr. Sholler. The Principal Investigator enrolling the patient will prepare a tumor board presentation. The presentation and reports will be sent to all tumor board members by the NMTRC coordinator. There will be a meeting of the tumor board within 4 days of receiving the report to decide on the treatment plan recommendation. The recommendation will be reviewed in depth for safety by the Pharmacist. The treatment plan and memo will be discussed with the subject and their parents and upon their signed agreement the treatment will begin within 1 week of the discussion with parents.

Each site will also participate in a 1 hour monthly video or teleconference meeting to review study progress and subjects currently enrolled. There will also be a yearly face-face study committee meeting hosted by a member institution.

10 ADVERSE EVENT REPORTING

10.1 Definitions

10.1.1 Adverse Event

An ***adverse event*** is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An untoward medical event which occurs outside the period of follow-up as defined in the protocol will not be considered an adverse event unless related to study drug. Worsening of a medical condition for which the efficacy of the study drug is being evaluated will not be considered an adverse event.

10.1.2 Unexpected Adverse Event

An ***unexpected adverse event*** is one for which the nature or severity of the event is not consistent with the applicable product information as outlined in package insert filed with the FDA.

10.1.3 Serious Adverse Event

A ***serious adverse event*** is any untoward medical occurrence that:

- Results in death
- Is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

10.1.4 Documenting Adverse Events

The Investigator should elicit information regarding the occurrence of adverse events through open-ended questioning of the subject, physical examination and review of laboratory results.

All adverse events, whether serious or not, will be described in the source documents and Grade 2 or higher (per CTCAE 4.0) adverse events that occur while on study should be captured on the adverse event case report form. All Baseline AE's will be captured on a separate baseline Adverse event case report form. All Grade 2 or higher new events, as well as those that worsen in intensity or frequency relative to baseline, which occur after administration of study drug through the period of protocol-specified follow-up, must be captured.

Information to be reported in the description of each adverse event includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event and relatedness to treatment regimen.
- The date of resolution of the event and whether the event is serious or not
- Action taken; drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required; diagnostic procedure performed; subject discontinued from the study
- Outcome: complete recovery or return to baseline; unknown/lost to follow-up; adverse event persisting; subject died (notify the NMTRC immediately)

Adverse events, regardless of suspected cause, will be collected for 30 days following the last treatment, suspected study drug-related toxicity at the 30 day follow-up visit must continue to be followed until resolution to baseline or $\leq$ Grade 2 or stabilization of the event.

10.1.5 Expedited Reporting of Serious Adverse Events

All fatal or life–threatening adverse events must be reported to the NMTRC immediately by telephone, fax, or e-mail within 24 hours of knowledge of the event. If full information is not known, additional follow-up by the Investigator will be required.

All other serious adverse events that are unexpected (not listed in the relevant appendices) which occur any time after the subject has been consented up to 30 days after the last dose of treatment, and are possibly probably, or definitely related to the research must be reported to the study chair and appropriate regulatory authorities (local IRB and FDA if required) within 7 days of notification of the event.

All Grade 3 and 4 (CTCAE), events that are not in the relevant appendices and that are possibly, probably, or definitely related to the research, but are not included in the SAE category above should also be reported to the study chair and appropriate regulatory authorities within 7 days of notification of the event.

The Investigator must report all serious adverse events reported to regulatory authorities in an expedited manner to the local IRB or IEC. All serious adverse events must be followed until resolution or stabilization. Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and all volunteer deaths related to participation in the study should be promptly reported to the NMTRC.

10.1.6 Grading and Relatedness of Adverse Events

10.1.6.1 Grading of Severity of an Adverse Event

Each adverse event (Grade 2 or higher) will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE V 4.0), and these criteria must be used in grading the severity of adverse events. The criteria can be found at: http://ctep.cancer.gov/reporting/ctc.html.

Grading of Severity of an Adverse Event Not Listed in Published Criteria:
For those adverse events which are not listed as part of the NCI CTCAE V 4.0, the same grading system should be used, where:

- **Mild** corresponds to an event not resulting in disability or incapacity and which resolves without intervention
- **Moderate** corresponds to an event not resulting in disability or incapacity but which requires intervention
- **Severe** corresponds to an event resulting in temporary disability or incapacity and which requires intervention
- **Life-threatening** corresponds to an event in which the subject was at risk of death at the time of the event
- **Fatal** corresponds to an event that results in the death of the subject

10.1.6.2 Relatedness to Study Drug

The Investigator must attempt to determine if an adverse event is in some way related to the use of the study drug and define an attribution category. This relationship should be described as follows:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention. The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, or a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unrelated to the use of the study drug.
	Unlikely	The AE *is **doubtfully related*** to the intervention. Adverse event does not have temporal relationship to intervention, could readily have been produced by the subject's clinical state, could have been due to environmental or other interventions, does not follow known pattern of response to intervention, does not reappear or worsen with reintroduction of intervention.
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug OR the event could be the effect of a concomitant medication.
	Probable	The AE ***is likely related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition OR the event cannot be the effect of a concomitant medication.
	Definite	The AE ***is clearly related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug. The adverse event improves upon discontinuation of the study drug and reappears upon repeat exposure.

11 SUBJECT WITHDRAWAL AND TRIAL DISCONTINUATION

11.1 Criteria for Subject Off-Therapy

Subjects will be removed from the study therapy for the following reasons:

- Progressive neoplastic disease
- Subject or guardian withdraws consent to continue in the trial
- Subject develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the subject in the subject's best interests
- Subject is lost to follow-up (defined as the inability to contact the subject on 3 separate occasions over a period of 2 weeks)
- Administrative reasons (e.g., the subject is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation or fulfills the protocol requirements for withdrawal
- Death

11.2 Criteria for Subject Off-Study

Subjects may be withdrawn from the study completely which includes withdrawal from survival follow-up for the following reasons:

- Completion of all study requirements
- Subject or guardian withdraws consent to continue in the trial (if this occurs, no further study visits or data may be collected)
- Subject is lost to follow-up (defined as the inability to contact the subject on 3 separate occasions over a period of 2 weeks)
- Death

11.3 Trial Discontinuation

The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) may discontinue the trial as a whole or at an individual investigational site at any time. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of treatment regimens, a request to discontinue the trial from a regulatory authority, protocol violations at an investigational site, violations of good clinical practice at an investigational site, or poor enrollment. The NMTRC will promptly inform all Investigators in the event of premature study discontinuation and provide all Investigators with instructions regarding the disposition of subjects still on study. Should the study be terminated prematurely, all case report forms and any other study material will be returned to the NMTRC.

12 DATA ANALYSIS

12.1 Data Quality Assurance

Electronic and paper case report forms will be checked for correctness against source document data by the independent study monitor. If any entries into the CRF are incorrect, incomplete or illegible, the study monitor will ask the Investigator or the study site staff to make appropriate corrections.

12.2 Data Safety Monitoring Board (DSMB)

An independent Data Safety and Monitoring Board (DSMB) will oversee the conduct of the study. The members of this Board will receive database summaries, including adverse event reports, and will convene either in person or via teleconference according to section 3.5. The Board will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.3 Process and Feasibility Analysis

Each of the process measures including the total time to treatment initiation and time to completion of the first cycle of treatment will be described using standard descriptive methods such as means, medians, standard deviations, and 95% confidence intervals. The total time duration to treatment initiation and time to completion of the first cycle of treatment will also be examined using Kaplan-Meier plots since some patients who are considered process failures or who do not complete the full duration to the completion of the first cycle of treatment may contribute censored data. The formal hypothesis testing of the feasibility or success is based upon the 2-stage Mini-Max testing process outlined in Section 8: *Sample Size Justification.* Further quantification of the feasibility success rate will be based upon the percentage of the n = 16 patients in each strata who achieve the specified overall time frame limits. This success rate will supplemented with an exact 95% confidence interval using a Binomial distribution model due to the small sample size involved.

12.4 Secondary Data Analysis

Overall response rates (ORR) will be examined using rates for each of the clinical response categories supplemented using exact 95% confidence intervals. Progression free survival (PFS) data for each of the three clinical strata will be examined using Kaplan-Meier time to event plots. Differences in the PFS for the current treatment protocol with historical PFS values will be explored using Cox proportional hazard rate methods when possible.

13 ADMINISTRATIVE PROCEDURES

13.1 Subject Informed Consent

No study related procedures will be performed until a subject or a subject's legal representative has given written informed consent. The NMTRC will provide the site Investigators with a sample informed consent document that conforms to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50). However, it is up to each site Investigator to provide a final informed consent that may include additional elements required by the Investigator's institution or local regulatory authorities. The IRB/EC for each investigational site must approve the consent form document prior to study activation; changes to the consent form during the course of the study may also require IRB/EC approval. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the informed consent will be given a copy of the signed dated and witnessed document. The original copy of the signed, dated and witnessed informed consent document will be retained by the Investigator in the study files. After the tumor board has made a therapy decision and that decision has been reviewed by the pharmacist, a therapy specific treatment memo will be signed.

The Investigator must also obtain authorization from the subject to use and/or disclose protected health information in compliance with the Health Insurance Portabiltiy and Accountability Act (HIPAA). Written HIPAA authorization may be obtained as part of the informed consent process.

13.2 Ethical Conduct of the Study and IRB/IEC Approval

The study will be conducted according to the principles of the 2004 version of the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The Investigator will submit the protocol, the informed consent and any other material used to inform subjects about the trial to the local IRB/IEC for approval prior to enrolling any subject into the trial. The IRB/IEC should be duly constituted according to applicable regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB/IEC or the Chairperson's designee, must be on IRB/IEC stationary and must include the protocol by name and/or designated number. If an Investigator is a member of the IRB/IEC, the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the trial. The Investigator will also inform the IRB/IEC of any serious adverse events that are reported to regulatory authorities and will provide to the IRB/IEC a final summary of the results of the trial at the conclusion of the trial.

Any amendments to the protocol will be done through the NMTRC, and will be submitted to the coordinating IRB/IEC for review and written approval before implementation.

13.3 Monitoring

An independent study monitor will make regularly scheduled trips to the investigational site to review the progress of the trial. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. At each visit, the monitor will review various aspects of the trial including, but not limited to, screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; facilities and staff.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor.

In addition to the above, representatives of the NMTRC or government inspectors may review the conduct/results of the trial at the investigational site. The Investigator at each site must promptly notify the NMTRC of any audit requests by regulatory authorities.

A separate monitoring plan will be provided for additional monitoring guidelines.

13.4 Pre-Study Documentation

Prior to initiating the trial, the Investigators at each site will provide to the NMTRC the following documents:

• A signed NMTRC008 Investigator Agreement Form

• A current curriculum vitae for the Principal Investigator and each sub-investigator listed on the Investigator Agreement Form

• A copy of the Investigator's medical license from the state in which the study is being conducted

• A letter from the IRB or EC stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g., advertisements)

• A copy of the IRB- or EC-approved informed consent document

• Current IRB membership list for IRB's without a multiple project assurance number or an IRB organization number under the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov).

• A signed Investigator Signature Sheet for each amendment put through local IRB- Found on page 9 of this protocol (original)

• A completed conflict of interest and financial disclosure form (copy of original) from each person listed in the Investigator Agreement Form.

• Current laboratory certification for the reference laboratory

• A list of current laboratory normal values for the reference laboratory

13.5 Confidentiality

It is the responsibility of the investigator to insure that the confidentiality of all subjects participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted must never contain the name of a trial participant. Each subject in the trial will be identified by a unique identifier that will be used on all CRF's and any other material submitted to the NMTRC. Case Report Forms for this study will be both paper and electronic. Electronic data will be stored in a HIPAA compliant data center. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

Personal medical information may be reviewed by representatives of the NMTRC, of the IRB or of regulatory authorities in the course of monitoring the progress of the trial. Every reasonable effort will be made to maintain such information as confidential.

The results of the study may be presented in reports, published in scientific journals or presented at medical meetings; however, subject names will never be used in any reports about the study.

13.6 Source Documents

The Investigator will maintain records separate from the case report forms in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the name and number of the trial and the date on which the subject signed informed consent prior to the subject's participation in the trial. Source documents must completely reflect the nature and extent of the subject's medical care, and must be available for source document verification against entries in

the case report forms when the monitor visits the investigational site. All information obtained from source documents will be kept in strict confidentiality.

13.7 Record Retention

The Investigator will retain the records of the study for 15 years. The NMTRC will notify Investigators when retention of study records is no longer required. All study records must be maintained in a safe and secure location that allows for timely retrieval, if needed.

Study records that must be retained include copies of case report forms, signed informed consents, correspondence with the IRB or IEC, source documents, clinic charts, medical records, laboratory results, radiographic reports and screening/enrollment logs.

Should the Investigator relocate or retire, or should there be any changes in the archival arrangements for the study records, the NMTRC must be notified. The responsibility for maintaining the study records may be transferred to another suitable individual, but the NMTRC must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage.

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Appendix I: Performance Status/Scores

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

Instructions for Core/Needle Biopsy Specimens

Interventional Radiologist:

Intervention Insights Sample

1. Obtain first core biopsy (if possible; otherwise 2nd core)
    a. At least 19 gauge guiding needle or larger in caliber
    b. Remove excess blood from the sample with sterile saline rinse (provided in the kit) without damaging the sample
2. ***DO NOT PLACE SAMPLE INTO FORMALIN*.** Place sample into the tube 1 containing RNA Later provided by the NTMRC. Note time of extraction and placement into tube on Form A

Standard Pathology Sample

3. Obtain second core biopsy from same track according to institutional protocol
4. Place core (for standard pathology) in neutral buffered formalin container per standard practices
5. Please fill out the Intervention Radiologist section of Form A; send all forms and all tissue to pathology

Pathologist:

1. Please complete the Pathologist section of Form A
2. Place the Tube 1 with the patient sample and Form A in the shipping kit. Affix the label to FedEx shipping bag in the kit and place the kit in the bag for shipment. Please ship via FedEx (if you do not have a scheduled FedEx pickup, call 800-GO-FEDEX - 800-463-3339)
3. Please hold Form B until the processing is complete for the Standard Pathology Sample. Upon the generation of a pathology report, please fill out Form B and fax both the pathology report and Form B to the NMTRC at 1-616-233-8934 (fax).

Note- CRL is unable to generate a patient OncInsights molecular report for the patient's physician without the completion of Form B - Thank you

For questions please call the NMTRC at *(616) 267-0326* or e-mail emily.arndt@vai.org

Instructions for Incision/Excision Surgery Specimen

Surgeon:

1. Obtain surgical excision/biopsy (operating room or office)
    a. **DO NOT PLACE SAMPLE INTO FORMALIN**
    b. Please wrap in sterile gauze soaked with the provided sterile saline (0.9% NaCl without dextrose), place in a labeled container and note time of extraction on container label

2. Send to Pathology/Histology ASAP; please hand deliver to pathology within 20 minutes

Pathologist/Pathology Assistant:

1. Do not ink specimen (prior to completing steps 2-4 below)

2. Section specimen with a sterile blade on a clean surface. Select tumor tissue that appears non-necrotic; avoid normal tissue. Obtain a sample with a maximum dimension of 0.5 cm^3 (approximately the size of a pencil eraser)

3. Place dissected sample in the tube filled with RNA Later provided by the NMTRC labeled Tube 1. Note time on Form A (Pathology)

4. Place Tube 1 with the patient sample and Form A (Pathology) in the shipping box. Affix a shipping label to the FedEx shipping bag and place the kit in the bag for shipment. Please ship via FedEx (if you do not have a scheduled FedEx pickup, call 800-GO-FEDEX - 800-463-3339)

5. Obtain a second specimen for histopathological analysis at your institution, adjacent to the initial specimen, again avoiding normal or necrotic tissue. Handle any remaining tissue as per your institutional protocols and in accordance with physician order

6. Please hold Form B until the processing is complete for the Standard Pathology Sample. Upon the generation of a pathology report, please fill out Form B and fax both the pathology report and Form B to the NMTRC at 1-(616) 267-1005 (fax).

Note- CRL is unable to generate a patient OncInsights molecular report for the patient's physician without the completion of Form B

For questions please call the NMTRC at (616) 267-0326 or e-mail emily.arndt@vai.org

Appendix III: Pharmacopeia Library

Drug Table:

acarbose	chlorambucil	ethosuximide	pemetrexed
acetazolamide	chlorothiazide	etodolac	pentamidine
acetylsalicylic acid	chlorproMAZINE	etoposide (Vepesid)	pentostatin
adalimumab	chlorproPAMIDE	everolimus	phentolamine
albendazole	chlorzoxazone	famotidine	piperazine
aldesleukin	ciclosporin	felbamate	piroxicam
alprazolam	ciprofloxacin	felodipine	pravastatin sodium
amantadine	cisplatin	Fenoprofen	prazosin hydrochloride
ambenonium chloride	citalopram	fexofenadine	prednisoLONE
amikacin	clemastine	flucytosine	prochlorperazine
amiloride hydrochloride	clindamycin	fludarabine	propylthiouracil
aminocaproic acid	clofarabine	fludrocortisone	pyridostigmine bromide
amitriptyline hydrochloride	clofibrate	fluoxetine	rabeprazole sodium
amoxapine	clomipramine	fluvastatin	raloxifene hydrochloride
amoxicillin	clonidine	fluvoxamine	ramipril
ampicillin	clopidogrel	folic acid	reserpine
anakinra	clotrimazole	furosemide	Rifamycin
anastrozole	clozapine	gabapentin	Rituxumab
ascorbic acid	colchicine	gefitinib	romidepsin
atorvastatin	cortisone	gemcitabine	rosiglitazone maleate
atovaquone	crizotinib	gentamicin	rosuvastatin calcium
azacitidine	cyanocobalamin	griseofulvin	Saha
azathioprine	cyclophosphamide	guaifenesin	simvastatin
aztreonam	cycloserine	guanfacine	sirolimus (rapamycin)
baclofen	cyclosporin	hydroxyurea	sodium phenylbutyrate
balsalazide	cyproheptadine	ibuprofen	sorafenib
BCNU	Cytarabine (Ara-C)	imatinib	sulfasalazine
betamethasone	dacarbazine	indomethacin	sulindac
bevacizumab	dantrolene	irinotecan	sulindac sulfide
biotin	dapsone	ixabepilone	sunitinib malate
bisacodyl	dasatinib	ketoprofen	Sunitinib
bortezomib (velcade)	DAUNOrubicin	ketorolac	tacrolimus
bromocriptine	decitabine	lansoprazole	tamoxifen
brompheniramine	deferoxamine	Lapatinib	Tarceva
budesonide	demecolcine sodium	leflunomide	temsirolimus
bumetanide	dexamethasone	lenalidomide	temozolomide
bupropion	dextromethorphan	lovastatin	thalidomide
buspirone	diazoxide	megestrol	theophylline
calcitriol	diclofenac	mercaptopurine	thioguanine
captopril	dicloxacillin	mesalamine	thioridazine hydrochloride
carbamazepine	diltiazem	metformin	Thio-tepa
carbidopa/Levodopa	diphenhydramine	methimazole	TOLBUTamide
carbinoxamine	dipyridamole	methotrexate	tolcapone

carboplatin	disopyramide	Methyl CCNU	tolmetin
CCNU	docetaxel	minocycline	topiramate
cefaclor	donepezil hydrochloride	mitoxantrone	topotecan
cefadroxil	DOXOrubicin	nabumetone	torsemide
cefazolin	doxycycline	naproxen	tranylcypromine
cefepime	droperidol	navelbine	trastuzumab
cefotaxime	enalapril	nitisinone	trazodone
cefotetan	epirubicin	omeprazole	tretinoin
cefoxitin	ergocalciferol	orlistat	valproic acid
ceftazidime	erlotinib	oxaliplatin	vandetanib
cefuroxime	erythromycin	oxaprozin	verapamil
celecoxib	Estradiol	paclitaxel	vinBLAStine
cetirizine	ethacrynic acid	pamidronate	vinorelbine
cetuximab	ethambutol	Pazopanib	vorinostat
	ethionamide	Peg-asparaginase	zolendronic acid

When referenced:

Frequency of Side Effects

Likely/Common = 21 to 100 subjects per 100 subjects

Less Likely = 1 to 20 subjects per 100 subjects

Rare but Serious = 1 to 4 subjects per 100 subjects

Acarbose

Common	Rare (<1%)
Diarrhea (31%) Flatulence (74%) Abdominal pain or distention (19%)	Erythema Exanthema urticaria Hypoglycemia lipid abnormalities Bowel obstruction Anemia Hepatotoxicity Elevated liver enzymes right upper quadrant pain dark urine jaundice hepatomegaly light-colored stools sleepiness weakness dizziness headache vertigo

- Instruct patient about signs/symptoms of hypoglycemia if patient is on concurrent antidiabetic medicine.

- Concurrent use with sulfonylureas may cause hypoglycemia. Patient should treat hypoglycemia with oral glucose (dextrose), and not sucrose (cane sugar). This is because acarbose may delay the absorption time of sucrose.
- This drug may cause abdominal pain, diarrhea, and flatulence. These side effects should subside in frequency and intensity with continued use.
- Patient should take drug with the first bite of food at each main meal.
- If dose is missed and meal completed, advise patient to skip dose and take at next meal.

Generic Drug Name: **ACETAZOLAMIDE**
Brand Name(s): **Diamox ; Sequels**

Adverse Effects
Serious:

- **Dermatologic:** Stevens-Johnson syndrome (rare), Toxic epidermal necrolysis due to drug (rare)
- **Endocrine metabolic:** Acidosis, Metabolic acidosis
- **Hematologic:** Agranulocytosis, Aplastic anemia, Thrombocytopenia
- **Hepatic:** Hepatic necrosis
- **Immunologic:** Anaphylaxis
- **Ophthalmic:** Angle-closure glaucoma
- **Other:** Sulfonamide adverse reaction (rare)

Common:

- Adrenal gland failure
- Chronic noncongestive angle-closure glaucoma
- Cirrhosis
- Hyponatremia/hypokalemia
- Hyperchloremic acidosis
- Hypersensitivity to acetazolamide
- Severe hepatic or renal disease

Patient Information

- Instruct patient to avoid activities requiring mental alertness or physical coordination until drug effects are realized.
- If used for prophylaxis of acute mountain sickness, advise patient a rapid ascent may still cause high-altitude pulmonary or cerebral edema.
- If used for seizure control, advise patient against sudden discontinuation of drug.
- This drug may cause weight loss, diarrhea, loss of appetite, nausea, altered sense of taste, vomiting, confusion, paresthesia, somnolence, depression, malaise, or metabolic acidosis.
- This drug may also cause tinnitus early in therapy.
- Instruct patient to report signs/symptoms of a sulfonamide adverse reaction. This would include severe skin reactions such as Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering), erythema multiforme (a less severe form of Stevens-Johnson), toxic epidermal necrolysis (widespread peeling/blistering of skin), and fulminant hepatic necrosis (symptoms of severe hepatic failure).
- Advise diabetics that this drug may increase blood sugar level.

- Instruct patient to report polyuria if increased urination affects sleep.
- Patient should avoid concomitant high-dose aspirin.

Contraindications

- adrenal gland failure
- chronic noncongestive angle-closure glaucoma
- cirrhosis
- hyponatremia/hypokalemia
- hyperchloremic acidosis
- hypersensitivity to acetazolamide
- severe hepatic or renal disease

Precautions

- adverse reactions common to sulfonamide derivatives may occur, including Stevens-Johnson syndrome and toxic epidermal necrosis
- concomitant high-dose aspirin
- high dose may decrease diuresis
- high dose may increase drowsiness and/or paresthesia
- pulmonary obstruction or emphysema
- rapid ascent may cause high-altitude pulmonary/cerebral edema

Acetylsalicylic acid

Common	Serious
Indigestion Nausea Vomiting	Bleeding (3.9%, high-dose use) Tinnitus dyspepsia Bronchospasm Angioedema Reye's syndrome Gastrointestinal ulcer (long term use)

- Warn patients that due to risk of Reye's syndrome. Drug should never be used in children and teenagers with chickenpox or flu symptoms.
- This drug may cause dyspepsia, nausea, vomiting, gastrointestinal ulcer, tinnitus, angioedema, or Reye's syndrome (persistent nausea/vomiting, somnolence, lethargy, confusion, combative behavior, decreased level of consciousness, seizure).
- Instruct patient to report signs/symptoms of bleeding or gastrointestinal distress.
- Patient should take drug with an 8-ounce glass of water.
- Patient may take with food or milk.
- Instruct patient to avoid alcohol during therapy.

Adalimumab

Common	Serious
Hypertension (5%) Injection site pain (12-19%) Injection site reaction (8-20%) Rash (12%) Antibody development (1-12%) Positive antinuclear antibody (12%) Headache (12%) Sinusitis (11%) Upper respiratory infection (17%)	Erythema multiforme Primary cutaneous vasculitis Stevens-Johnson syndrome Aplastic anemia (rare) Erythrocytosis (< 5%) Leukopenia (<5%) Pancytopenia (<5%) Thrombocytopenia (rare) Anaphylaxis (rare) Immune hypersensitivity reaction (1%) Malignant lymphoma (rare) Central nervous system demyelinating disease (rare) Multiple sclerosis (<5%) Paresthesia (<5%) Subdural hematoma (<5%) Interstitial lung disease Pulmonary fibrosis Tuberculosis (rare) Angioedema Cancer Infectious disease

- Advise patient of increased risk of lymphoma and other malignancies.
- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- Instruct patient to report a latex-sensitivity prior to administration, as needle cover of prefilled syringe contains dry natural rubber (latex derivative).
- Drug may cause headache, rash, nausea, upper respiratory infection, and injection site reaction.
- Instruct patient to report signs/symptoms of infection (including tuberculosis) or lupus-like syndrome (arthralgias, myalgias, fatigue, skin rashes).
- Advise patient to report signs/symptoms of heart failure (new onset or exacerbation of disease).
- Tell patient to report signs/symptoms of hepatitis B during and after drug therapy.
- Advise patient to report signs/symptoms of pancytopenia or cytopenia.
- Advise patient to rotate injection sites.
- Patient should avoid concomitant use of anakinra due to possible development of serious infections.

Albendazole

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome

- **Hematologic:** Agranulocytosis (less than 1%), Aplastic anemia, Granulocytopenic disorder (less than 1%), Leukopenia (less than 1%), Pancytopenia (less than 1%), Thrombocytopenia (less than 1%)
- **Hepatic:** Hepatotoxicity, With elevated liver enzymes
- **Renal:** Acute renal failure (rare)
- **Neurologic:** Seizures, Increased intracranial pressure, meningeal signs

Common:

- **Gastrointestinal:** Abdominal pain, Nausea, Vomiting
- **Neurologic:** Headache

Aldesleukin

Risks and side effects related to Aldesleukin (IL-2) include those which are:

Likely	Less Likely	Rare But Serious
• **Fever and chills including shaking chills** • **Flu like symptoms with headache, tiredness, aches and pains** • **Diarrhea** • **Loss of Appetite** • **A feeling of weakness and/or tiredness not relieved by sleep or rest** • **A mild drop in blood pressure** • **Skin rash including rash with the presence of macules (flat discolored areas) and papules (raised bumps)** • **Itching** • **Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight** • **Increased levels of a chemical (creatinine) in the blood which could mean kidney damage** • **A temporary decrease in the amount of urine which could mean the kidneys are not working as well** • **Elevation in the blood**	• **Nausea and vomiting** • **Low levels of certain salts in the body like sodium, calcium, magnesium and phosphate which may require treatment** • **High levels of uric acid in the blood which could damage the kidneys** • **Upset of the normal acid levels in your blood** • **Low levels of sugar in the body which may require that you take replacement** • **A condition (vascular or capillary leak syndrome) in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure which may lead to multiple organ failure such as kidney, heart or liver failure and shock.** • **Heart problems including an irregular or rapid heartbeat leading to unpleasant sensation in the chest** • **Dizziness** • **Cough** • **Stuffy or runny nose** • **Headache or head pain** • **Enlarged abdomen (belly)** • **Weight gain** • **Pain in the abdomen (belly) or other parts of the body** • **High blood sugar which may require treatment** • **Mood changes including depression, inability to sleep or excessive sleepiness, irritability and agitation, anxiety,**	• **A severe allergic reaction that can be life-threatening and may lead to difficulty in breathing, a drop in blood pressure, and an irregular heart beat.** • **Heart attack or severe pain in the chest (angina) that can be life-threatening or fatal.** • **Abnormal electrical conduction within the heart which can cause irregular heartbeat and may be life threatening** • **Inflammation of the heart muscle which could lead to heart failure** • **A severe drop in blood pressure that will require treatment** • **A decrease in the factors in the blood that help your blood to clot normally** • **Bleeding which can occur in the head, stools, the nose, urine and other parts of the body** • **Convulsion or Seizures** • **Prolonged loss of consciousness (coma)** • **Inflammation of your colon (large bowel) which could lead to bloody diarrhea and may be life threatening or a hole may develop in the intestines which would cause leakage into the abdomen (belly) with pain and**

of certain enzymes or bilirubin which could indicate liver irritation or damage • **An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions** • **An increase in the number of white blood cells in the blood** • **Fewer red blood cells and platelets in the blood** ○ **a low number of red blood cells can make you feel tired and weak** ○ **a low number of platelets causes you to bruise and bleed more easily**	**confusion, and mood swings such as feelings of suicide, feelings of aggressiveness** • **Noticeable changes in a person's personality, behavior, and thinking** • **Trouble with memory** • **Aches and pains in the muscles and joints, sleep difficulties, a feeling of extreme tiredness or not feeling well** • **Muscular discomfort or pain from infection or an unknown cause** • **Nerve damage that may cause pain, burning, numbness, and tingling** • **Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)** • **Severe rashes which can result in loss of skin** • **Hair loss** • **Infections including those caused by bacteria, virus, and fungus which may require treatment** • **Blurred vision** • **A flushing of your skin with redness and a feeling of warmth** • **Widening of blood vessels** • **Fewer white cells in the blood** ○ **a low number of white blood cells may make it easier to get infections** • **Decrease or increase in your thyroid hormones** • **Shortness of breath** • **Poor blood supply to the arms and legs**	**infection** • **Inflammation of your pancreas which could cause pain in your abdomen and may be life-threatening** • **Severe kidney damage (which may be permanent)** • **If you have ever been told that you have a disease such as lupus, rheumatoid arthritis or other disease that is caused by a disturbance in your immune system "autoimmune disease", aldesleukin (IL-2) may cause these to be worse.** • **Damage to your lungs which could lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in the blood** • **Stopping of breathing** • **Clotting of blood vessels which can lead to pain and swelling in the area of the clot. Such clots may break loose and cause damage or be life-threatening depending on where they go** • **Sudden death**

Alprazolam

Common	Rare
Hypotension (10%)	tachycardia
Dermatitis (4%)	palpitations
Nausea (9-15%)	light sensitivity
Vomiting (9-15%)	bullous
Diarrhea (9-15%)	taste alteration
Constipation (9-15%)	abnormal liver function test
Increased salivation (4.2%)	anaphylactic reaction
Increased appetite	
Weight change	
Coordination problem	
Dizziness	
Dysarthria	
Memory impairment	
Somnolence	
Depression	
Reduced libido	

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause increased appetite, changes in weight, constipation, dizziness, dysarthria, memory impairment, somnolence, depression, or reduced libido.
- Advise patient and family to monitor for confusion with use, especially with elderly patients.
- Advise patient against abrupt discontinuation of drug to prevent withdrawal symptoms.
- Patient should avoid alcohol while taking drug.
- Patient should not eat grapefruit or drink grapefruit juice while taking drug.

Amantadine

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac arrest (rare), Cardiac dysrhythmia (rare), Congestive heart failure (0.1% to 1%), Hypotension (rare), Tachycardia (rare)
- **Dermatologic:** Malignant melanoma
- **Hematologic:** Agranulocytosis (Rare), Leukopenia (less than 0.1%), Neutropenia (less than 0.1%)
- **Immunologic:** Immune hypersensitivity reaction
- **Neurologic:** Neuroleptic malignant syndrome (rare)
- **Psychiatric:** Suicidal intent (less than 0.1%)
- **Respiratory:** Acute respiratory failure (rare), Pulmonary edema (rare)
- **Genitourinary:** Urinary retention (0.1-1%)

Common:

- **Cardiovascular:** Orthostatic hypotension (1% to 5%), Peripheral edema (1% to 5%)
- **Gastrointestinal:** Constipation (1% to 5%), Diarrhea (1% to 5%), Loss of appetite (1% to 5%), Nausea (5% to 10%), Xerostomia (1% to 5%)
- **Neurologic:** Ataxia (1% to 5%), Confusion (1% to 5%), Dizziness (5% to 10%), Headache (1% to 5%), Insomnia (5% to 10%), Somnolence (1% to 5%)
- **Psychiatric:** Agitation (1% to 5%), Anxiety (1% to 5%), Depression (1% to 5%), Dream disorder (1% to 5%), Feeling nervous (1% to 5%), Hallucinations (1% to 5%), Irritability (1% to 5%)
- **Other:** Fatigue (1% to 5%)
-

Ambenonium Chloride

Common	Rare
Sweating symptom Epigastric discomfort Excessive salivation Muscle cramp Muscle fasciculation Vertigo Blurred vision Excessive tear production Miosis Anxiety Urgent need to urinate Bronchorrhea Malaise	Pulmonary edema Abdominal cramps Diarrhea Sialorrhea Nausea Vomiting Bradycardia

- This drug may cause sweating, epigastric discomfort, excessive salivation, cramp, muscle fasciculation, vertigo, blurred vision, excessive tear production, miosis, anxiety, urgent desire to urinate, bronchorrhea, or malaise.
- Patient should report signs/symptoms of a cholinergic crisis.
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).
- Instruct patient to call healthcare professional if a dose is missed, as drug should be given on a regular schedule.

Amikacin

Adverse Effects

Serious:

- **Neurologic:** Neuromuscular blockade finding, tremor, paresthesia, weakness,
- **Central Nervous System:** Fever, headache, drowsiness, dizziness, ataxia, vertigo
- **Otic:** Ototoxicity

- **Renal:** Nephrotoxicity
- **Respiratory:** Respiratory tract paralysis

Common:

- **None indicated**

Amiloride Hydrochloride

Common	Serious
Orthostatic hypotension Hyperkalemia (10%) Diarrhea (3-8%) Loss of appetite (3-8%) Nausea (3-8%) Vomiting (3-8%) Headache (3-8%)	Aplastic anemia Neutropenia (rare)

- Instruct patient to rise slowly from a sitting/supine position, as drug may cause orthostatic hypotension.
- This drug may cause diarrhea, loss of appetite, nausea, vomiting, or headache.
- Instruct patient to immediately report signs/symptoms of hyperkalemia (paresthesia, muscular weakness, fatigue, flaccid paralysis of extremities).
- Advise patient against sudden discontinuation of drug.
- Patient should take tablet with food.
- Patient should not drink alcohol while taking this drug.
- Tell patient to avoid other potassium-conserving agents, such as spironolactone or triamterene, and potassium-containing supplements/salt substitutes while taking this drug.

Aminocaproic acid

Adverse Effects

Serious:

- **Cardiovascular:** Bradyarrhythmia, Hypotension, peripheral ischemia,
- **Dermatologic:** Rash
- **Hematologic:** Thrombosis, Agranulocytosis,Leukopenia
- **Musculoskeletal:** Drug-induced myopathy, Rhabdomyolysis
- **Renal:** Renal failure
- **Otic:** Tinnitus, deafness
- **Respiratory:** Nasal congestion, pulmonary embolism, dyspnea
- **Endocrine:** Hyperkalemia

Common:

- **Gastrointestinal:** Nausea, Vomiting
- **Neurologic:** Asthenia, Dizziness, Headache

Amitriptyline Hydrochloride

Common	Serious
Weight gain Bloating symptom Constipation Xerostomia Asthenia Dizziness Headache Somnolence Blurred vision Fatigue	Atrioventricular conduction pattern Cardiac dysrhythmia Hypertension Myocardial infarction (rare) Orthostatic hypotension Syncope Agranulocytosis (rare) Aplastic anemia (rare) Drug-induced eosinophilia (rare) Leucopenia (rare) Pancytopenia Purpuric disorder (rare) Thrombocytopenis (rare) Decreased liver function (rare) Jaundice (rare) Cerebrovascular accident (rare) Seizure (rare) Worsening depression (rare) Suicidal thoughts (rare) Suicide (rare)

- Instruct patient to report use of a MAO inhibitor within 14 days prior to initiating drug therapy.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause anticholinergic symptoms, weight gain, bloating, fatigue, orthostatic hypotension, or syncope.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk for these effects during the first few months of therapy.
- Advise patient that symptomatic improvement may not be seen for a few weeks.
- Warn patient against sudden discontinuation of drug.
- Patient should not drink alcohol while taking this drug.

Amoxapine

Adverse Effects

Serious:

- **Cardiovascular:** Heart block, Myocardial infarction, Prolonged QT interval
- **Hematologic:** Agranulocytosis (less than 1%)
- **Neurologic:** Neuroleptic malignant syndrome (less than 1%), Seizure (less than 1%), Tardive dyskinesia
- **Psychiatric:** Depression, Worsening, Suicidal thoughts, Suicide

Common

- Central Nervous System: Drowsiness (14%)
- **Gastrointestinal:** Constipation (12%), Xerostomia (14%)
- **Neurologic:** Somnolence (14%)
- **Ophthalmic:** Blurred vision (7%)
- **Dermatologic:** Edema, Skin Rash
- **Other:** Fatigue (14%)

Amoxicillin

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Hemorrhagic colitis
- **Immunologic:** Anaphylaxis

Common

- **Gastrointestinal:** Diarrhea (frequent)

AMPICILLIN

Brand Name(s): **Amcill ; Omnipen ; Penbritin ; Pfizerpen-A ; Polycillin ; Rosampline ; Totacillin**

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme, Erythroderma, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Hematologic:** Agranulocytosis, Thrombocytopenia
- **Immunologic:** Anaphylaxis, Hypersensitivity reaction

Common

- **Dermatologic:** Rash, Urticaria
- **Gastrointestinal:** Diarrhea

Patient Information

- Drug may decrease effectiveness of oral contraceptives with concurrent use. Recommend additional form of birth control.
- This drug may cause diarrhea, nausea, vomiting, or rash.
- Advise patient to report the development of a late skin rash with symptoms of fever, fatigue, and sore throat.
- Patient should take 1/2 h before or 2 h after meals.

Contraindications

- hypersensitivity to ampicillin products/penicillins

Precautions

- hypersensitivity to cephalosporins
- patients with mononucleosis; increased risk for rash

Anakinra

Common	Serious
Injection site reaction (71%)	Cardiorespiratory arrest Bacterial cellulitis Malignant melanoma Neutropenia (0.4%) Infectious disease (2-3%) Malignant lymphoma Bacterial musculoskeletal infection Bacterial pneumonia Breast cancer cancer

- Advise patient to avoid live vaccines during therapy due to drug-induced immunosuppression.
- Instruct patient to report a rubber or latex sensitivity prior to administration, as needle cover of prefilled syringe contains latex.
- Instruct patient to report signs/symptoms of infection.
- Advise patient to rotate injection sites.

Anastrozole

Common	Serious
Hypertension (2-13%) Peripheral edema (5-10%) Vasodilatation (25-36%) Rash (6-11%) Nausea (11-20%) Vomiting (8-11%) Increased liver test (1-10%) Lymphedema (10%) Arthralgia (2-15%) Arthritis (17%) Backache (10-12%) Bone pain (6-12%) Osteoporosis (11%) Asthenia (13-19%)	Chest pain (5-7%) Ischemic heart disease (adjuvant therapy, 4%) Myocardial infarction (adjuvant therapy, 1.2%) Thrombophlebitis (adjuvant therapy, 2-5%) Hypercholesterolemia (9%) Anemia (2-5%) Deep venous thrombosis (2%) Leukopenia (2-5%) Thromboembolic disorder (2-4%) Hepatitis (0.01-1%) Immune hypersensitivity reaction (0.01%) Bone fracture (2-10%)

Headache (9-18%) Insomnia (2-10%) Depression (2-13%) Mood change (19%) Menopausal flushing (11-36%) Dyspnea (8-11%) Increasing frequency of cough 97-1150 Pharyngitis (6-14%) Fatigue (11-17%) Pain (11-17%)	Cerebral ischemia (2%) breast cancer (6%) Malignant neoplasm of endometrium of corpus uteri (0.2%) Vaginal bleeding (1-5%) Cancer (5%) Tumor flare (3%)

- This drug may cause peripheral edema, vasodilation, nausea, arthralgia, arthritis, back or bone pain, asthenia, headache, depression, dyspnea, cough, or pharyngitis.
- Instruct patient to report signs/symptoms of bone loss, including osteopenia, osteoporosis, and bone fracture.
- Instruct patient to report signs/symptoms of anemia, thrombophlebitis, or profuse vaginal bleeding.

Ascorbic acid

Adverse Effects

Serious:

- **None indicated**

Common:

- **Dermatologic:** Injection site reaction, Pain and swelling
- **Gastrointestinal:** Diarrhea, Large doses
- **Hematologic:** Iron overload, Large doses
- **Renal:** Nephrolithiasis, Large doses

Atorvastatin

Common	Rare ≤3%
Adominal pain (3.8%) Diarrhea (5.3%) Headache (2.5% to 16.7%) Rash (1.1% to 3.9%) Arthralgia (up to 5.1%) Myalgia (up to 5.6%) Asthenia (3.8%) Sinusitis (2.8% to 6.4%) Infection (2.8% to 10.3%)	Rhabdomyolysis (rare) Rupture of Tendon Alopecia Thrombocytopenia (<0.1%) Short term memory loss (rare) Constipation (2.5%) Flatulence (1.15 to 2.8%) Indigestion (1.3% to 2.8%) Increased liver enzymes, mild (0.2% to 2.3%) Immune hypersensitivity reaction (up to 2.8%) Backache (2.8%) Dizziness (2% or more) Insomnia (2% or more) Arthritis (2% or more)

	Nausea (2% or more) Chest pain (2% or more) Swelling of arm and legs (2% or more) Albuminuria (2% or more) Hematuria (2% or more) Urinary tract infection (2% or more) Bronchitis(2% or more) Pharyngitis (2.5%) Rhinitis (2% or more) Flu-like illness (2.5%)

- This drug may cause headaches.
- Instruct patient to report signs/symptoms of rhabdomyolysis (myalgias, dark urine, arthralgias, fatigue).
- Patient should not drink alcohol while taking drug.
- Patient should not eat grapefruit or drink grapefruit juice while taking drug.

Atovaquone

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome
- **Hematologic:** Methemoglobinemia
- **Hepatic:** Liver failure

Common:

- **Dermatologic:** Rash (6.3% to 46%)
- **Gastrointestinal:** Abdominal pain (4% to 21%), Diarrhea (3.2% to 42%), Nausea (4.1% to 32%), Vomiting (2.2% to 22%)
- **Neurologic:** Asthenia (8% to 31%), Headache (16% to 31%), Insomnia (10% to 19%)
- **Respiratory:** Cough (14% to 25%), Dyspnea (15% to 21%), Rhinitis (5% to 24%)
- **Hematologic:** Anemia (4-6%), Neutropenia (3-5%)
- **Other:** Fever (0.6% to 40%), Infectious disease (18% to 22%)

Azacitidine

Adverse Effects

Serious:

- **Cardiovascular:** Atrial fibrillation (less than 5%), Cardiorespiratory arrest (less than 5%), Congestive cardiomyopathy (less than 5%), Heart failure (less than 5%)
- **Dermatologic:** Cellulitis (less than 5%)
- **Hematologic:** Anemia, Grade 3 and 4 (13.7%), Febrile neutropenia (13.7% to 16.4%), Neutropenia, Grade 3 and 4 (61.1%), Pancytopenia (less than 5%), Sepsis, Associated with neutropenia (less than 5%), Thrombocytopenia, Grade 3 and 4 (58.3%)

- **Immunologic:** Septic shock (less than 5%)
- **Neurologic:** Cerebral hemorrhage (less than 5%), Coma, Intracranial hemorrhage (less than 5%), Seizure (less than 5%)
- **Renal:** Renal failure, Renal tubular acidosis
- **Respiratory:** Interstitial lung disease, Respiratory distress (less than 5%)

Common:

- **Cardiovascular:** Chest pain (16.4%), Pallor (16%), Pitting edema (15%), Peripheral edema (7-19%)
- Central nervous system: Fever (30% to 52%), fatigue (13% to 36%), headache (22%), dizziness (19%), anxiety (5% to 13%), depression (12%), insomnia (9% to 11%), malaise (11%), pain (11%)
- Endocrine & metabolic: Hypokalemia (6% to 13%)
- **Dermatologic:** Erythema (7.4% to 16.8%), Erythema at injection site (35% to 42.9%), Induration of skin (less than 5%), Injection site bruising (5.1% to 14.1%), Injection site pain (18.9% to 22.7%), Injection site reaction (13.6% to 29.1%), Petechiae (11.4% to 23.6%), Pruritic rash (less than 5%), Pruritus (6.8% to 12%)
- **Gastrointestinal:** Constipation, Diarrhea, Loss of appetite, Nausea, Vomiting
- **Hematologic:** Anemia, Any grade (51.4% to 69.5%), Ecchymosis (30.5%), Leukopenia (18.3% to 48.2%), Neutropenia, Any grade (32.3% to 65.7%), Thrombocytopenia, Any grade (65.5% to 69.7%)
- **Musculoskeletal:** Arthralgia
- **Neurologic:** Dizziness (18.6%), Headache (21.8%), Insomnia (8.6% to 10.9%), Lethargy (7.4% to 7.7%)
- **Respiratory:** Dyspnea (14.9% to 29.1%), Nasopharyngitis (14.5%), Pneumonia (10.9%), Upper respiratory infection (9.1% to 12.7%)
- **Other:** Fatigue (24%), Fever (30.3% to 51.8%), Lymphadenopathy (10%), herpes simplex (9%), night sweats (9%), transfusion reaction (7%), mouth hemorrhage (5%)

Azathioprine

Common	Serious
Gastritis medicamentosa Nausea (12%) Vomiting (12%) Rash (infrequent) Diarrhea (infrequent)	Pancreatitis (2-12%) Leukopenia (5-16%) Megaloblastic anemia Thrombocytopenia Hepatotoxicity (3-10%) Cancer (rare) Infection (20% in renal transplant patients) Immune hypersensitivity reaction (<0.1%)

- This drug may cause myelosuppression and gastrointestinal toxicity.
- Instruct patient to report any unusual bleeding or bruising.
- Instruct patient to report signs/symptoms of infection.
- Patient may take drug with food or in divided doses to decrease gastrointestinal intolerance.

- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).

Aztreonam

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme (adults, less than 1%), Toxic epidermal necrolysis (adults, less than 1%)
- **Gastrointestinal:** Diarrhea, GI bleeding, nausea, pseudomembranous colitis, vomiting
- **Hematologic:** Neutropenia (up to 3.2%), Pancytopenia (adults, less than 1%), Thrombocytopenia (adults, less than 1%)
- **Immunologic:** Anaphylaxis (adults, less than 1%)
- **Otic:** Ototoxicity
- **Renal:** Nephrotoxicity
- **Other:** Angioedema (adults, less than 1%)

Common:

- **Cardiovascular:** Chest discomfort (inhalation solution, 8%)
- **Gastrointestinal:** Abdominal pain (inhalation solution, 7%), Vomiting (inhalation solution, 6%)
- **Hepatic:** Alkaline phosphatase raised, ALT/SGPT level raised (6.5%), AST/SGOT level raised (3.8%)
- **Renal:** Serum creatinine raised (pediatrics, 5.8%)
- **Respiratory:** Cough (inhalation solution, 54%), Nasal congestion (inhalation solution, 16%), Pain in throat (inhalation solution, 12%), Wheezing (inhalation solution, 16%)
- **Other:** Fever (up to 1%)

Baclofen

Adverse Effects

Serious:

- **Neurologic:** Aseptic meningitis, with intrathecal administration, Coma, Seizure
- **Other:** Death, Abrupt withdrawal

Common:

- **Gastrointestinal:** Constipation (; oral: 2% to 6%), Nausea (4% to 12%)
- **Neurologic:** Asthenia (5% to 15%), Dizziness (5% to 15%), Somnolence (10% to 63%)
- **Other:** Fatigue (2% to 4%), Hypotension (0-9%), Vision changes

Balsalazide

Common	Serious
Abdominal pain (6%) Diarrhea (5%) Nausea (5%) Headache (8%) Vomiting (4%) Arthralgia (4%) Respiratory tract infection (4%)	Abnormal electrolytes Colitis Exacerbation Pancreatitis hepatotoxicity

BCNU

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Burning feeling in the vein while drug is being given, nausea, vomiting	Inflammation and/or blockage of a vein at the injection site (L), sudden redness of the face	Burning feeling in the chest while the medication is being given by vein, brown discoloration where the medication comes in contact with the skin
Prompt: Within 2-3 weeks, prior to next course	Decrease in the number of red and white blood cells and platelets made in the bone marrow(L), hair loss (L)	Abnormal function of the liver (L)	Abnormal function of the kidneys (L)
Delayed: Any time later during therapy, excluding the above conditions	Abnormal lung function (L)		Damage/scarring of lung tissue (L)
Late: Any time after completion of treatment			A new cancer or leukemia resulting from this treatment.

(L) Toxicity may also occur later.

Betamethasone

Adverse Effects

Serious:

- **Endocrine metabolic:** Cushing's syndrome, Hyperglycemia, Primary adrenocortical insufficiency
- **Musculoskeletal:** Osteoporosis
- **Ophthalmic:** Cataract, Glaucoma
- **Respiratory:** Pulmonary tuberculosis

Common:

- **Cardiovascular:** Hypertension
- **Dermatologic:** Atrophic condition of skin, Finding of skin healing Skin infections (16-43%)**Endocrine metabolic:** Decreased body growth
- **Gastrointestinal:** Disord**er of gastrointestina**l tract
- **Immunologic:** At risk for infection
- **Psychiatric:** Depression, Euphoria

Bevacizumab

The following table outlines the side effects of bevacizumab that we know about. The side effects presented may not be dose-dependent, which means that a higher dose of bevacizumab many not result in more severe side effects. More importantly, it means that a lower dose may not mean fewer side effects and that serious side effects may occur even at the lowest doses tested.

	Common Happens to 21-100 patients out of every 100	Occasional Happens to 5-20 patients out of every 100	Rare Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	High blood pressure, low blood pressure, fever, chills, shaking chills, headache, nausea, vomiting	Difficulty breathing, cough or voice change	Allergic Reaction
Prompt or delayed: Within 2-3 weeks or any time after, during treatment	High blood pressure, Excess amount of protein in the urine, nosebleeds	Mouth sores, sore throat, vomiting blood, blood in sputum or spit, rash, peeling of the skin, hives, blood clot in vein or artery	Kidney damage, liver function test elevations
Late: Anytime after completion of treatment.			
Unknown Timing and Frequency		Infection, joint pains, chest pains, low blood counts*, fatigue, weight loss, loss of appetite, change in bowel habits.	Clots in the arteries,**Severe bleeding in the tumor, lungs, or in the brain, intestinal leakage*, slow wound healing, heart strain*, fluid around the heart or in the lungs*, collection of air in the chest that causes part or all of a lung to collapse *, Abnormal heart rhythm*, Clotting abnormalities,* mental status changes*, seizure*, fainting spells,* tingling in the hands and feet*, visual changes* and frequent urination*

* There have been reported cases but the relationship to the study drug is unclear.
**The use of bevacizumab is associated with an increased risk of conditions related to clots in the arteries, including stroke or heart attack; these conditions can be life-threatening or fatal. When several studies were looked at together, problems due to clots in arteries were increased up to 4-

5% in patients receiving chemotherapy plus bevacizumab compared to chemotherapy alone (2%). Patients who were elderly and with past history of clots in the arteries appeared to be at a greater risk for these problems.

There is currently no experience using bevacizumab in children. Studies of the drug in animals showed a decrease in ovarian function and abnormal bone growth. These side effects appeared to be at least partially reversible, but have not been assessed in cases of long-term use of the drug. The greatest effects on growth were on the long leg bones of growing animals. Adult women of child-bearing age who have received bevacizumab have continued to have normal periods. The potential risks for impaired growth and development are of particular concern to children.

In studies in adults, many patients experience mild to moderate increases in blood pressure which may need to be lowered with medication. Uncontrolled high blood pressure can be serious or life-threatening. Some patients have also experienced excessive amounts of protein in the urine which has rarely progressed to permanent and serious kidney disease. Because this drug acts on blood vessels bleeding and blood clots appear to be more common than with other therapies. Minor bleeding episodes including nosebleeds are not uncommon. However, bleeding has occurred in the brain, the stomach and intestines and within the tumor itself, occasionally causing it to rupture. Blot clots are most often associated with intravenous catheters, but can also involve the brain (stroke), the lungs (pulmonary embolus) and the blood supply to other vital organs of the body. In adults these side effects, while infrequent, have been life-threatening and even fatal. We will closely monitor children on this study for all of these effects.

Patients who develop anemia or low platelet counts may require red blood cell or platelet transfusions and as a result transfusion of blood and/or blood components may be necessary. Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

If a person gets pregnant while receiving bevacizumab, it could be dangerous for the baby. You should not become pregnant or father a baby while on this study. You should not nurse (breast feed) a baby while on this study. Ask about counseling and more information about preventing pregnancy.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

BIOTIN

Brand Name(s): **Appearex**

Adverse Effects

- gastrointestinal upset
- administration of anticonvulsant medications may impair Biotin absorption

Patient Information

- **None indicated**

Contraindications

- hypersensitivity to Biotin

Precautions

- **None indicated**

BISACODYL

Brand Name(s): **Alophen Pills ; Bisac-Evac**

Adverse Effects

Serious:

- **Gastrointestinal:** Atony of colon

Common:

- **Gastrointestinal:** Abdominal colic, Abdominal discomfort, Diarrhea, Proctitis, With suppository use

Patient Information

- This drug may cause diarrhea or abdominal pain, discomfort, and cramping. The suppositories may cause proctitis.
- Patient should expect to have a bowel movement within 15 to 60 min after suppository administration.
- Instruct patient to report rectal bleeding or failure to have bowel movements within 12 h after taking oral formulation.
- Patient should not take bisacodyl tablets within 1 h of antacids, milk, or milk products.
- Patient should not take bisacodyl for more than 7 days, unless approved by healthcare professional.

Contraindications

- appendicitis
- intestinal obstruction
- gastroenteritis

Precautions

- abdominal pain, nausea, vomiting
- rectal bleeding or failure to have bowel movements after administration
- inflammatory bowel disease
- sudden, persistent change in bowel habits
- ulcerated hemorrhoids of rectal fissures
- use for more than 7 days is not recommended

Bortezomib

Risks and side effects related to the bortezomib include those which are:

Likely

- Decrease in a red blood cell protein that carries oxygen in the body
- Decreased number of blood cells that help to clot the blood
- Fatigue
- Fever
- Loss of appetite
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Infection
- Swelling of the arms and legs
- Nerve damage causing numbness, tingling, burning

Less Likely

- Decreased total number of white blood cell
- Decreased number of a type of white blood cell
- Low blood pressure
- Difficulty sleeping or falling asleep
- Chills, shivering
- Rash/flaking or shedding of outer layer of skin
- Dehydration
- Heartburn
- Abnormally slow bowel contraction
- Irritation or sores in the lining of the throat
- Bleeding of the digestive tract
- Nosebleed
- Fever with dangerously low white blood cell count
- Blood infection
- Pneumonia
- Infection which occurs due to a decreased number of a type of white blood cell
- Muscle weakness of the whole body
- Dizziness
- Anxiety
- Weakness or paralysis caused by damage to nerves
- Fainting
- Blurred vision
- Belly pain
- Back pain
- Bone pain
- Leg pain
- Head pain
- Joint pain
- Muscle pain
- Nerve pain

- Cough
- Shortness of breath
- Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs

Rare but serious

- A hole in the digestive tract
- Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings
- Kidney failure

Bromocriptine

Serious:

- **Cardiovascular:** Coronary artery thrombosis, Postpartum, Heart valve disorder, Myocardial infarction, Postpartum (rare), Pericardial effusion
- **Gastrointestinal:** Gastrointestinal ulcer
- **Neurologic:** Cerebrovascular accident (rare), Seizure (rare)
- **Psychiatric:** Delusions, Hallucinations, Psychotic disorder
- **Respiratory:** Pleural effusion, Pulmonary fibrosis, Thickening of pleura

Common:

- **Cardiovascular:** Hypotension (type 2 diabetes, 2.2%)
- **Endocrine:** Hypoglycemia (type 2 diabetes 3.7-8.6%);
- **Gastrointestinal:** Constipation (acromegaly, 14%; hyperprolactinemic indications, 3%; type 2 diabetes, 5.8% to 11.3%), Diarrhea (hyperprolactinemic indications, 3%; type 2 diabetes, 8.1% to 8.8%), Indigestion (acromegaly, 4%; type 2 diabetes, 7.5%), Nausea (acromegaly, 18%; hyperprolactinemic indications, 49%; type 2 diabetes, 25.4% to 32.5%), Vomiting (acromegaly, 2%; hyperprolactinemic indications, 5%; type 2 diabetes, 5.3% to 8.1%)
- **Neurologic:** Asthenia (type 2 diabetes, 12.5% to 18.9%), Dizziness (hyperprolactinemic indications, 17%; type 2 diabetes, 11.9% to 14.8%), Headache (hyperprolactinemic indications, 19%; type 2 diabetes, 11.4% to 16.8%), Somnolence (3% to 6.6%)
- **Ophthalmic:** Amblyopia (type 2 diabetes, 5.3% to 7.5%)
- **Respiratory:** Rhinitis (type 2 diabetes 10.7% to 13.8%), Sinusitis (type 2 diabetes, 7.4% to 10%)
- **Other:** Fatigue (hyperprolactinemia indications, 7%; type 2 diabetes, 13.9%)

Brompheniramine

Serious:

- **None indicated**

Common:

- **Gastrointestinal:** Xerostomia
- **Neurologic:** Somnolence
- **Respiratory:** Thick sputum, Bronchial

Budesonide

Serious:

- **Cardiovascular:** Syncope (inhalation, 1% to 3%); Chest Pain (0-3%), Palpitations (0-5%), Tachyarrythmia (0-5%)
- **Endocrine metabolic:** Cushing's syndrome, Secondary hypocortisolism
- **Immunologic:** Cow's milk protein sensitivity, Immune hypersensitivity reaction (rare)
- **Ophthalmic:** Cataract (rare), Glaucoma (rare)

Common:

- Dermatologic: Contact dermatitis (0.75-4%), Eczema (0-3%), Rash (0-4%)
- **Gastrointestinal:** Diarrhea (inhalation, 4%; oral, 10%), Nausea (inhalation, 1.8% to 6%; oral, 11%)
- **Musculoskeletal:** Arthralgia (inhalation, 6%; oral, 5%)
- **Neurologic:** Headache (inhalation, 3%; oral, 21%)
- **Respiratory:** Epistaxis (intranasal, 8%; inhalation, 2% to 4%), Nasal stinging/burning (intranasal, greater than 1%), Respiratory tract infection (inhalation, 3% to 38%; oral, 11%), Sinusitis (inhalation, 3% to 16%; oral, 8%)

Bumetanide

Common	Serious
Hypotension (0.8%) Hyperuricemia (18.4%) Hypokalemia (14.7%) Nausea (0.6%) Dizziness (1.1%) Headache (0.6%)	Thrombocytopenia (0.2%)

- Instruct patient to report signs/symptoms hypokalemia, dehydration, or persistent fluid retention.
- Patient may take drug with food to minimize gastric irritation.
- Patient should not drink alcohol while taking this drug.

Bupropion

Known side effects of Bupropion:

Bupropion may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- drowsiness
- excitement
- dry mouth
- dizziness
- headache
- nausea
- vomiting
- uncontrollable shaking of a part of the body
- weight loss
- constipation
- excessive sweating

Some side effects can be serious. If you experience any of the following symptoms or those listed in the IMPORTANT WARNING section, call your doctor immediately:

- seizures
- confusion
- hallucinating (seeing things or hearing voices that do not exist)
- irrational fears
- fever
- rash or blisters
- itching
- hives
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- chest pain
- muscle or joint pain
- rapid, pounding, or irregular heartbeat

Buspirone

Serious:

- **Cardiovascular:** Congestive heart failure (rare), Myocardial infarction (rare)
- **Neurologic:** Cerebrovascular accident (rare)

Common:

- **Gastrointestinal:** Nausea (3%)

- **Neurologic:** Asthenia (2%), Confusion (2%), Dizziness (9%), Excitement (2%), Headache (3%), Numbness (2%)
- **Ophthalmic:** Blurred vision (2%)
- **Psychiatric:** Feeling angry (2%), Feeling nervous (4%), Hostile behavior (2%)

Calcitriol

Adverse Effects

Serious:

- **Dermatologic:** Dermatitis, Acute blistering
- **Endocrine metabolic:** Poisoning by vitamin D, Hypercalcemia syndrome

Common:

- **Endocrine metabolic:** Hypercalcemia

Captopril

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome
- **Gastrointestinal:** Intestinal angioedema
- **Hematologic:** Agranulocytosis (0.1% to 0.2%), Neutropenia (0.1% to 0.2%)
- **Immunologic:** Anaphylactoid reaction
- **Neurologic:** Seizures
- **Other:** Angioedema (0.1%)

Common:

- **Cardiovascular:** Hypotension
- **Dermatologic:** Rash (4-7%), Pruritis (2%),
- **Endocrine metabolic:** Hyperkalemia (11%)
- **Gastrointestinal:** Disorder of taste(2-4%), Diarrhea (0.5-2%), Nausea (0.5-2%)
- **Respiratory:** Cough (0.5% to 2%)

Carbamazepine

Common	Serious
Hypertension Hypotension Lightheadedness Nausea (frequent) Vomiting (frequent) Clumsiness Confusion Dizziness Nystagmus Somnolence Blurred vision Diplopia	Atrioventricular block Cardiac dysrhythmia Congestive heart failure Syncope Stevens-Johnson syndrome Toxic epidermal necrolysis Hypocalcemia Hyponatremia (4% to 21.7%) Acute intermittent porphyria Garanulocytosis Aplastic anemia Bone marrow depression Drug-induced eosinophilia Leukocytosis Leukopenia Pancytopenia Thrombocytopenia Hepatitis Acute renal failure Nephrotoxicity angioedema

- Instruct patient to report use of an MAO inhibitor within 14 days prior to initiation of drug therapy.
- This drug may decrease effectiveness of oral contraceptives with concurrent use. Recommend additional form of birth control.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- Drug may cause dizziness, drowsiness, unsteadiness, nausea, or vomiting.
- Advise patient to report signs/symptoms of serious dermatologic reactions, such as Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering) or toxic epidermal necrolysis (widespread peeling/blistering of skin).
- Instruct patient to report signs/symptoms of myelosuppression or hepatic toxicity.
- Advise patients to report signs/symptoms of psychosis, confusion, or agitation.
- Patient should take drug with food.
- Advise patient against sudden discontinuation of drug.
- Patient should not take the drug suspension with other liquid medicinal agents or diluents, as precipitation may occur.
- Patient should not eat grapefruit or drink grapefruit juice while taking this drug.

Carbidopa/LEVOdopa

Common	Serious
Loss of appetite Nausea Vomiting	Heart disease Othostatic hypotension (1%) Dyskinesia (frequent) Psychotic disorder

- This drug may cause loss of appetite, nausea, or vomiting.
- Instruct patient to report signs/symptoms of gastrointestinal bleeding and dyskinesia.
- Advise diabetic patients to monitor for and report difficulties with glycemic control.
- Patients with history of asthma or severe pulmonary disease should report an exacerbation of symptoms.
- Drug may increase risk of suicidal behavior. Tell patient to report exacerbation of underlying depression or psychosis.
- Advise patient against sudden discontinuation of drug.
- Patients using concomitant antihypertensives may be at increased risk for postural hypotension.
- Advise patient that use of MAO inhibitors concurrently or within 2 wks of levodopa/carbidopa is contraindicated.
- Instruct patient using regular tablets to take a missed dose as soon as possible, but if next dose is in less than 2 h, skip the missed dose.

Carbinoxamine

Adverse Effects

Serious:

- **None indicated**

Common:

- **Dermatologic:** Contact dermatitis
- **Gastrointestinal:** Xerostomia, Anorexia, Diarrhea, Nausea, Vomiting
- **Neurologic:** Dizziness, Headache, Sedated, Somnolence
- **Respiratory:** Nasal mucosa dry

Carboplatin

Risks and side effects related to carboplatin include those which are:

Likely	Less Likely	Rare but serious
• Nausea and vomiting • Fewer red blood cells and white blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets causes you to bruise and bleed more easily	• Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure) • Rash • Metallic taste • Numbness and tingling in the fingers and toes • Hair loss • Constipation or diarrhea • Pain in your abdomen • Temporary changes in vision • Damage to the ear causing	• Damage to the liver • Damage to the kidney • Leukemia later in life

• Abnormal levels of certain salts in the body like sodium and potassium •	hearing and balance problems • A feeling of weakness and/or tiredness • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)	

*CCNU (*lomustine*)*

Possible side effects of lomustine:

	Common	Occasional	Rare
Immediate: Within 1-2 days of receiving drug.	Nausea, vomiting		Diarrhea, hair loss, confusion, loss of muscle coordination, sleepiness, mouth sores, blindness caused by lack of function in an area of the brain responsible for vision
Prompt: Within 2-3 weeks of receiving the drug.	Low number of red and white blood cells and platelets in the blood. This often results in weakness, increased risk of infection and increased bleeding.	Loss of appetite	High level of liver enzymes in the blood
Delayed: Anytime later during therapy excluding the above conditions.			Lung damage, kidney damage, low number of white blood cells and platelets
Late: Anytime after completion of treatment.			Continued decrease in the number of white blood cells and platelets made in the bone marrow, which may become more of a problem after repeated doses.

Cefaclor

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Hematologic:** Hemolytic anemia
- **Other:** Serum sickness due to drug (0.024% to 0.5%)

Common:

- **Gastrointestinal:** Diarrhea (1.4%)

Cefadroxil

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome
- **Gastrointestinal:** Clostridium difficile diarrhea
- **Hematologic:** Thrombocytopenia
- **Hepatic:** Liver failure
- **Immunologic:** Anaphylaxis, Hypersensitivity reaction

Common:

- **None indicated**

Cefazolin

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome
- **Gastrointestinal:** Clostridium difficile colitis, Pseudomembranous enterocolitis
- **Hematologic:** Leukopenia**Immunologic:** Anaphylaxis, Immune hypersensitivity reaction
- **Neurologic:** Encephalopathy, Seizure
- **Renal:** Renal failure

Common:

- **Dermatologic:** Pruritus
- **Gastrointestinal:** Diarrhea
- **Hematologic:** Drug-induced eosinophilia

Cefepime

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Immunologic:** Anaphylaxis
- **Neurologic:** Encephalopathy, Myoclonus, Seizure

Common:

- **Dermatologic:** Rash (1.1% to 4%) , Pruritis (0.1-1%)
- **Endocrine metabolic:** Hypophosphatemia (2.8%)
- **Gastrointestinal:** Diarrhea (0.1% to 3%)
- **Hematologic:** Direct Coombs test positive (16.2%)
- **Hepatic:** ALT/SGPT level raised (2.8%), AST/SGOT level raised (2.4%)

Cefotaxime

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac dysrhythmia
- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Hematologic:** Agranulocytosis/Leukopenia/Thrombocytopenia (less than 1%), Granulocytopenic disorder
- **Immunologic:** Hypersensitivity reaction (2.4%)

Common:

- **Dermatologic:** Injection site reactions,, Rash (2.2%),
- **Gastrointestinal:** Diarrhea, Vomiting, Nausea

Cefotetan

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Hematologic:** Hemolytic anemia, Blood coagulation disorder (3.2%), Leukopenia (2%), Thrombocytopenia (3.5%)
- **Immunologic:** Anaphylaxis
- **Neurologic:** Seizure

Common:

- **Dermatologic: Rash (0.6-1.5%)**
- **Gastrointestinal:** Diarrhea (0.6% to 1.25%), Nausea (0.14% to 1.25%)

Cefoxitin

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Immunologic:** Anaphylaxis
- **Neurologic:** Seizure

Common:

- **Dermatologic:** Injection site reaction
- **Hematologic:** Thrombophlebitis

Ceftazidime

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Hematologic:** Increased prothrombin time (0.5%),
- **Immunologic:** Anaphylaxis
- **Neurologic:** Asterixis, Coma, Encephalopathy, Myoclonia, Seizure

Common:

- **Gastrointestinal:** Diarrhea

Cefuroxime

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme (rare), Stevens-Johnson syndrome (rare), Toxic epidermal necrolysis (rare)
- **Hematologic:** Thrombocytopenia (rare)
- **Immunologic:** Anaphylaxis (rare), Hypersensitivity reaction
- **Renal:** Interstitial nephritis (rare)

Common:

- **Hematologic:** Eosinophilia (14-32%),

Celecoxib Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	May mask fever in neutropenic patients (L)	Dyspepsia, diarrhea	Anaphylaxis (especially with history of sulfa or aspirin hypersensitivity, or asthma triad: asthma with nasal polyps, and urticaria), angioedema, flatulence, nausea, headache, dizziness, rashes (including Stevens-Johnson syndrome, erythema multiforme)
Prompt: Within 2-3 weeks, prior to the next course		Upper respiratory tract infection	Fluid retention (L), peripheral edema, GI bleed, or bleeding from peptic ulcer disease (L), sinusitis, pharyngitis, rhinitis
Delayed: Any time later during therapy, excluding the above conditions		Mild elevation of SGOT (AST)/SGPT (ALT)	Severe hepatic reactions (jaundice, fatal fulminant hepatitis, liver necrosis, hepatic failure), decreased renal function, renal papillary necrosis, anemia, cardiovascular and thromboembolic complications (aggravated hypertension, coronary artery disorder, myocardial infarction, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, ischemic cerebrovascular accidents)
Unknown Frequency and Timing:	Administration of celecoxib to animals early in pregnancy caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused, sternebrae misshapen and diaphragmatic hernias. Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Limited data from one subject indicate that celecoxib is also excreted in human milk		

(L) Toxicity may also occur later.

Cetirizine

Adverse Effects

Serious:

- **None indicated**

Common:

- **Gastrointestinal:** Xerostomia
- **Neurologic:** Headache, Somnolence (13.7%), Asthenia (5.2%)
- **Other:** Fatigue (5.9%)

CETUXIMAB

Brand Name(s): **Erbitux**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiorespiratory arrest (squamous cell carcinoma of the head and neck, 2% to 3%), Myocardial infarction, Shock, Sudden cardiac death (squamous cell carcinoma of the head and neck, 2% to 3%)
- **Dermatologic:** Abscess, Acneiform eruption, Grades 3 and 4 (1% to 17%), Radiation dermatitis, Grades 3 and 4 (squamous cell carcinoma of the head and neck (with radiation), 23%)
- **Endocrine metabolic:** Hypomagnesemia, Grades 3 and 4 (5% to 17%)
- **Hematologic:** Leukopenia, Grades 3 and 4 (colorectal cancer (with irinotecan), 17%)
- **Immunologic:** Immune hypersensitivity reaction, Infection due to Staphylococcus aureus, Sepsis (1% to 4%)
- **Neurologic:** Loss of consciousness
- **Renal:** Renal failure (colorectal cancer, 1%)
- **Respiratory:** Interstitial lung disease (less than 0.5%), Pulmonary embolism
- **Other:** Complication of infusion, Grades 3 and 4 (2% to 5%)

Common:

- **Dermatologic:** Acneiform eruption, Any grade (70% to 88%), Application site reaction (squamous cell carcinoma of the head and neck (with radiation), 18%), Dry skin (squamous cell carcinoma of the head and neck (with platinum plus 5-FU), 14%; colorectal cancer (monotherapy), 49%), Nail changes (colorectal cancer (monotherapy), 21%), Pruritus (squamous cell carcinoma of the head and neck (with radiation), 16%; colorectal cancer (monotherapy), 40%), Radiation dermatitis, Any grade (squamous cell carcinoma of the head and neck (with radiation), 86%), Rash (87% to 89%; squamous cell carcinoma of the head and neck (with platinum plus 5-FU), 28%)
- **Endocrine metabolic:** Dehydration (squamous cell carcinoma of the head and neck (with radiation), 25%), Hypomagnesemia, Any grade (55%; squamous cell carcinoma of the head and neck (with platinum plus 5-FU), 11%), Weight loss (squamous cell carcinoma of the head and neck (with radiation), 84%)
- **Gastrointestinal:** Abdominal pain (colorectal cancer (monotherapy), 59%), Constipation (colorectal cancer (monotherapy), 46%), Diarrhea (19% to 39%; colorectal cancer (with irinotecan), 72%), Loss of appetite (squamous cell carcinoma of the head and neck (with platinum plus 5-FU), 25%), Nausea (49% to 55%), Stomatitis (colorectal cancer (monotherapy), 25%), Vomiting (29% to 37%)
- **Immunologic:** Infectious disease (35% to 44%; squamous cell carcinoma of the head and neck (with radiation), 13%)
- **Neurologic:** Asthenia, Any grade (56% to 73%), Confusion (colorectal cancer, 15%), Headache (19% to 33%), Insomnia (colorectal cancer (monotherapy), 30%)
- **Psychiatric:** Anxiety (colorectal cancer (monotherapy), 14%), Depression (colorectal cancer (monotherapy), 13%)
- **Respiratory:** Cough (colorectal cancer (monotherapy), 29%), Dyspnea (colorectal cancer (monotherapy), 48%), Pharyngitis (squamous cell carcinoma of the head and neck (with radiation), 26%)

Patient Information

- Drug causes sun-sensitivity and can exacerbate any skin reactions which may occur. Advise patient to wear sunscreen and hats and to avoid tanning beds.
- This drug may cause hypomagnesemia, weight loss, abdominal pain, constipation, diarrhea, gastrointestinal mucositis, nausea, anemia, asthenia, headache, insomnia, depression, cough, dyspnea, pain, or fever.
- Advise patient, especially those receiving concomitant radiation therapy, to report signs/symptoms of dermatologic toxicity. This may be characterized as a severe acneform rash (acne, rash, maculopapular rash, pustular rash, dry skin, exfoliative dermatitis).
- Instruct patient to report signs/symptoms of acute or worsening pulmonary symptoms, as this may indicate pulmonary toxicity.
- Advise patients with preexisting cardiac disease to report acute or worsening cardiac symptoms.

Contraindications

- specific contraindications have not been determined

Precautions

- cardiopulmonary arrest and/or sudden death have been reported in patients with squamous cell carcinoma of the head and neck treated with concomitant radiation therapy or platinum-based therapy with 5-fluorouracil; patients with a history of arrhythmias, congestive heart failure, or coronary artery disease may be at increased risk; monitoring of serum electrolytes recommended
- infusion reactions, some serious (eg, bronchospasm, stridor, hypotension, shock, loss of consciousness, myocardial infarction, cardiac arrest) and fatal, have been reported; immediately and permanently discontinue for serious infusion reactions
- concomitant use with radiation therapy and cisplatin (unapproved use); death and serious cardiotoxicity have been reported in patients with squamous cell carcinoma of the head and neck
- dermatologic toxicities, including acneform rash, hypertrichosis, and infectious sequelae (eg, Staphylococcus aureus sepsis, abscess formation, cellulitis) have been reported; monitoring and dosage modifications recommended for severe acneform rash
- electrolyte abnormalities (eg, hypomagnesemia, hypocalcemia, hypokalemia) have occurred; monitoring recommended
- interstitial lung disease (ILD) has been reported; permanently discontinue for confirmed ILD
- sun exposure; limit exposure for up to 2 months following the last cetuximab dose
- report suspected adverse reactions to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Chlorambucil

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme (rare), Skin reaction - finding, Stevens-Johnson syndrome (rare), Toxic epidermal necrolysis (rare)
- **Hematologic:** Acute leukemia, Leukopenia, Myelosuppression, Neutropenia, Pancytopenia
- **Hepatic:** Hepatotoxicity
- **Immunologic:** Drug fever, Immune hypersensitivity reaction
- **Neurologic:** Peripheral neuropathy, Seizure
- **Psychiatric:** Hallucinations
- **Reproductive:** Infertility, Reversible or permanent
- **Respiratory:** Pneumonitis, acute
- **Other:** Secondary malignant neoplastic disease

Common:

- **Hematologic:** Anemia, Thrombocytopenia

Chlorothiazide

Common	Serious
Hypotension Alopecia Light sensitivity Phototoxicity Rash Urticaria Hyperglycemia Hyperuricemia Constipation Diarrhea Loss of appetite Nausea Vomiting Spasticity Dizziness Headache Blurred vision Xanthopsia Impotence	Scaling eczema (rare) Stevens-Johnson syndrome (rare) Toxic epidermal necrolysis (rare) Abnormal electrolytes Disorder of hematopoietic structure (rare) Hepatotoxicity (rare) Systemic lupus erythematosus (rare)

- Patient should avoid activities requiring coordination until drug effects are realized, as this drug may cause dizziness or spasticity.

- This drug may cause alopecia, hyperglycemia, constipation, diarrhea, loss of appetite, nausea, vomiting, headache, blurred vision, xanthopsia, or impotence.
- Instruct patient to report symptomatic hypotension.
- Patient should not drink alcohol while taking this drug.
- Avoid concomitant use of lithium.

chlorproMAZINE

Common	Serious
Hypotension Orthostatic hypotension Diminished sweating Light sensitivity Constipation Xerostomia Akathisia Dizziness Drug-induced tardive dystonia Dystonia Extrapyrmidal disease Parkinsonian Somnolence Tardive dyskinesia Blurred vision Epithelial keratopathy Eye/vision changes Retinitis pigmentosa Nasal congestion	Prolonged QT interval (rare) Torsades de pointes (rare) Obstipation (rare) Paralytic ileus (rare) Agranulocytosis (rare) Hematopoietic structure disorder (rare) Leucopenia (rare) Thrombocytopenia (rare) Cholestatic jaundice syndrome (rare) Neuroleptic malignant syndrome (rare) Seizure (rare) Priapism (rare) Death

- Patient should avoid activities requiring mental alertness, coordination, or visual acuity until drug effects are realized.
- Drug can cause sun-sensitivity. Advise patient to use sunscreen and avoid tanning beds.
- Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- Advise patient to report any visual disturbances. Patients receiving moderate to high-dose therapy for long periods of time may need to have periodic eye exams.
- This drug may cause anticholinergic effects, hypotension, diminished sweating, akathisia, or somnolence.
- Instruct patient to report signs/symptoms of agranulocytosis (eg, sudden appearance of sore throat or other signs of infection), especially between the fourth and tenth weeks of therapy.
- Advise patient to report signs/symptoms of neuromuscular adverse effects such as parkinsonian extrapyramidal disease, tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities), or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Patients on concurrent antipsychotic therapy should report signs/symptoms of encephalopathic syndrome (weakness, lethargy, fever, tremulousness, confusion).
- Advise patient against sudden discontinuation of drug.

- Patient should not drink alcohol or use other CNS depressants while taking this drug.
- Patient should avoid exposure to organophosphorus insecticides during drug therapy.

chlorproPAMIDE

Common	Serious
Cutaneous hypersensitivity Hypoglycemia Nausea Vomiting Hematopoietic structure disorder	Hypoglycemia (severe)

- This drug may cause cutaneous hypersensitivity, nausea, or vomiting.
- Advise diabetic patients to monitor for signs/symptoms hypoglycemia and to report difficulties with glycemic control. Elderly or debilitated patients may be at increased risk for severe hypoglycemia.
- Patient should take drug with breakfast.
- Patient should avoid alcohol while taking this drug.

Chlorzoxazone

Adverse Effects

Serious:

- **Gastrointestinal:** Gastrointestinal hemorrhage (rare)
- **Hepatic:** Hepatotoxicity (rare)
- **Immunologic:** Anaphylaxis (rare)

Common:

- **Cardiovascular:** Lightheadedness
- **Neurologic:** Dizziness, Excitement, Paradoxical, Somnolence
- **Other:** Malaise

Ciclosporin

Common	Serious
Hirsutism Pruritus Diarrhea Nausea Vomiting Headache (2% to 25%) Seizure (1% to 25%) Tremor (3% to 55%) Burning sensation in eye (with ophthalmic	Hypertension (frequent) Hyperkalemia (rare) Hypomagnesemia Gingival enlargement Pancreatitis (rare) Hepatotoxicity Anaphylaxis (with IV use, rare) Post-transplant lymphoproliferative disorder (rare) Paresthesia (1-11%)

emulsion, 17%) Conjunctival hyperemia Eye discharge Excessive tear production Pain in eye (with ophthalmic emulsion, 1-5%) Visual disturbance (with ophthalmic emulsion, 1-5%)	Hemolytic uremic syndrome (rare) Nephrotoxicity (frequent) Infection

- Patient should not use ophthalmic preparation in an infected eye.
- Advise patient to avoid vaccines during therapy unless approved by a healthcare professional.
- To decrease the risk of skin malignancies, advise patient to avoid excessive exposure to ultraviolet light.
- Drug may cause hypertension, renal dysfunction, hirsutism, diarrhea, nausea, vomiting, headache, tremor, or gingival enlargement.
- The ophthalmic preparation may cause a foreign body or burning sensation in the eye.
- Instruct patient to report signs/symptoms of transplant rejection or infection.
- Advise patient to report signs/symptoms of hepatotoxicity or encephalopathy, especially patients receiving high-dose therapy.
- Instruct patients to report signs/symptoms of nephrotoxicity, especially when on concomitant nephrotoxic drugs.
- Patients using the ophthalmic preparation should report visual disturbances, conjunctival hyperemia, eye pain, or discharge from eye.
- Patient should allow at least 5 minutes between instillation of this drug and other ophthalmic products.
- Warn patient that rinsing the oral solution syringe with water either before or after use will cause a variation in dose and should be avoided.
- Tell patient to remove contact lenses prior to instilling ophthalmic formulation. Lenses may be reinserted 15 minutes following instillation.
- Patient should not eat grapefruit or drink grapefruit juice while taking this drug.
- Patient should avoid concomitant potassium-sparing drugs, potassium supplements, and foods/salt substitutes that are high in potassium.
- Tell patient that there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).

Ciprofloxacin

Serious:

- **Cardiovascular:** Cardiorespiratory arrest (less than 1%), Myocardial infarction (less than 1%), Prolonged QT interval, Syncope (less than 1%), Torsades de pointes
- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Clostridium difficile infection, Gastrointestinal hemorrhage (less than 1%), Pancreatitis (less than 1%), Pseudomembranous enterocolitis (less than 1%)
- **Hematologic:** Agranulocytosis, Aplastic anemia, Bone marrow depression, Hemolytic anemia, Leukopenia, Pancytopenia, ThrombocytopeniaHepatic: Elevated liver function tests, Hepatotoxicity,
- **Immunologic:** Immune hypersensitivity reaction, Serious (rare)

- **Musculoskeletal:** Myasthenia gravis, Exacerbation, Rupture of tendon, **Tendinitis, Arthropathy**
- **Neurologic:** Raised intracranial pressure, Seizure (less than 1%)
- **Psychiatric:** Depression (less than 1%), Psychotic disorder (less than 1%)
- **Renal:** Acute renal failure (less than 1%), Hemorrhagic cystitis (less than 1%)

Common:

- **Dermatologic:** Rash (up to 1.8%), Pruritis (2-3%)
- **Gastrointestinal:** Diarrhea (1.6% to 4.8%), Nausea (2.5% to 2.7%), Vomiting (1% to 4.8%)
- **Musculoskeletal:** Arthralgia (9.3-13.7%), Myalgia (9.3%)
- **Neurologic:** Headache (2% to 3.9% .)
- **Ophthalmic:** Burning sensation in eye, Pain in eye

Cisplatin

There is a risk of very uncommon or previously unknown side effects occurring. Treatment may result in allergic reactions, the decreased ability of the body to fight infection, and abnormalities in growth or structure of the fetus. Very rarely, one or a combination of these side effects may cause death. These drugs may interact with other drugs to produce unexpected side-effects.

Cisplatin

	Common **Happens to 21-100 children out of 100**	Occasional **Happens to 5-20 children out of every 100**	Rare **Happens to <5 children out of every 100**
Immediate: Within 1-2 days of receiving drug	**Nausea (L), vomiting (L)**	**Metallic Taste (L)**	**Allergic reaction**
Prompt: Within 2-3 weeks, prior to the next course	**Loss of appetite (L), low level of magnesium salts in the blood (L), hearing loss (high sounds [L]), damage to kidney tissue (L), Decrease in the number of red and white blood cells and platelets made in the bone marrow**	**Abnormal levels of certain salts in the body like sodium and potassium (L)**	**Numbness, tingling, clumsiness (L), ringing in the ears (L), seizure (L), damage to the liver (L)**
Delayed: Any time later during therapy, excluding the above conditions			**Hearing Loss**
Late: Any time after completion of treatment			Cancer caused by treatment for a previous cancer or leukemia

(L) Toxicity may also occur later.

Citalopram

Adverse Effects

Serious:

- **Cardiovascular:** Myocardial infarction (0.1% to 1%), Prolonged QT interval (0.5% to 1.9%), Torsades de pointes, Tachycardia (0.5-1%)
- **Neurologic:** Cerebrovascular accident (0.1% to 1%)
- **Psychiatric:** Depression, worsening (rare), Suicidal thoughts, Suicide
- **Other:** Serotonin syndrome

Common:

- **Dermatologic:** Diaphoresis (5% to 18%)
- **Gastrointestinal:** Constipation (13%), Diarrhea (8%), Nausea (20% to 21%), Vomiting (4% to 20%), Xerostomia (17% to 20%)
- **Musculoskeletal:** Arthralgia (2%), Myalgia (2%)
- **Neurologic:** Dizziness (up to 14%), Headache (up to 18%), Insomnia (15%), Sedated (15%), Somnolence (18%), Tremor (8% to 16%)
- **Psychiatric:** Agitation (3% to 10%)
- **Reproductive:** Disorder of ejaculation (6.1%)

Respiratory: Rhinitis (5%), Sinusitis (3%), Upper Respiratory Tract Infection (5%)**Other:** Fatigue (5%);

Clemastine

Adverse Effects

Serious:

- **None indicated**

Common:

- **Gastrointestinal:** Xerostomia
- **Neurologic:** Sedated, Somnolence
- **Renal:** Urinary retention

Clindamycin

Adverse Effects

Serious:

- **Dermatologic:** Erythema multiforme
- **Gastrointestinal:** Pseudomembranous enterocolitis
- **Hematologic:** Agranulocytosis
- **Hepatic:** Increased liver function test, Jaundice

Common:

- **Dermatologic:** Dry skin, Rash
- **Gastrointestinal:** Abdominal pain, Diarrhea, Nausea
- **Reproductive:** Candida vaginitis (14% vaginal cream ; 1.5% vaginal suppository), Vaginal pain (up to 2% vaginal suppository)

Clofarabine

Risks and side effects related to the clofarabine include:

Likely	Less Likely	Rare but serious
• A fast heartbeat which may cause pain in the chest • A feeling of extreme tiredness not relieved by sleep • A decrease in blood pressure • Pain in the abdomen (belly) • Diarrhea • Nausea and/or vomiting • Headache • Fever • Chills • Anxiety • Fever with a low white blood cell count which could mean that you have an infection and might require hospitalization and treatment with antibiotics • Loss of appetite • Elevation in the blood of certain enzymes found in the liver and bilirubin (a substance that comes from the liver breaking down waste products) which may mean the liver is not working as well as normal • Skin rash • Skin rash with inflammation • Itching • Red spots on the skin from low platelets • Bloody nose • Fewer white blood cells, red blood cells and platelets in the blood (may be prolonged) o a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make you feel	• The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys. • Fluid build-up in the tissues • Sleepiness and weakness • Changes to your emotions such that you feel depressed, anxious, agitated, irritable or confused • Difficulty sleeping or falling asleep • High blood pressure • Cough or shortness of breath • Reddening of the face with feelings of warmth when the drug is infusing • A fast rate of respiration that may cause pain in the chest • A change in alertness, concentration, and memory • Allergic reaction • Constipation • Dizziness • Tremor (shakiness usually of the hands) • Shaking chills • Fainting • Low levels of oxygen in the blood which may make you feel short of breath • Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)	• Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such as sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening • Capillary leak syndrome: a condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure. Capillary leak syndrome may lead to multiple organ failure such as kidney, heart or liver failure and shock. • Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly) which can be severe and may increase the blood sugar • Severe inflammation and damage to the large intestine wall which can be life threatening • Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the

tired and weak o a low number of platelets causes you to bruise and bleed more easily • Abnormal levels of potassium or magnesium in the body which may require that you take extra potassium by mouth or vein • An increase in an enzyme (called lipase) that helps break down fats in the body	• Pain including back, bone, arm, or leg pain • The skin and the whites of the eyes appears yellow as a result of too much bilirubin (a substance that comes from the liver breaking down waste products) in the blood • Weight loss • Aches and pains in the muscles and joints • Bleeding from the bladder, gut, mouth, or gums • Vomiting or coughing blood • Fluid build-up in the lungs that can make you feel short of breath • A life threatening condition in which the level of oxygen in the blood becomes too low or the level of carbon dioxide in the blood becomes too high • Damage to the sac around the heart which can lead a build-up of fluid around the heart which may be painful and affect the ability of the heart to work normally but in most cases is only mild and temporary • Severe rash with redness and pain on the palms of the hand and soles of the feet • Bruising of the skin from low platelets • Rash with redness or red bumpy rash • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Occasional sudden sharp pain in the rectal area • Infections including those caused by bacteria, virus, and fungus and can be found in the lung, the blood, the skin and other places in the body • A life-threatening form of severe blood infection that usually results from the presence of bacteria and their toxins in the bloodstream and is	esophagus (the passage that leads from the throat to the stomach), a yellow appearance to the skin and fluid collection in the abdomen which makes it look larger • Abnormal clotting of the blood that can lead to formation of blood clots and/or bleeding with abnormal findings on neurologic exam • Severe kidney damage (which may be permanent) • Severe rashes which can result in loss of skin and damage to mucous membranes and which may be life-threatening (occurred in combination of other drugs known to cause this effect) • Failure of the bone marrow to produce blood cells and platelets which can be life threatening. • A change to the heart such that it does not pump the blood as well which may make you tired, weak, feel short of breath, and retain fluid

	characterized especially by persistent hypotension with reduced blood flow to organs and tissues and often organ dysfunction • Abnormal high level of potassium in the blood which may cause irregular heart beat and require drug treatment to lower the level • An increase in an enzyme (called amylase) that helps break down starch and sugars in the body • Numbness and tingling in the fingers and toes • A problem in nerve function that may cause pain, numbness, tingling, and muscle weakness in various parts of the body and may affect the ability to perform tasks that require fine movements	

Clofibrate

Common	Serious
Abdominal pain	Cardiac arrhythmias
Constipation	Cardiomyopathy (very rare)
Diarrhea	Peripheral vascular disease (rare)
Nausea	pulmonary embolism (rarae)
Headache	thrombophlebitis (rare)
Rash	angina pectoris (rare)
dry skin	cardiac arrhythmias (rare)
dry hair	cardiomyopathy
urticaria	cardiomegaly
alopecia	intermittent claudication
weight gain	Thrombophlebitis
constipation (2%)	Pruritus
epigastric pain (frequent)	erythema multiforme
nausea (10%)	toxic epidermal necrolysis
vomiting (10%)	Stevens-Johnson Syndrome
diarrhea (10%)	Fevers
flatulence (10%)	gallstones
Fatigue	Pancreatitis (rare)
Weakness	Leukopenia (rare)
Drowsiness	Anemia (rare)
dizziness	Eosinophilia (rare)
headache	Agranulocytosis (rare)
Light intolerance	increase in liver transaminases

Lethargy Somnolence tiredness	Systemic lupus erythematosus Drug-induced myopathy flu-like symptoms (rare) myositis (rare) arthralgia (rare) rhadomyolysis (rare) mood disorders cognitive disorders sleep disorders perception disorders Impotence decreased libido dysuria hematuria proteinuria renal failure

Clomipramine

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac arrest, Orthostatic hypotension (4% to 6%), Prolonged QT interval, Syncope (2%)
- **Endocrine metabolic:** Hyperglycemia, Increased body temperature
- **Hematologic:** Agranulocytosis, Leukopenia, Pancytopenia, Thrombocytopenia
- **Hepatic:** Hepatotoxicity (1% to 3%)
- **Neurologic:** Seizure (0.7%), Serotonin syndrome, Neuromuscular blockade
- **Psychiatric:** Suicidal thoughts, Suicide

Common:

- **Dermatologic:** Diaphoresis (9% to 29%)
- **Endocrine metabolic:** Weight increased (18%)
- **Gastrointestinal:** Constipation (22% to 47%), Diarrhea (13%), Indigestion (13% to 22%), Loss of appetite (12% to 22%), Nausea (33%), Xerostomia (63%% to 84%)
- **Musculoskeletal:** Myalgia (13%)
- **Neurologic:** Dizziness (41% to 54%), Feeling nervous (2% to 18%), Headache (28% to 52%), Insomnia (11% to 25%), Myoclonus (13%), Somnolence (46% to 54%), Tremor (33% to 54%)
- **Ophthalmic:** Abnormal vision (7% to 18%)
- **Renal:** Disorder of the urinary system (14%)
- **Reproductive:** Disorder of ejaculation (6% to 42%), Impotence (20%), **Respiratory: P**haryngitis (14%)
- **Other:** Fatigue (35% to 39%)

Clonidine

Adverse Effects

Serious:

- **Cardiovascular:** Atrioventricular block, Bradyarrythmia, Rebound Hypertension ,

Common:

- **Dermatologic:** Contact dermatitis (5% to 47%), Erythema (26%), Pruritus, Hyperpigmentation of skin (5%)
- **Gastrointestinal:** Xerostomia (25%)
- **Neurologic:** Dizziness (2%), Headache (5%), Sedated (3%), Somnolence (12%)
- **Other:** Fatigue (6%)

Clopidogrel

Common	Serious
Chest pain	Acute myocardial infarction, rebound effect
Hypertension (4.3%)	Atrial fibrillation (1% to 2.5%)
Pruritus (3.3%)	Congestive heart failure (1% to 2.5%)
Purpuric disorder (5.3%)	coronary artery stent thrombosis
Rash (4.2%)	erythema multiforme
Hypercholesterolemia	Stevens-Johnson syndrome
Abdominal pain	Gastrointestinal hemorrhage (2%, 2.7% with aspirin)
Constipation	Gastrointestinal ulcer
Diarrhea	Agranulocytosis (<1%)pancytopenia (severe)
Gastritis	Thrombotic thrombocytopenic purpura (rare)
Indigestion	Drug-induced liver disorder
Epistaxia (2.9%)	Hepatitis (rare)
Purpura (5.3%)	Hepatotoxicity
Arthralgia	Abnormal liver function test (rare)
Backache	Anaphylaxis (rare)
Headache (7.6%)	Abnormal renal function (< 1%)
	Acute renal failure (< 1%)
	Non-cardiogenic pulmonary edema

- This drug may cause chest pain, edema, purpuric disorder, abdominal pain, constipation, diarrhea, dyspepsia, gastritis, gastrointestinal ulcer, arthralgia, back pain, dizziness, or headache.
- Instruct patient to report signs/symptoms of bleeding, especially if used concomitantly with anticoagulant therapy.
- Patient should avoid aspirin or aspirin-containing products during drug therapy unless approved by healthcare professional.

Clotrimazole

Common	Rare
Diarrhea (frequent) Nausea (frequent) Vomiting (frequent) Pruritus Skin irritation (topical application) Abnormal liver enzymes Depression Drowsiness Disorientation Vision changes	Erythema Stinging Burning Urticaria Edema Loss of appetite Urinary frequency Lower abdominal cramps Dyspareunia

- Oral form may cause nausea or vomiting.
- Advise patients using the intravaginal formulation to not use tampons during treatment.
- Instruct patients using the topical formulation to not use occlusive dressings over the treated area.
- Patient should avoid douches or other intravaginal products during drug therapy.

Clozapine

Common	Serious
Hypotension Tachyarrhythmia (25%) Rash (2%) Sweating symptom (6%) Excessive salivation (31%) Nausea (5%) Xerostomia (6%) Motor function behavior changes (4%) Muscle rigidity (3%) Akathisia (3%) Confusion (3%) Dizziness (19%) Headache (7%) Insomnia (2%) Somnolence (39%) Tremor (6%) Vertigo (19%) Visual disturbance (5%) Agitation (4%) Dyssomnia Nightmares (4%) Restlessness (4%) Urinary tract disorder (2%) Fatigue (2%) Fever (2%)	Cardiac arrest (rare) Myocarditis Orthostatic hypotension Pericardial effusion (rare) Sudden cardiac death Syncope (5%) Hyperglycemia (rare) Bowel obstruction Colitis Necrotizing Fecal impaction Gastrointestinal hypomotility Ischemic bowel disease Pancreatitis Paralytic ileus Perforation of intestine Agranulocytosis (1.3%) Drug-induced eosinophilia (1%) leucopenia neutropenia (3%) thrombocytopenia (rare) decreased white blood cells hepatitis (rare) neuroleptic malignant syndrome seizure (5%) tardive dyskinesia (rare) pulmonary embolism (rare) respiratory arrest (rare)

	death

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause anticholinergic symptoms, hypotension, sweating, abdominal discomfort, excessive salivation, nausea, headache, tremor, vertigo, dyssomnia, fever, orthostatic hypotension, syncope, or seizure.
- May cause hypotension, especially with first dose and with dose adjustments.
- Drug may also cause neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Instruct patient to report signs/symptoms of hyperglycemia.
- Advise patient to report signs/symptoms of infection, as drug can cause leukopenia.
- Instruct patient to report signs/symptoms of heart failure, myocarditis, or cardiomyopathy.
- Patient should report signs/symptoms of extrapyramidal effects or tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities), especially when taking high doses or with prolonged treatment.
- Advise patient against sudden discontinuation of drug.
- Encourage patient to maintain adequate hydration during drug therapy.
- If dose has been missed for more than two days, advise patient to consult healthcare professional for instructions as dose may not be the same.

Colchicine

Adverse Effects

Serious:

- **Hematologic:** Myelosuppression

Common:

- **Gastrointestinal:** Diarrhea (high dose, 77%; low-dose, 23%), Nausea (high dose, 17%; low-dose, 4%), Vomiting (17%)

Cortisone

Adverse Effects

Serious:

- **Endocrine metabolic:** Hyperglycemia, Primary adrenocortical insufficiency
- **Musculoskeletal:** Osteoporosis
- **Ophthalmic:** Cataract, Glaucoma

Common:

- **Cardiovascular:** Hypertension
- **Dermatologic:** Atrophic condition of skin, Finding of skin healing, Impaired
- **Endocrine metabolic:** Cushing's syndrome, Decreased body growth
- **Gastrointestinal:** Disorder of gastrointestinal tract
- **Immunologic:** At risk for infection
- **Psychiatric:** Depression, Euphoria

Crizotinib

Common >10%:

- **Cardiovascular**: Edema (28%)
- **Central nervous system**: Fatigue (20%), dizziness (16%)
- **Gastrointestinal**: Nausea (53%), diarrhea (43%), vomiting (40%), constipation (27%), appetite decreased (19%), taste alteration (12%), esophageal disorder (11%; includes dyspepsia, dysphagia, epigastric burning/discomfort/pain, esophageal obstruction/pain/spasm/ulcer, esophagitis, gastroesophageal reflux, odynophagia, reflux esophagitis)
- **Hematologic**: Lymphopenia (grades 3/4: 11%)
- **Hepatic**: ALT increased (13%; grades 3/4: 5%)
- **Neuromuscular & skeletal:** Neuropathy (13%; grades 3/4: <1%)
- **Ocular**: Vision disorder (62%; onset: <2 weeks; includes blurred vision, diplopia, photophobia, photopsia, visual acuity decreased, visual brightness, visual field defect, visual impairment, vitreous floaters)

Rare/Occasional 1% to 10%:

- **Cardiovascular**: Bradycardia (5%), chest pain (1%)
- **Central nervous system**: Headache (4%), insomnia (3%)
- **Dermatologic**: Rash (10%)
- **Gastrointestinal**: Abdominal pain (8%), stomatitis (6%)
- **Hematologic**: Neutropenia (grades 3/4: 5%)
- **Hepatic**: AST increased (9%; grades 3/4: 2%)
- **Neuromuscular & skeletal:** Arthralgia (2%)
- **Renal**: Renal cysts (1%)
- **Respiratory**: Cough (4%), dyspnea (2%), pneumonitis (2%), upper respiratory infection (2%)

Cyanocobalamin

	Common	Occasional	Rare
Immediate: Within 1-2 days of receiving drug		Injection site pain	Skin rash, pruritis, urticaria, diarrhea, anaphylaxis, hypokalemia (secondary to erythrocyte production in severe megaloblastic anemia)
Prompt: Within 2-3 weeks, prior to next course			Optic atrophy in Leber's disease
Delayed: Any time later during therapy, excluding the above conditions			Pulmonary edema, congestive heart failure, peripheral vascular thrombosis, unmasking of polycytemia vera
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities:** Vitamin B-12 crosses the placenta. Vitamin B12 is an essential vitamin and requirements are increased during pregnancy. Amounts of Vitamin B12 that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 mcg daily) should be consumed during pregnancy. Vitamin B12 is distributed into breast milk. The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.		

[1]The product may contain aluminum which can accumulate in patients with renal dysfunction and premature infants. The product may contain benzyl alcohol dependent upon the manufacturer and should be avoided in premature infants.

CYCLOPHOSPHAMIDE*:*

	Common	Occasional	Rare
Immediate:	Loss of appetite (L), nausea (L), vomiting (L)	Metallic taste (L), abnormal hormone function affecting levels of salt in the blood and urine, causing too much or too little urine[1]	Temporary blurred vision[1], heart damage with abnormal heart rhythms[1], decay of muscle tissue in the heart[2]
Within 2-3 wks:	Decrease in the number of red and white blood cells and platelets made in the bone marrow, hair loss	Bleeding and inflammation of the urinary bladder (L)	
Delayed:	decreased ability of the body to fight infection or disease, absence of sperm or stopped monthly periods, inability to have children(L)		Damage/scarring of lung tissue [3] (L)
Late:			Cancer caused by treatment for a previous cancer or leukemia, damage/scarring of bladder tissue
Unknown Timing and Frequency: Abnormalities in unborn and breast-fed children			

-
- ***[1] Less common with lower doses.***
- ***[2]Only with very high doses.***
- ***[3] Risk increased in someone who has had chest radiation.***

CYCLOSERINE

Brand Name(s): **Seromycin**

Adverse Effects

Serious:

- **Neurologic:** Seizure

Common:

- **Neurologic:** Confusion, Dizziness, Headache, Somnolence

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause confusion, dizziness, headache, somnolence, or seizure.
- Instruct patient to report depression, suicidal ideation, or unusual changes in behavior.
- Advise patients receiving daily doses greater than 500 mg to monitor for and report signs/symptoms of CNS toxicity.
- Patient should not drink alcohol while taking this drug.

Contraindications

- hypersensitivity to cycloserine
- epilepsy (current or history of)
- depression, anxiety, psychosis (current or history of)
- severe renal insufficiency (creatinine clearance less than 50 mL/min)
- alcohol abuse

Precautions

- **None indicated**

CYCLOSPORIN

Brand Name(s): **Gengraf ; Neoral ; Restasis ; Sandimmune**

Adverse Effects

Serious:

- **Endocrine metabolic:** Hyperkalemia, Hypomagnesemia
- **Hepatic:** Hepatotoxicity (7% or less)
- **Immunologic:** Infectious disease
- **Neurologic:** Coma, Encephalopathy, Leukoencephalopathy, Seizure (1% to 5%)
- **Renal:** Hemolytic uremic syndrome, Nephrotoxicity (25% to 38%)

Common:

- **Cardiovascular:** Hypertension (13% to 53%)
- **Dermatologic:** Hirsutism (21% to 45%)
- **Gastrointestinal:** Drug-induced gingival hyperplasia (4% to 16%)
- **Neurologic:** Headache (2% to 15%), Tremor (12% to 55%)
- **Ophthalmic:** Burning sensation in eye (17%)

Patient Information

- Patient should not use ophthalmic preparation in an infected eye .
- Advise patient to avoid vaccines during therapy unless approved by a healthcare professional .
- To decrease the risk of skin malignancies, advise patient to avoid excessive exposure to ultraviolet light .
- Drug may cause hypertension, renal dysfunction, hirsutism, diarrhea, nausea, vomiting, headache, tremor, or gingival enlargement .
- The ophthalmic preparation may cause a foreign body or burning sensation in the eye .
- Instruct patient to report signs/symptoms of transplant rejection or infection .
- Advise patient to report signs/symptoms of hepatotoxicity or encephalopathy, especially patients receiving high-dose therapy .
- Instruct patients to report signs/symptoms of nephrotoxicity, especially when on concomitant nephrotoxic drugs .
- Patients using the ophthalmic preparation should report visual disturbances, conjunctival hyperemia, eye pain, or discharge from eye .
- Patient should allow at least 5 minutes between instillation of this drug and other ophthalmic products .
- Warn patient that rinsing the oral solution syringe with water either before or after use will cause a variation in dose and should be avoided .
- Tell patient to remove contact lenses prior to instilling ophthalmic formulation. Lenses may be reinserted 15 minutes following instillation .
- Patient should not eat grapefruit or drink grapefruit juice while taking this drug .
- Patient should avoid concomitant potassium-sparing drugs, potassium supplements, and foods/salt substitutes that are high in potassium .
- Tell patient that there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs) .

Contraindications

- hypersensitivity to cyclosporine or any of ingredient in the formulation of the product including polyoxyethylated castor oil (Cremophor(R) EL) in Sandimmune(R) injection
- ocular infections, active (ophthalmic emulsion)

Precautions

- multiple immunosuppressant treatment regimens; increased risk for lymphomas, malignancies, some fatal, and/or infections
- bioequivalence, Sandimmune(R) and Neoral(R) are NOT bioequivalent; monitoring during conversion recommended
- concomitant use with nephrotoxic drugs; increased risk of renal dysfunction
- concomitant use with potassium sparing diuretics should be avoided
- concomitant use with PUVA, UVB or other radiation therapy should be avoided
- encephalopathy, (eg, impaired consciousness, convulsions, visual disturbances, motor function loss, movement disorders, psychiatric disturbances); has been reported; most cases reversible upon dose reduction or discontinuation
- high dose cyclosporine; increased risk of hepatotoxicity and nephrotoxicity
- hyperkalemia, significant, sometimes associated with hyperchloremic metabolic acidosis; has been reported
- hyperuricemia, significant; has been reported
- hypertension; common effect that may require antihypertensive therapy and/or dose reduction
- malabsorption conditions; risk of inadequate therapeutic levels with cyclosporine capsules or oral suspension
- nephrotoxicity, mild, severe, chronic progressive cyclosporine-associated; has been reported
- opportunistic infections (eg, activation of latent viral infections); increased risk associated with immunosuppression; BK-virus associated nephropathy may lead to renal allograft loss; monitoring and dose adjustment recommended
- optic disc edema, including papilloedema, with possible visual impairment secondary to intracranial hypertension; has been reported
- radiation therapy; excessive immunosuppression possible and subsequent risk of malignancies
- seizure, particularly with concomitant high-dose methylprednisolone; has been reported
- serious infections; increased risk of; fatalities have been reported
- vaccination; may be less effective; avoid use of live attenuated vaccines during cyclosporine therapy

CYPROHEPTADINE HYDROCHLORIDE

Brand Name(s): **Periactin**

Adverse Effects

Serious:

- **Hepatic:** Hepatitis

Common:

- **Endocrine metabolic:** Increased appetite, Weight gain
- **Gastrointestinal:** Abdominal discomfort, Diarrhea, Nausea, Vomiting, Xerostomia
- **Neurologic:** Central nervous system depression, Somnolence
- **Respiratory:** Thick sputum, Bronchial

Patient Information

- Patient should avoid activities requiring mental alertness until drug effects are realized, as drug may cause somnolence.
- This drug may cause increased appetite, weight gain, abdominal discomfort, nausea, xerostomia, diarrhea, vomiting, or thickened bronchial sputum.
- Advise patient to take with food to minimize gastric irritation.
- Patient should avoid concomitant use of alcohol or other CNS depressants during therapy.
- Tell patient to not take concurrent MAO inhibitors, as this may intensify anticholinergic effects.

Contraindications

- angle-closure glaucoma
- elderly, debilitated patients
- hypersensitivity to cyproheptadine products
- MAOI therapy
- newborn or premature infants
- nursing mothers
- stenosing peptic ulcer, pyloroduodenal obstruction
- symptomatic prostatic hypertrophy, bladder neck obstruction

Precautions

- avoid use during activities which require mental alertness
- avoid use with alcohol and other central nervous system depressants
- cardiovascular disease
- elderly are more susceptible
- history of bronchial asthma
- hypertension
- hyperthyroidism
- increased intraocular pressure

may cause drowsiness in adults and excitation in children

Cytarabine

Risks and side effects related to cytarabine include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Hair loss
• Mouth sores
• Loss of desire to eat
• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
  ○ Redness, pain and inflammation of the eye with higher doses
	• Rash
	• Severe rash with redness and pain on the palms of the hand and soles of the feet
	• Flu type symptoms with fever, tiredness, aches and pains
	• Diarrhea
	• Low levels of certain salts in the body like potassium and calcium
	• Difficulty emptying the bladder
	• High levels of uric acid in the blood which could damage the kidneys
	• With higher doses of cytarabine fluid may accumulate in the lungs making it difficult to breathe
		• Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure)
		• A syndrome called Ara-C syndrome where there is fever, aches, pains, sometimes chest pain, a rash and inflammation of the eye
		• With higher doses of cytarabine there can be effects on the brain which can lead to headaches, incoordination of the muscles when walking, rapid jerky eye movements, difficulty with speech, sleepiness, personality changes, coma
		• With higher does of cytarabine there can be effects on the heart which can lead to chest pain and damage to the heart muscle
		• Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger.
		• Kidney Damage
		• Muscle breakdown which can lead to injury to the kidneys and other organs

Dantrolene

Common	Serious
Lightheadedness Constipation Diarrhea Asthenia Dizziness Headache Somnolence Diplopia Visual disturbance Fatigue Malaise Sun-sensitivity	Abnormal blood pressure Heart failure (infrequent) Phlebitis Tachyarrhythmia Aplastic anemia Leukopenia Malignant lymphoma (small lymphocytic) Thrombocytopenia (infrequent) Disease of liver (fatal and non-fatal)

- Drug causes sun-sensitivity. Advise patient to use sunscreen and avoid tanning beds.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause light-headedness, dizziness, or somnolence.
- This drug may cause constipation, diarrhea, asthenia, headache, diplopia, visual disturbance, fatigue, or malaise.
- Instruct patient to report any difficulties with swallowing.

Dasatinib

Likely:

- Low platelet count which may lead to bleeding or bruising
- Diarrhea

Less Likely:

- *Low Blood Counts:* low red blood cell count may make you feel tired; low white blood cell count increases the risk of infection, fever or pneumonia.
- *Skin-related:* reddening of the face with feelings of warmth; itching; rash with peeling of the skin.
- *Stomach/Intestine-related:* loss of appetite; excessive gas in the intestines; nausea; vomiting; bloating; loss of water from the body; stomach pain
- *General:* infection; headache; tingling, burning, or prickling sensation; fatigue; fever
- *Laboratory test-related:* abnormal liver function; temporary increase in the blood of creatinine which may indicate kidney damage

- *Risk of Bleeding:* there is a risk of bleeding which may be life-threatening. Specifically, damage to the intestine may result in bleeding.

- *Fluid Retention:* fluid buildup in the lungs that can make you feel short of breath

Rare But Serious:

- Damage to the sac around the heart which can lead to a build-up of fluid around the heart which may be painful and affect the ability of the heart to work normally.

- *Tumor Lysis Syndrome:* very rapid death of cancer cells releases chemicals which may lead to reduced kidney function. Accumulation of these chemicals may harm muscle or nerve function.

Side effects reported by patients, but it is not certain yet if they are related to taking the drug Dasatinib:

- *Low Blood Counts:* decrease in the number of immune system cells; low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life threatening.

- *Heart-related:* a rapid heart rate of over 100 beats per minute; chest pain that may mean heart damage; irregular heartbeat; problems with the electrical system of the heart; high blood pressure

- *General:* inability to sleep; rigors/chills; changes in your weight

- *Skin-related:* an allergic reaction in the blood vessels of the skin which turn the skin red, inflamed and bumpy and which may lead to skin breakdown; acne; changes in your nails; open sores on the skin; hives; puffiness or swelling around the eyes

- *Stomach/Intestine-related:* constipation; dry mouth; inflammation of the small intestine; difficulty or discomfort in swallowing; ulcer in the small intestine; heartburn; painful mouth sores

- *Fluid Retention:* excess buildup of fluids in body tissues; usually the tissues of the head, neck, buttocks, and genital areas

- *Laboratory test-related:* high levels of enzymes in the blood which could affect liver, kidney, and heart functions; decrease in the level of magnesium in the blood.

- *Muscle/Joint-related:* stiffness of the neck, pain in the muscles and bones; pain throughout the body; back pain; pain in the arms and legs.

- *Nervous system-related:* anxiety; depression; dizziness; seizure; damage to a nerve of the brain which may affect hearing and balance; a feeling of sleepiness, an inability to stay awake or aware or be aroused by someone else.

- *Breathing-related:* shortness of breath; buildup of fluid in the lungs which can also make you feel short of breath.

- *Kidney-related:* damage to the kidney that may be serious and life-threatening; increased need to urinate

- *Vein-related:* inflammation of a vein; problems with blood clotting which may be life-threatening.

Daunorubicin

Risks and side effects related to the daunorubicin include:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, sclerosis of the vein	Diarrhea, anorexia, abdominal pain, extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, rash, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis),hepatotoxicity	Radiation recall reactions, myocarditis-pericarditis syndrome, conjunctivitis and lacrimation
Delayed: Any time later during therapy			Cardiomyopathy1 (uncommon at cumulative doses ≤ 550 mg/m², 400 mg/m² with mediastinal radiation, 300 mg/m² in children, or 10 mg/kg in children < 2 yrs or 0.5 m²) (L), hyper-pigmentation of nail beds
Late: Any time after completion of treatment		Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients), secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of daunorubicin have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

Decitabine

While on the study, you are at risk for side effects (see table below). You should discuss these with your child's doctor. If you experience any side effects you may be given other medications to make them less serious or uncomfortable. We believe that most side effects will go away shortly after treatment with decitabine is stopped, but in some cases side effects may be serious, long lasting or permanent. There may also be other side effects that we cannot predict. There is also a small, but real possibility that life-threatening complications, death, or a second cancer may occur.

Known risks and side effects related to the decitabine include:

	Common (21-100% Frequency)	Occasional (5-20% Frequency)	Rare (< 5% Frequency)
Immediate: Within 1-2 days of receiving drug		Fever with a low white blood cell count making you more susceptible to infection (potentially life-threatening), nausea, and vomiting.	Allergic reactions, which appear as a rash and bumps. Tiredness, peritonitis (inflammation in the lining of your abdomen, poor appetite, difficulty staying awake, increased chance of liver damage, stomach pain or cramping, and diarrhea.
Prompt: Within 2-3 weeks, prior to next course.	Anemia* (making you weak and tired), low white blood cell count which increases your risk for infection and low platelet count* which may cause bruising or bleeding	Soreness, and sores in mouth or throat.	Kidney or liver damage
Delayed: Anytime after above.	Anemia* (making you weak and tired), low white blood cell count which increases your risk for infection and low platelet count* which may cause bruising or bleeding		Hair loss.
Late: Anytime after completion of treatment			
Unknown Timing and Frequency			

*Patients who develop anemia or low platelet counts may require red blood cell or platelet transfusions and as a result transfusion of blood and/or blood components may be necessary. Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

Other toxicities that may or may not be related to decitabine have been reported in adult patients.

These include: allergy, irregular heart beats, blood clots, swelling of veins, decreased blood flow to heart, face swelling, low blood pressure, heart attacks, veno-occlusive disease (blood vessels that carry blood through the liver become swollen or clogged), build up of fluid in the stomach, heart failure, fever, chills, weight loss, skin rash, itching, inability to taste, constipation, inflammation of the gallbladder, blood in the urine, liver failure, increased alkaline phosphatase, reactivation of an
infection caused by the herpes virus, low levels of salts in the blood, weakness or pain due to nerve injury, depression, dizziness, headache, lightheadedness, restlessness, sleep disorder, seizures, paralysis of arm/leg on the same side of the body, muscle pain, bone pain, shortness of breath, hiccups, fluid in the lungs, difficulty in breathing caused by a collapse of a lung, cough, painful urination, kidney failure, and decreased blood flow to brain, or flow of blood to the lungs.

If a person gets pregnant while receiving decitabine, it could be dangerous for the baby. You should not become pregnant or father a baby while on this study. You should not nurse (breast feed) a baby while on this study. Ask about counseling and more information about preventing pregnancy.

DEFEROXAMINE MESYLATE

Brand Name(s): **Desferal**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac complication, Hypotension, Shock, Tachyarrhythmia
- **Immunologic:** Immune hypersensitivity reaction (frequent)
- **Neurologic:** Ototoxicity (frequent)
- **Ophthalmic:** Eye / vision finding (frequent)
- **Other:** Mucormycosis (rare)

Common:

- **Dermatologic:** Injection site pain

Patient Information

- Warn patient that drug may cause a reddish discoloration of the urine.
- If dizziness or vision or hearing impairment are experienced, advise patient to avoid driving or performing other hazardous tasks.
- Instruct patient to report signs/symptoms of hypotension or tachyarrhythmia.
- Patient should not use vitamin C concurrently, unless approved by healthcare professional.

Contraindications

- anuria
- hypersensitivity to deferoxamine mesylate
- renal disease, severe

Precautions

- aluminum overload, comorbid; may result in decreased serum calcium and aggravation of hyperparathyroidism

- dialysis and comorbid aluminum-related encephalopathy; may cause neurological dysfunction (seizures) or dialysis dementia
- ferritin levels, low; ocular disturbances (blurry vision; cataracts in chronic iron overload; decreased visual acuity; impaired peripheral, color, and night vision; optic neuritis, cataracts, corneal opacities, and retinal pigmentary abnormalities) and auditory disturbances (tinnitus and hearing loss including high frequency sensorineural hearing loss), reversible in most cases, have been reported; monitoring recommended
- geriatric patients; may have an increased risk of ocular and auditory disturbances, including deafness and hearing loss; dose adjustment recommended
- high-dose therapy; ocular (blurry vision; cataracts in chronic iron overload; decreased visual acuity; impaired peripheral, color, and night vision; optic neuritis, cataracts, corneal opacities, and retinal pigmentary abnormalities) and auditory disturbances (tinnitus and hearing loss including high frequency sensorineural hearing loss), reversible in most cases, have been reported; monitoring recommended
- increased susceptibility to Yersinia enterocolitica, Yersinia pseudotuberculosis; drug discontinuation recommended
- IV administration; excessively high doses has resulted in respiratory distress syndrome; rapid injection has resulted in urticaria, hypotension, and shock; use proper administration
- mucormycosis, including fatalities have been reported; if suspected discontinue therapy and institute medical management
- pediatric patients; high doses and concomitant low ferritin levels have been associated with growth retardation; monitoring recommended
- prolonged use; ocular (blurry vision; cataracts in chronic iron overload; decreased visual acuity; impaired peripheral, color, and night vision; optic neuritis, cataracts, corneal opacities, and retinal pigmentary abnormalities) and auditory disturbances (tinnitus and hearing loss including high frequency sensorineural hearing loss), reversible in most cases, have been reported; monitoring recommended
- renal toxicity, including increases in serum creatinine (possibly dose-related), acute renal failure, and renal tubular disorders, has been reported; monitoring recommended
- scintigraphy with gallium-67; imaging may be distorted; discontinue deferoxamine 48 hours prior to procedure is recommended

Deferoxamine

Common	Serious
Injection site pain Abdominal discomfort Vomiting diarrhea	Cardiac complication Hypotension Shock Tachyarrhythmia Immune hypersensitivity reaction (frequent) Ototoxicity (frequent) Eye/vision changes (frequent) Mucormycosis (rare) Rash (rare) Seizure (rare Renal failure (rare) Acute respiratory distress (rare)

- Warn patient that drug may cause a reddish discoloration of the urine.
- If dizziness or vision or hearing impairment are experienced, advise patient to avoid driving or performing other hazardous tasks.

- Instruct patient to report signs/symptoms of hypotension or tachyarrhythmia.
- Patient should not use vitamin C concurrently, unless approved by healthcare professional.

Demecolcine Sodium

Common	Serious
Application site reaction (gel: all reactions, 7%; dermatitis, 4% to 11%) Blood coagulation disorder (1% to 10%) Burning sensation in eye (15%) Keratitis (up to 28%) Lacrimation and lacrimal drainage – finding (up to 30%) Raised intraocular pressure (up to 15%)	Congestive heart failure Hypertension Myocardial infarction (rare) Thrombotic tendency observations Erythema multiforme (rare) Generalized exfoliative dermatitis (rare) Stevens-Johnson syndrome (rare) Toxic epidermal necrolysis (rare) Gastrointestinal hemorrhage Gastrointestinal perforation Gastrointestinal ulcer (1% to 10%) Inflammatory disorder of digestive tract Melena pancreatitis (rare) Agranulocytosis (rare) Aplastic anemia (rare) Hemolytic anemia (rare) Hepatic necrosis Liver failure (rare) Anaphylactoid reaction (rare) Cerebrovascular accident Meningitis (rare) Seizure (rare) Acute renal failure Papillary necrosis Angioedema (rare)

- Advise patient to avoid use in late pregnancy as drug may cause premature closure of ductus arteriosus.
- The topical formulation of this drug can cause sun-sensitivity. Advise patient to avoid exposure to sunlight and tanning beds.
- This drug may cause edema, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, dizziness, headache, bronchospasm, or tinnitus. The ophthalmic formulation may also cause a burning sensation, conjunctivitis, corneal deposit/opacity/edema, or discharge from eye. The topical formulation may also cause application site skin reactions.
- Advise patient to report signs/symptoms of serious cardiovascular thrombotic events such as myocardial infarction or stroke.
- Instruct patient to report signs/symptoms of serious gastrointestinal adverse events such as bleeding, ulceration, and perforation of stomach or intestines.
- Instruct patient to report signs/symptoms of hepatotoxicity (nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms).
- Patient should promptly report skin rash, blistering, or any symptoms of a serious skin reaction.

- Patient should take tablet with a full glass of water, food, or milk to minimize gastric irritation.
- Instruct patient on proper instillation technique of ophthalmic formulation.
- Tell patient using ophthalmic form to avoid wearing soft contact lenses during drug therapy.
- Instruct patient using topical form to avoid applying this drug to open wounds, infections, or inflamed areas and to avoid contact of this drug with eyes and mucous membranes
- Patient should avoid showering, bathing or washing any area where drug is applied, including treated hands, for at least one hour after topical application of this drug.
- Patient should not use occlusive dressing or external heat over areas treated with the topical formulation.
- Patient should not drink alcohol while taking oral form of this drug.
- Tell patient to avoid use of additional NSAIDs during therapy, unless approved by healthcare professional.
- Patient using ophthalmic form should not use other ophthalmic medications, unless approved by healthcare professional.
- Advise patient to avoid concomitant use of the topical form of this drug with other topical products, including sunscreens, cosmetics, lotions, moisturizers and insect repellants.

DEXTROMETHORPHAN HYDROBROMIDE

Brand Name(s): **Delsym**

Adverse Effects

Serious:

- **None indicated**

Common:

- **Neurologic:** Dizziness (mild), Somnolence (mild)
- **Other:** Fatigue (mild)

Patient Information

- Instruct patient to report use of a MAO inhibitor within the last 14 days prior to initiating therapy.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause dizziness, somnolence, or fatigue.

Contraindications

- hypersensitivity to dextromethorphan or levorphanol
- Coadministration with monoamine oxidase inhibitors

Precautions

- Not to be used for chronic, persistent cough accompanying a disease state or for cough associated with excessive secretions
- Cough accompanied by other symptoms (fever, rash, headache, nausea, vomiting) to be treated with DEXTROMETHORPHAN only under medical supervision

DIAZOXIDE

Brand Name(s): **Hyperstat ; Proglycem**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac arrest, Congestive heart failure
- **Endocrine metabolic:** Diabetic ketoacidosis
- **Gastrointestinal:** Bowel obstruction, Pancreatitis
- **Hematologic:** Thrombocytopenia
- **Ophthalmic:** Optic nerve infarction

Common:

- **Cardiovascular:** Hypotension (7%)
- **Endocrine metabolic:** Hyperglycemia
- **Gastrointestinal:** Nausea and vomiting (4%)
- **Neurologic:** Asthenia, Dizziness (2%)

Patient Information

- Instruct patient to rise slowly from a sitting/supine position, especially if patient is taking concurrent diuretics.
- This drug may cause angina, palpitations, tachyarrhythmia, hirsutism, abdominal pain, constipation, diarrhea, loss of appetite, loss of taste, nausea, vomiting, and dizziness.
- Drug may also cause serious adverse effects such as congestive heart failure, bowel obstruction, or extrapyramidal disease.
- Tell patient to report signs/symptoms of hyperglycemia, infection, unusual bleeding/bruising, or fluid retention.
- Advise diabetic patients to regularly monitor urine for sugar and ketones and to immediately report abnormal findings.
- If injectable formulation is used, advise patient to report signs/symptoms of extravasation immediately.
- Patient should remain supine for at least 1 h after IV injection, as drug may cause hypotension.

Contraindications

- functional hypoglycemia
- hypersensitivity to diazoxide or to other thiazides

Precautions

- cardiac reserve, compromised; risk of congestive heart failure
- concomitant use of coumarin (or its derivatives), diphenylhydantoin, or thiazides (or other diuretics); use with caution
- gout, history
- hyperuricemia
- ketoacidosis and nonketotic hyperosmolar coma have been reported
- newborns with increased bilirubinemia; diazoxide may displace bilirubin from albumin
- prolonged treatment; regular monitoring of urine for sugar and ketones is required
- renal function, impaired; risk of drug toxicity

Dexamethasone

Risks and side effects related to dexamethasone include those which are:

Likely	Less Likely	Rare But Serious
• Overeating • Difficulty sleeping or falling asleep • Decreased ability of the body to fight infection • Personality changes with mood swings • Changes in hormone production that cause weight gain especially around the abdomen and shoulders, puffy cheeks, muscle weakness and make your body less able to deal with stress • Pimples	• Damage to the joints which can result in pain and loss of motion usually involving the joints of the hip and knee* • Red face • Fluid retention • Wounds don't heal as well • Slowed growth • Upset and irritated stomach with heartburn • Stomach ulcers • High blood sugar which may require treatment • Stretch marks and easy bruising of the skin • Abnormal amounts of uric acid in the blood • Increased pressure in the eyes • High blood pressure • Lessening of calcium in the bones making them more susceptible to fracture • Cataracts which are usually more reversible in children • Headache • Dizziness • Kidney stones that may cause back, stomach or pelvic pain and /or may lead to the appearance of blood in the urine	• Inflammation of the pancreas • Stomach and intestinal tract bleeding from ulcers • Infections • Increased pressure in the brain which can lead to difficulty seeing, pressure in the eyes and headache • Bone fractures • Serious changes in mood, personality and/or severe depression

* This effect happens less often in patients less than 10 years of age.

Steroid drugs, such as dexamethasone (and less frequently prednisone), are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. ON can cause pain and if severe, the patient may need to have surgery. The exact reason why corticosteroids cause ON is not known.

DICLOXACILLIN SODIUM

Brand Name(s): **Dycill ; Dynapen ; Pathocil**

Adverse Effects

Serious:

- **Gastrointestinal:** Hemorrhagic colitis
- **Hepatic:** Hepatotoxicity
- **Immunologic:** Anaphylaxis (0.015% to 0.04%)
- **Renal:** Nephrotoxicity

Common:

- **Gastrointestinal:** Diarrhea, Nausea, Vomiting

Patient Information

- Drug may cause nausea, vomiting, diarrhea, stomatitis, or black tongue.
- Patient should take drug 1 h before or 2 h after meals.

Contraindications

- hypersensitivity to penicillins

Precautions

- hypersensitivity to cephalosporins

DILTIAZEM HYDROCHLORIDE

Brand Name(s): **Cardizem ; Cartia ; Dilacor ; Tiazac ; Taztia**

Adverse Effects

Serious:

- **Cardiovascular:** Congestive heart failure (less than 2%), Heart block, Myocardial infarction
- **Hepatic:** Hepatotoxicity

Common:

- **Cardiovascular:** Bradyarrhythmia (1.7% to 3.6%), Peripheral edema (4.6% to 8%)
- **Neurologic:** Dizziness (3.5% to 6.4%), Headache (4.6%)
- **Respiratory:** Cough (2%)
- **Other:** Fatigue (4.8%)

Patient Information

- Patient should avoid activities requiring coordination until drug effects are realized, as drug may cause dizziness.
- This drug may cause gingival hyperplasia, headache, or dermatologic reactions such as exfoliative dermatitis (reddened skin, skin peeling/flaking) or erythema multiforme (flu-like symptoms, spreading red rash, may progress to more severe form with blistering).
- Instruct patient to report symptomatic hypotension, bradyarrhythmia, peripheral edema, or syncope.
- Advise patient against sudden discontinuation of drug.
- This drug is available in multiple brand names with varying properties by brand. Instruct patient to follow administration instructions specific to the prescribed brand with regards to meals and timing.
- Patient should avoid concomitant use of beta-blockers or digitalis during drug therapy, unless otherwise directed by healthcare professional.
- Patient should not drink alcohol while taking this drug.

Contraindications

- acute MI with pulmonary congestion on x-ray (Oral only)
- administration of IV beta-blockers within a few hours of IV diltiazem

- atrial fibrillation or flutter associated with an accessory bypass tract (Wolff-Parkinson-White or short PR syndromes); risk of potentially fatal heart rate fluctuations (IV only)
- cardiogenic shock (IV only)
- heart block, second or third-degree atrioventricular without a functioning ventricular pacemaker
- hypersensitivity to diltiazem
- hypotension, symptomatic (90 mmHg or less systolic)
- newborns; some injections contain benzyl alcohol (IV only)
- sick sinus syndrome without a functioning ventricular pacemaker
- ventricular tachycardia; may lead to hemodynamic deterioration and ventricular fibrillation (IV only)

Precautions

- coadministration with other drugs known to decrease peripheral resistance, intravascular volume, or myocardial contractility or conduction (IV only)
- concomitant use of beta blockers or digitalis; additive effect on heart rate (Oral only)
- dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported
- hepatic impairment; increased risk of toxicity
- hypotension
- renal impairment; increased risk of toxicity
- supraventricular arrhythmias with hemodynamic compromise (IV only)
- ventricular function, impaired; worsening congestive heart failure has been reported

DIPHENHYDRAMINE HYDROCHLORIDE

Brand Name(s): **Antitussive ; Beldin ; Belix ; Benadryl ; Benylin ; Dibenil ; Diphen ; Hydramine ; Silphen ; Vicks Formula 44**

Adverse Effects

Serious:

- **Immunologic:** Anaphylaxis

Common:

- **Gastrointestinal:** Xerostomia
- **Neurologic:** Dizziness, Dyskinesia, Sedated
- **Psychiatric:** Somnolence
- **Respiratory:** Nasal mucosa dry, Pharyngeal dryness, Thick sputum, Bronchial

Patient Information

- Young children may experience a paradoxical excitation effect.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause drowsiness.
- This drug may cause anticholinergic effects. Elderly patients may be more susceptible to these effects.
- Patient should not use topical form on eyes or eyelid.
- Instruct patient to avoid applying occlusive dressings, cosmetics, or other skin products over areas treated with topical formulation.
- Patient should avoid concomitant use of MAO inhibitors or CNS depressants.

- Patient should not drink alcohol while taking this drug.

Contraindications

- hypersensitivity to diphenhydramine
- newborns or premature infants
- nursing mothers

Precautions

- bladder neck obstruction
- concurrent MAOI therapy
- concurrent use of central nervous system depressants
- decreases mental alertness and psychomotor performance
- do not use topical form on eyes or eye lids
- elderly are more susceptible to the side effects of diphenhydramine
- history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension
- may cause excitation in young children
- narrow angle glaucoma
- pyloroduodenal obstruction
- stenosing peptic ulcer
- symptomatic prostatic hypertrophy
- use of the topical form on patients with chicken pox, measles, blisters, or large areas of skin unless directed by a physician

DIPYRIDAMOLE

Brand Name(s): **Persantine**

Adverse Effects

Serious:

- **Cardiovascular:** Angina, Exacerbation with IV (19.7%), Myocardial infarction (rare), Ventricular arrhythmia (rare)
- **Respiratory:** Bronchospasm (rare)

Common:

- **Cardiovascular:** Electrocardiogram abnormal (15.9%), Hypotension, IV (4.6%)
- **Gastrointestinal:** Abdominal discomfort, Oral (6.1%), Nausea, IV (4.6%)
- **Neurologic:** Dizziness (12%), Headache, IV (12.2%), Headache, Oral (2.3%)

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause abdominal discomfort or dizziness. The IV formulation may also cause headache or an exacerbation of angina.
- Advise patient to take oral formulation on an empty stomach 1 h before or 2 h after meals. If gastric irritation occurs, tell patient to take drug with food or milk.
- Patient should avoid caffeine prior to cardiac stress testing.

Contraindications

- hypersensitivity to dipyridamole or any other product component

Precautions

- anaphylactoid reactions have been reported (IV)
- asthma, history; may be at increased risk for bronchospasm; IV aminophylline may be administered (IV)
- cardiac impulse abnormalities; may be at increased risk for asystole, sinus node arrest, sinus node depression, and conduction block (IV)
- asystole, sinus node arrest, sinus node depression, and conduction block have been reported; risk may be increased with cardiac impulse formation/conduction abnormalities or severe coronary artery disease (IV)
- bronchospasm has been reported (IV)
- cardiovascular events, serious and some fatal (including cardiac death, myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia), have been reported (IV)
- chest pain, severe; monitoring recommended; IV aminophylline and SL nitroglycerin may be needed (IV)
- coronary artery disease (unstable angina or recently sustained myocardial infarction), severe; chest pain may be aggravated due to vasodilatory effect of dipyridamole (oral) ; may also be at increased risk for asystole, sinus node arrest, sinus node depression, and conduction block (IV)
- hepatic insufficiency; hepatic enzyme elevations and hepatic failure have been reported (oral)
- hypotension; may produce peripheral vasodilation (oral)
- seizures have been reported (IV)
- unstable angina, history; may be at greater risk for severe myocardial ischemia (IV)

DISOPYRAMIDE PHOSPHATE

Brand Name(s): **Norpace**

Adverse Effects

Serious:

- **Cardiovascular:** Congestive heart failure, Heart block, Hypotension, Prolonged QT interval, Torsades de pointes
- **Endocrine metabolic:** Hypoglycemia (rare)
- **Hematologic:** Agranulocytosis (rare), Thrombocytopenia (rare)
- **Hepatic:** Hepatotoxicity (rare)

Common:

- **Cardiovascular:** Negative inotropic effect on myocardium
- **Gastrointestinal:** Constipation (11%), Nausea (3% to 9%), Xerostomia (32%)
- **Musculoskeletal:** Muscle weakness
- **Ophthalmic:** Blurred vision (3% to 9%)
- **Renal:** Delay when starting to pass urine (14% to 23%), Urinary retention (3% to 9%)
- **Other:** Generalized aches and pains (3% to 9%), Malaise and fatigue (3% to 9%)

Patient Information

- Patient should avoid activities requiring coordination until drug effects are realized.
- Instruct patient to rise slowly from a sitting/supine position to minimize dizziness.
- This drug may cause anticholinergic effects, especially xerostomia, urinary hesitancy, and constipation.
- Instruct patient to report signs/symptoms of cardiac failure or dysrhythmia.
- Tell patient to report worsening depression, hallucinations, or unusual changes in behavior.
- Advise patient against sudden discontinuation of drug.
- Tell patient to not drink alcohol while taking this drug.
- Patient should not take this drug within 48 h before or 24 h after verapamil administration.

Contraindications

- cardiogenic shock
- congenital QT prolongation
- hypersensitivity to disopyramide
- second or third degree AV block

Precautions

- congestive heart failure
- digitalization to be used in patients with atrial fibrillation or flutter prior to disopyramide
- dosage reductions or withdrawal if heart block develops
- ECG abnormalities (ie, QRS widening /QT/QTc prolongation)
- electrolyte abnormalities (ie, hypokalemia/hyperkalemia)
- geriatrics
- glaucoma
- hypoglycemia
- liver disease
- myasthenia gravis

- renal impairment
- sick sinus syndrome/ Wolff-Parkinson-White syndrome/bundle branch block
- urinary retention (including benign prostatic hypertrophy)

DOCETAXEL

Brand Name(s): **Taxotere**

Adverse Effects

Serious:

- **Cardiovascular:** Edema (Severe) (6.5% to 8.9%)
- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Gastrointestinal:** Colitis
- **Hematologic:** Anemia, less than 8 g/dL (4.3% to 9.2%), Febrile neutropenia (5.2% to 24.7%), Leukopenia, less than 1000 cells/mm(3) (31.6% to 43.7%), Neutropenia, less than 500 cells/mm(3) (65.5% to 85.9%), Thrombocytopenia (8% to 9.2%)
- **Hepatic:** Hepatotoxicity
- **Immunologic:** Anaphylaxis (rare)
- **Renal:** Renal failure
- **Respiratory:** Interstitial pneumonia, Pulmonary embolism
- **Other:** Infectious disease (21.6% to 39.4%)

Common:

- **Cardiovascular:** Edema (47% to 64.1%), Vasodilatation (27%)
- **Dermatologic:** Alopecia (56.3% to 97.8%), Disorder of nail (11.4% to 18.5%), Disorder of skin AND/OR subcutaneous tissue, Nail changes (8.1% to 30.6%), Pruritus, Rash
- **Gastrointestinal:** Diarrhea (32.8% to 42.6%), Nausea (38.8% to 80.5%), Stomatitis (41.7% to 69.4%), Vomiting (22.3% to 44.5%)
- **Hematologic:** Anemia (89.1% to 93.6%), Leukopenia (95.6% to 98.6%), Neutropenia (71.4% to 99.5%)
- **Neurologic:** Asthenia (61.8% to 80.8%), Neuropathy
- **Reproductive:** Amenorrhea (61.7%)
- **Other:** Fever of unknown origin (31.2% to 46.5%)

Patient Information

- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- This drug may cause edema, alopecia, diarrhea, nausea, stomatitis, vomiting, asthenia, fever, or colitis.
- Elderly patients have an increased risk of adverse events.
- Instruct patient to report severe edema or signs/symptoms of myelosuppression, hepatotoxicity, or neuropathy (paresthesia, dysesthesia, pain).
- Advise patient to report signs/symptoms of cutaneous toxicity such as Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering) or toxic epidermal necrolysis (widespread peeling/blistering of skin).

Contraindications

- neutrophil count less than 1500 cells/mm(3)
- severe hypersensitivity to docetaxel or any other drugs formulated with polysorbate 80

Precautions

- fluid retention (eg, peripheral edema, generalized edema, pleural effusion, ascites) has occurred; pretreatment with oral corticosteroids recommended prior to each dose
- hepatic impairment; increased risk of severe or life-threatening toxicities; do not use in patients in patients with a bilirubin level greater than the ULN or SGOT and/or SGPT levels greater than 1.5 x ULN concomitant with an alkaline phosphatase (AP) level greater than 2.5 x ULN; monitor LFTs prior to each treatment cycle; dosage adjustment recommended for LFT elevations during treatment; discontinue treatment in patients who develop AST/ALT levels greater than 5 x ULN and/or AP level greater than 5 x ULN
- hypersensitivity reactions, some cases severe (eg, generalized rash/erythema, hypotension, bronchospasm, fatal anaphylaxis), have been reported despite the recommended 3 days of corticosteroids premedication
- severe (grade 4) neutropenia has been reported, with some cases associated with infection; monitor blood cell counts frequently and for signs of febrile neutropenia or neutropenic infections; dose reduction or therapy discontinuation may be warranted; do not retreat with subsequent cycles until the neutrophil count is greater than 1500 cells/mm(3)
- treatment-related mortality has been reported; increased risk in patients with abnormal liver function, receiving higher doses, and with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m(2)
- acute myeloid leukemia has been reported rarely in patients with breast cancer who received adjuvant therapy with docetaxel, doxorubicin, and cyclophosphamide; hematological follow-up recommended in this patient population
- concomitant use with CYP3A4 inhibitors should be avoided; if coadministration with a potent CYP3A4 inhibitor is necessary, closely monitor patients for toxicity and consider a docetaxel dosage adjustment
- cutaneous toxicity (eg, localized erythema of the extremities with edema followed by desquamation) has occurred; dose reduction or therapy discontinuation may be warranted if severe skin toxicity develops
- elderly patients (aged 65 yr or older); higher incidence of serious adverse events compared with younger patients
- severe neurosensory symptoms (eg, paresthesia, dysesthesia, pain) have been reported; dose reduction or therapy discontinuation may be warranted
- severe thrombocytopenia has occurred; monitor blood cell counts frequently; do not retreat with subsequent cycles until the platelet count is greater than 100,000 cells/mm(3)
- report suspected adverse events to Sanofi-Aventis US LLC at 1-800-633-1610 or the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

Donepezil Hydrochloride

Common	Serious
Hypertension (3%) Diarrhea Loss of appetite Nausea Vomiting Muscle cramps Insomnia	Atrioventricular block Torsades de pointes

Fatigue	

- This drug may cause diarrhea, loss of appetite, nausea, vomiting, muscle cramps, insomnia, or fatigue.
- Advise patient that adverse effects may be more frequent at dose escalation and tend to resolve with continued use.
- Instruct patient to report signs/symptoms of gastrointestinal bleeding, especially with concomitant NSAID use.
- Patient should take in the evening at bedtime.

Doxorubicin

Risks and side effects related to Doxorubicin include those which are:

Likely	Less Likely	Rare But Serious
• Nausea • Vomiting • Temporary hair loss • Pink or red color to urine, sweat, tears, saliva • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily • Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function	• Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores) • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid • Facial Flushing • Fever/chills • Hives • High levels of uric acid in the blood which could damage the kidneys • Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed. • Damage to the skin if the medication leaks from a vein • Thickening and hardening of the veins through which the medication is given • Reddening reaction of the vein through which the drug is given. • Elevation in the blood of certain enzymes found in the liver which may	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Ulceration of the lower intestinal tract • An irregular heart beat which can be life-threatening • Severe damage to the heart muscle which may lead to severe heart failure • A new cancer or leukemia resulting from this treatment.

	indicate liver irritation or damage. • Tearing and inflammation of the eyes • Loss of appetite • Redness and burning at sites which have received radiation in the past • Diarrhea	

The risk of heart damage may be greater in very young children than in older ones.

Doxycycline

Common	Serious
Light sensitivity Drug-induced gastrointestinal disturbance Serum blood urea nitrogen raised Loss of appetite Nausea Vomiting Diarrhea Esophagitis Glossitis Dysphagia enterocoliti	Bulding fontanelle (rare)

- Instruct patient to report severe diarrhea and consult healthcare professional prior to taking anti-diarrhea medicine.
- Drug causes sun-sensitivity. Advise patient to use sunscreen and avoid tanning beds.
- Drug may decrease effectiveness of oral contraceptives with concurrent use. Recommend additional form of birth control.
- This drug may cause a gastrointestinal disturbance.
- Advise patient to take drug with adequate fluid to prevent esophageal irritation or ulceration.
- Patient may take tablet and suspension with food, milk, or a carbonated beverage if gastric irritation occurs.

DROPERIDOL

Brand Name(s): **Inapsine**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac arrest, Prolonged QT interval, Torsades de pointes, Ventricular tachycardia
- **Immunologic:** Anaphylaxis
- **Neurologic:** Neuroleptic malignant syndrome (very rare)

Common:

- **Cardiovascular:** Hypotension, Tachycardia
- **Neurologic:** Somnolence, Postoperative
- **Psychiatric:** Anxiety, Dysphoric mood, Hyperactive behavior, Restlessness

Patient Information

- his drug may cause extrapyramidal effects, somnolence, anxiety, or dysphoric mood.
- Patient should report signs/symptoms of arrhythmias, hypotension, or respiratory depression.

Contraindications

- any use other than for the treatment of perioperative nausea and vomiting in patients for whom other treatments are ineffective or inappropriate
- hypersensitivity to droperidol
- QT interval prolongation (greater than 440 msec, males; greater than 450 msec, females), known or suspected, including patients with congenital long QT syndrome; serious or life-threatening arrhythmias may occur

Precautions

- QT prolongation, dose-dependent, and serious arrhythmias (eg, torsade de pointes, ventricular arrhythmias, cardiac arrest, and death) have been reported; risk factors include bradycardia (less than 50 beats/min), clinically significant cardiac disease, treatment with Class I and Class III antiarrhythmics, treatment with MAOIs, concomitant treatment with other drugs known to prolong the QT interval, and electrolyte imbalance (especially hypokalemia or hypomagnesemia) or concomitant treatment with drugs (eg, diuretics) that may cause electrolyte imbalance; monitoring recommended
- anesthesia, conduction (eg, spinal and some peridural); altered respiration or circulation or hypotension may occur
- concomitant use with potentially arrhythmogenic agents (eg, class I or III antiarrhythmics, antihistamines that prolong the QT interval, antimalarials, calcium channel blockers, neuroleptics that prolong the QT interval, and antidepressants); avoid use
- elderly, debilitated, or poor-risk patients, dose adjustment recommended
- electroencephalogram, patterns may be slow to return to normal
- hepatic impairment; risk of drug toxicity
- neuroleptic malignant syndrome (altered consciousness, muscle rigidity, and autonomic instability) has occurred rarely and may be difficult to differentiate from malignant hyperpyrexia; consider treating with dantrolene
- pheochromocytoma, diagnosed or suspected, severe hypertension and tachycardia have been reported
- pulmonary arterial pressure may decrease; use caution when interpreting results
- renal impairment; kidney is important in metabolizing and excreting drugs

ENALAPRIL MALEATE

Brand Name(s): **Vasotec**

Adverse Effects

Serious:

- **Gastrointestinal:** Intestinal angioedema
- **Hematologic:** Agranulocytosis
- **Hepatic:** Hepatotoxicity, Liver failure (rare)
- **Renal:** Acute renal failure (0.5% to 1%), Renal impairment
- **Other:** Angioedema (0.1% to 1%)

Common:

- **Cardiovascular:** Hypotension (0.9% to 6.7%)
- **Endocrine metabolic:** Hyperkalemia (1% to 3.8%)
- **Neurologic:** Dizziness (4.3% to 7.9%)
- **Renal:** Serum blood urea nitrogen raised (0.2% to 11%), Serum creatinine raised (0.2% to 11%)
- **Respiratory:** Cough (1% to 15%)
- **Other:** Fatigue (3%)

Patient Information

- Patient should avoid activities requiring coordination until drug effects are realized, as drug may cause dizziness.
- Instruct patient to rise slowly from a sitting/supine position.
- This drug may cause nausea, vomiting, or asthenia.
- Instruct patient to report signs/symptoms of hypotension or persistent cough.
- Tell patient to report signs/symptoms of angioedema (deep swelling around eyes and lips and sometimes hands and feet) or intestinal angioedema (abdominal pain).
- Advise patient to maintain adequate hydration during therapy.
- Patient should avoid use of potassium-sparing diuretics or potassium-containing supplements or salt substitutes, as this may cause increased potassium levels

Contraindications

- angioedema, hereditary or idiopathic
- angioedema related to prior therapy with an ACE inhibitor (history of)
- hypersensitivity to enalapril or enalaprilat, an active metabolite of enalapril

Precautions

- pregnancy, second and third trimesters; can cause fetal and neonatal morbidity and death; discontinue enalapril therapy
- anaphylaxis during lipid apheresis with dextran sulfate membranes and hemodialysis with high flux membranes has been reported
- angioedema, head and neck; has occurred; discontinue therapy
- angioedema (intestinal) has been reported; increased risk in patients with history of intestinal angioedema
- aortic stenosis/hypertrophic cardiomyopathy, history of; vasodilation
- cerebrovascular disease; history of; excessive hypotension may result in cerebrovascular accident
- CHF, history of; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death
- concomitant diuretic therapy, high dose; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death
- hepatic failure has occurred; discontinue therapy in patients who develop jaundice or have marked elevations in hepatic enzymes
- hyperkalemia has been reported; increased risk with renal disease, diabetes, and concomitant use of potassium supplements, potassium containing salt substitutes, and potassium-sparing diuretics
- hyponatremia, presence of; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death

- insect venom allergy, hymenoptera venom immunotherapy; may exacerbate the allergic response
- ischemic heart disease, history of; excessive hypotension may result in myocardial infarction
- renal dialysis therapy; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death
- renal impairment; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death
- renal impairment, especially in the presence of collagen vascular disease; agranulocytosis and neutropenia have occurred
- surgery/anesthesia; excessive hypotension has been reported
- volume and/or salt depletion (severe), presence of; risk for excessive hypotension sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death

Epirubicin

Common	Serious
Alopecia Rash Abnormal skin appearance Hot sweats Diarrhea Inflammatory disease of mucous membrane Nausea Vomiting Lethargy Amenorrhea Fever Infection Radiation recall syndrome	Abnormal ECT Cardiotoxicity Possibly fatal CHF Tissue necrosis (skin, local) Hyperuricemia Tumor lysis syndrome Acute myeloid leukemia (secondary) Myelosupperssion (possibly severe) Anaphylaxis Immune hypersensitivity reaction

- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- Warn patient that urine may have red-discoloration for 1 to 2 days after treatment.
- Patients with prior radiation therapy may experience an inflammatory recall reaction (inflamed skin at the old radiation sites when a new chemotherapy drug is administered).
- This drug may cause alopecia, hot flashes, diarrhea, inflamed mucous membranes, nausea, vomiting, lethargy, amenorrhea, or fever.
- Instruct patient to report signs/symptoms of extravasation immediately, as drug is caustic.
- Advise patient to report signs/symptoms of congestive heart failure, which may indicate cardiac toxicity.
- Patient should report signs/symptoms of myelosuppression, hepatic dysfunction, or renal dysfunction.
- Tell patient to maintain adequate hydration during drug therapy.

ERGOCALCIFEROL

Brand Name(s): **Drisdol**

Adverse Effects

Serious:

- **Endocrine metabolic:** Hypercalcemia, Hypervitaminosis D, Renal impairment, calcification of soft tissues, bone demineralization, growth retardation, nausea, constipation, mild acidosis, weight loss

Common:

- **None indicated**

Patient Information

- Patient should report signs/symptoms of hypercalcemia (nausea, vomiting, muscle weakness or tetany, increased thirst, confusion, abdominal pain).
- Maintain adequate dietary intake of calcium as instructed by healthcare professional.
- Patient should avoid additional supplemental sources of vitamin D, unless approved by healthcare professional.

Contraindications

- abnormal sensitivity to the toxic effects of vitamin D
- hypercalcemia
- hypervitaminosis D
- malabsorption syndrome

Precautions

- adequate dietary calcium; necessary for clinical response to vitamin D therapy
- evaluate vitamin D intake from fortified foods, dietary supplements, and self-administered and prescription drug sources
- hyperphosphatemia may occur; must maintain normal serum phosphorus levels by aluminum gel administration and/or dietary phosphate restriction to prevent metastatic calcification
- hypersensitivity to vitamin D, particularly in infants with idiopathic hypercalcemia
- hypoparathyroidism; dihydrotachysterol, intravenous calcium, and/or parathyroid hormone may be required during treatment
- tartrazine (FD&C Yellow No. 5) sensitivity; increased risk of allergic reactions including bronchial asthma in susceptible patients, especially in patients with concomitant aspirin sensitivity (Drisdol(R))
- vitamin D-resistant rickets; the range between therapeutic and toxic doses is narrow

Erlotinib (Tarceva/OSI-774)

We know about the following side effects of OSI-774:

	Common (happens in 21-100 patients out of 100)	Occasional (happens in 5-20 patients out of 100)	Rare (happens in less than 5 patients out of 100)
The timing of these side effects	Acne-like skin rash, diarrhea, nausea,	Dry skin, dry mouth, decreased	Peeling of the skin, hives and itching, elevation in liver function tests,

(how soon they happen after taking OSI-774) is not known.	**vomiting, tiredness, weariness, ill feeling**	**appetite, mouth sores, heartburn**	**redness/inflammation of the eye/damage to the cornea, dry eye, inward growth of eyelashes, tearing, kidney damage, headache, inflammation of the lungs, lung tissue changes and damage and scarring of lung tissues, blurry vision, allergic reaction, changes to taste, increase in bilirubin**

Allergic reactions may occur with any medicine.

Also reported on OSI-774 trials but with the relationship to OSI-774 unknown: low levels of red blood cells, low levels of white blood cells, increased numbers of white blood cells in the blood, low number of platelets in the blood which may increase the risk of bleeding, poor blood supply to an area of bone causing bone death, blockage of the pulmonary artery (1 case), a clot blocking a vein, shaking chills, fever, hair loss, sore throat, burning or painful sensation in the tongue, inflammation and cracking of the skin of the lips, constipation, abdominal pain or cramping, sores in the stomach, too much gas produced in the intestines, difficulty swallowing, decreased blood flow to the intestines, inflammation of the pancreas, blood in the urine, nose bleed, dark, bloody bowel movement, blood in sputum or spit, bleeding in the intestines, elevated liver enzyme levels, inflammation of the lungs, urinary tract infection, infection with or without decrease in a type of white blood cell called a neutrophil, low levels of potassium and sodium in the blood, dryness in the nose, runny nose, depression, anxiety, sleeplessness, a skin sensation, such as burning, prickling, itching, or tingling, with no apparent cause, dizziness, blockage of the blood vessels of the brain (1 case), back pain, cough, difficulty breathing, too much protein in the urine, kidney failure, inflammation of the lining of the uterus, confusion, dehydration and increased levels of urea in the blood which is likely directly related to diarrhea, changes in blood clotting in patients also taking Coumadin, inflammation of the cornea causing watery painful eyes and blurred vision, inflammation of the eye, inflammation of the pancreas, the presence of air or gas in abnormal places in the body, and secondary skin infection from rash.

If a person gets pregnant while receiving OSI-774, it could be dangerous for the baby. You should not become pregnant or father a baby while on this study. You should not nurse (breast feed) a baby while on this study. Ask about counseling and more information about preventing pregnancy. Women of child-bearing potential and males must agree to use an adequate form of birth control while on this protocol.

ERYTHROMYCIN

Brand Name(s): **Ak-mycin ; Akne-Mycin ; Eryc ; Erymax ; Erythrocin ; Robimycin ; Sansac ; Staticin ; T-Stat**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiac dysrhythmia, Prolonged QT interval, Torsades de pointes, Ventricular tachycardia
- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis due to drug
- **Gastrointestinal:** Clostridium difficile colitis, Pancreatitis
- **Hepatic:** Cholestatic hepatitis, Hepatitis
- **Immunologic:** Anaphylaxis
- **Neurologic:** Seizure
- **Otic:** Ototoxicity

- **Renal:** Interstitial nephritis

Common:

- **Gastrointestinal:** Diarrhea, Loss of appetite, Nausea, Stomach cramps, Vomiting

Patient Information

- This drug may cause loss of appetite, nausea, stomach cramps, or vomiting.
- Elderly patients are more susceptible to development of dysrhythmia and torsade de pointes.
- Elderly patients with renal or hepatic dysfunction are at increased risk of ototoxicity.
- Instruct patient to report severe diarrhea and consult healthcare professional prior to taking anti-diarrhea medicine.
- Elderly patients on concomitant anticoagulant therapy should monitor for signs/symptoms of bleeding, as drug may have additive effects.
- Patients with a history of myasthenia gravis should report signs/symptoms of disease exacerbation during therapy.
- Patients using the topical gel should avoid contact with eyes and all mucous membranes.
- Do not use with astemizole, cisapride, pimozide, terfenadine, or lovastatin

Contraindications

- concomitant therapy with astemizole, cisapride, dihydroergotamine, ergotamine, pimozide, or terfenadine
- hypersensitivity to erythromycin or any component of the product

Precautions

- concomitant therapy with colchicine; colchicine toxicity has been reported; potential to be life-threatening and may occur at recommended doses
- concomitant therapy with lovastatin; rhabdomyolysis, with or without renal impairment, has been reported in seriously ill patients; monitoring recommended
- early syphilis in pregnancy; oral erythromycin may not prevent congenital syphilis; administer appropriate penicillin regimen to infant born to woman treated with oral erythromycin for early syphilis
- elderly patients, especially with renal or hepatic dysfunction; increased risk of erythromycin-associated hearing loss
- elderly patients; increased susceptibility to torsades de pointes arrhythmias
- hepatotoxicity (eg, increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice) has been reported with use of oral erythromycin products
- impaired hepatic function; erythromycin primarily excreted by the liver
- infantile hypertrophic pyloric stenosis has been reported
- myasthenia gravis, exacerbation or new onset, has occurred
- superinfection; may occur as a result of overgrowth of nonsusceptible organisms; discontinue if superinfection occurs

Estradiol

Common	Serious
Edema (transdermal system, 0.5% to 13%) Application site irritation (transdermal spray, 1.3%; transdermal system, 5.7% to 56.7%) Chloasma Hirsutism Persistent erythema of skin (transdermal patch, 17%) Pruritus (topical emulsion, 4%; topical gel, 4.8%) Weight change Bloating symptom Nausea Vomiting Migraine Depression (transderamal system, 1% to 8%) Mood disturbance Breast tenderness (topical gel, 2.5% to 8.8%; transdermal spray, 5% to 7%; transdermal system, 6.5% to 17%) Menstruation disorder Leucorrhea Breast swelling Vaginal discomfort (vaginal cream, 5%; vaginal ring, 5%) Withdrawal bleeding	Heart disease Hypertension Myocardial infarction Body fluid retention Breast cancer Diabetes mellitus Hypercalcemia Gallbladder disorder Venous thromboembolism Anaphylaxis Cerebrovascular accident Dementia Impaired cognition Thrombosis of retinal vein Malignant neoplasm of endometrium of corpus uteri Ovarian cancer Pulmonary embolism

- This drug may cause edema, chloasma, change in weight, nausea, vomiting, headache, depression, amenorrhea, break-through bleeding, breast tenderness, swollen breast, breast cancer, or endometrial cancer. The vaginal insert formulation may also cause vaginal discomfort.
- Instruct patient to report abnormal vaginal bleeding or signs/symptoms of a thromboembolic disorder.
- Advise patients using the vaginal insert, tablet, or cream to report signs/symptoms of a vaginal infection.
- Instruct patient on proper administration technique depending on form.
- If the vaginal insert falls out after insertion, patient may rinse it in lukewarm water and reinsert.
- Advise patient that the transdermal patch should never be placed on the breast or the waistline. At least 1 week should be allowed between applications to a particular site.
- Patients should not smoke during therapy, as this increases the risk of thromboembolic events.
- Advise patients using the topical emulsion to not use sunscreen over the application site, as this may increase the estrogen absorption.
- Avoid eating grapefruit or drinking grapefruit juice while taking oral preparations this drug.

Ethacrynic acid

Common	Serious
Injection site reaction (irritation, pain) Rash Abnormal electrolytes Diarrhea Dyphagia Loss of appetite Nausea Vomiting Gout Confusion Headache Vertigo Blurred vision Fatigue	Pancreatitis (rare) Agranulocytosis Neutropenia Thrombocytopenia Hepatotoxicity (rare) Jaundice (rare) Ototoxicity Deafness Tinnitus Hematuria

- This drug may cause hyper- or hypoglycemia, abdominal pain, diarrhea, dysphagia, loss of appetite, nausea, vomiting, gout, confusion, headache, vertigo, blurred vision, fatigue, pancytopenia, or hematuria.
- Instruct patient to report severe, watery diarrhea or signs/symptoms of ototoxicity.
- Patient should avoid lithium during drug therapy.

ETHAMBUTOL HYDROCHLORIDE

Brand Name(s): **Myambutol**

Adverse Effects

Serious:

- **Hematologic:** Neutropenia, Thrombocytopenia
- **Immunologic:** Anaphylactoid reaction
- **Neurologic:** Peripheral neuropathy
- **Ophthalmic:** Blindness AND/OR vision impairment level, Optic neuritis (1-6%)

Common:

- **Endocrine metabolic:** Hyperuricemia
- **Gastrointestinal:** Nausea and vomiting
- **Psychiatric:** Mania

Patient Information

- This drug may cause nausea, vomiting, hyperuricemia, or mania.
- Drug may cause vision impairment or loss. Instruct patient to promptly report any visual changes.
- Patient should report signs/symptoms of neutropenia, thrombocytopenia, or peripheral neuropathy

Contraindications

- hypersensitivity to ethambutol hydrochloride
- inability to appreciate and report visual side effects or changes in vision (eg, young children or unconscious patients)

- optic neuritis, unless clinical judgment determines that it may be used

Precautions

- blindness, irreversible, has been reported
- concomitant use of antacids that contain aluminum hydroxide should be avoided for 4 hours following administration
- liver toxicities, including fatalities, have been reported; monitoring recommended
- renal impairment; dose adjustment recommended
- visual acuity has been reduced, possibly due to optic neuritis and related to dose and treatment duration
- visual defects (eg, cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy); monitoring recommended

ETHIONAMIDE

Brand Name(s): **Trecator**

Adverse Effects

Serious:

- **Hepatic:** Hepatitis
- **Neurologic:** Encephalopathy
- **Ophthalmic:** Optic neuritis (rare .)
- **Psychiatric:** Psychiatric sign or symptom

Common:

- **Gastrointestinal:** Abdominal pain, Diarrhea, Metallic taste, Nausea, Stomatitis, Vomiting

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause drowsiness or dizziness.
- This drug may cause gynecomastia, nausea, vomiting, diarrhea, metallic taste, postural hypotension, or impotence.
- Patient should report visual changes or signs/symptoms of optic neuritis.
- Advise diabetic patients to monitor for signs/symptoms of hypoglycemia and to report difficulties with glycemic control.
- Patient should take drug with a meal to minimize gastric irritation.
- Advise patient against excessive alcohol consumption during therapy.

Contraindications

- hypersensitivity to ethionamide or components
- severe hepatic damage

Precautions

- drug malabsorption may be a problem in patients with concomittant AIDS infection
- diabetes control may be disrupted by ethionamide
- pregnancy

ETHOSUXIMIDE

Brand Name(s): **Zarontin**

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome
- **Hematologic:** Agranulocytosis, Aplastic anemia, Drug-induced eosinophilia, Leukopenia, Pancytopenia
- **Immunologic:** Systemic lupus erythematosus
- **Neurologic:** Seizure

Common:

- **Gastrointestinal:** Loss of appetite, Nausea, Stomach cramps, Vomiting
- **Neurologic:** Ataxia, Dizziness, Headache, Somnolence
- **Other:** Hiccoughs

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized as drug may cause dizziness, drowsiness, and fatigue.
- This drug may cause anorexia, nausea, stomach cramps, abdominal pain, diarrhea, vomiting, ataxia, and headaches.
- Advise patient or caregiver to report worsening depression, suicidal ideation, or unusual changes in behavior.
- Patient should report signs/symptoms of systemic lupus erythematosus (arthralgia, myalgia, fatigue, skin rash) or a severe skin reaction such as Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering).
- Instruct patient to report signs/symptoms of blood dyscrasias (eg, sore throat, fever, malaise, bruising, petechiae, skin rash, or epistaxis) or hepatic dysfunction.
- Advise patient against sudden discontinuation of drug, as this may precipitate petit mal seizures.

Contraindications

- hypersensitivity to succinimides

Precautions

- abrupt withdrawal should be avoided due to the potential for status epilepticus
- blood dyscrasias, some fatal, have been reported; monitoring recommended
- grand mal seizures may occur more frequently when used as monotherapy for mixed types of epilepsy
- liver disease, preexisting; liver function abnormalities have been reported; monitoring recommended
- pregnancy; may increase risk for birth defects in newborns; assess risk/benefit
- renal disease, preexisting; renal function abnormalities have been reported; monitoring recommended
- suicidality, increased risk of; monitoring recommended
- systemic lupus erythematosus has been reported

Etodolac

Common	Serious
Edema Abdominal pain Diarrhea Flatulence Indigestion Nausea Dizziness Malaise	Congestive heartfailure (<1%) Myocardial infarction Thrombotic tendency observations Scaling eczema Stevens-Johnson syndrome (<.0.1%) Toxic epidermal necrolysis (<0.1%) Gastrointestinal hemorrhage (<1%) Gastrointestinal perfoatin (<1%) Inflammatory disorder of digestive tract Melena (<3%) Agranulocytosis (rare) Anemia (<1%) Neutropenia (rare) Thrombocytopenia (<1%) Hepatitis (<1%)

	Increased liver function test (up to 15%) Jaundice (<1%) Liver failure (<0.1%) Anaphylactoid reaction Immune hypersensitivity reaction (rare) Cerebrovascular accident Papillary necrosis (rare) Renal failure (rare) Bronchospasm (<2%)

- Avoid use in late pregnancy as drug may cause premature closure of ductus arteriosus.
- This drug may cause edema, abdominal pain, diarrhea, dyspepsia, flatulence, nausea, dizziness, or malaise.
- Instruct patients to report signs/symptoms of serious gastrointestinal adverse events such as bleeding, ulceration, perforation of stomach or intestines. Elderly and debilitated patients are at a higher risk for these effects.
- Patients should report signs/symptoms of serious cardiovascular thrombotic events, such as myocardial infarction and stroke. Patients with a cardiovascular disease history or on prolonged therapy are at a higher risk of these events.
- May be taken with food or milk to minimize stomach upset.
- Patient should avoid all other NSAIDs during therapy, unless approved by a healthcare professional.
- Patient should not drink alcohol while taking this drug.

<u>Etoposide</u> (Vepesid)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Decreased or loss of appetite, drop in blood pressure while receiving this drug	Allergic reaction
Prompt: Within 2-3 weeks, prior to next course	Decrease in the number of red and white blood cells and platelets made in the bone marrow	Hair loss (L), worsens side effects due to radiation treatments, diarrhea	Numbness, tingling, clumsiness, mouth sores, damage to the liver
Delayed: Any time later during therapy			
Late: Any time after completion of			A new cancer or leukemia resulting from this treatment, inability of the ovaries to

treatment			produce eggs and/or hormones resulting in inability to have children and/or hormonal problems

(L) Toxicity may also occur later.

Everolimus

Adverse Effects

Serious:

- **Hematologic:** Decreased hemoglobin, Grade 4 (advanced renal cancer, 1% ; advanced pancreatic neuroendocrine tumor, 15%), Decreased lymphocyte count, Grade 4 (advanced renal cancer, 2% ; advanced pancreatic neuroendocrine tumor, 16%), Hemorrhage (3%), Leukopenia (kidney transplant recipients, 3% ; subependymal giant cell astrocytoma, 54% ; advanced pancreatic neuroendocrine tumor, 43%), Thrombosis, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura
- **Immunologic:** Infectious disease (advanced renal cancer, 37% ; kidney transplant recipients, 62%)
- **Neurologic:** Seizure (29%)
- **Renal:** Hemolytic uremic syndrome, Renal failure (3%), Thrombosis of renal artery (1% to less than 10%)
- **Respiratory:** Non-infectious pneumonia (14% to 17%), Pleural effusion (7%), Pneumonia, Pulmonary embolism

Common:

- **Cardiovascular:** Hypertension (kidney transplant recipients, 30% ; advanced renal cancer, 4%; subependymal giant cell astrocytoma, 4%), Peripheral edema (kidney transplant recipients, 45% ; advanced renal cancer, 25%; subependymal giant cell astrocytoma, 4%)
- **Dermatologic:** Infection of skin AND/OR subcutaneous tissue (18%), Rash (advanced renal cancer, 29%; subependymal giant cell astrocytoma, 18%; advanced pancreatic neuroendocrine tumor, 59%)
- **Endocrine metabolic:** Decreased phosphate level (37% to 40%), Dyslipidemia (15%), Hyperlipidemia (21%), Increased glucose level, All grades (advanced pancreatic neuroendocrine tumor, 75%; advanced renal cell cancer, 57%; subependymal giant cell astrocytoma, 25%), Serum cholesterol raised (advanced renal cancer, 77%; subependymal giant cell astrocytoma, 68% ; advanced pancreatic neuroendocrine tumor, 66%), Serum triglycerides raised (advanced renal cell cancer, 73%; subependymal giant cell astrocytoma, 43% ; advanced pancreatic neuroendocrine tumor, 39%)
- **Gastrointestinal:** Constipation (kidney transplant recipients, 38% ; subependymal giant cell astrocytoma, 11%), Diarrhea (kidney transplant recipients, 19% ; advanced renal cancer, 30%; subependymal giant cell astrocytoma, 25%; advanced pancreatic neuroendocrine tumor, 50%), Loss of appetite (25% to 30%), Nausea (26% to 29%), Oropharyngeal mucositis, Stomatitis (kidney transplant recipients, 8% ; advanced renal cancer, 44%; advanced pancreatic neuroendocrine tumor, 70%; subependymal giant cell

astrocytoma, 86%), Ulcer of mouth, Vomiting (advanced renal cancer, 20%; subependymal giant cell astrocytoma, 21%; advanced pancreatic neuroendocrine tumor, 29% ; kidney transplant recipients, 15%)

- **Hematologic:** Anemia (kidney transplant recipients, 26% ; renal cell cancer, 50% or higher), Decreased hemoglobin, All grades (advanced renal cancer, 92%; subependymal giant cell astrocytoma, 39% ; advanced pancreatic neuroendocrine tumor, 86%), Decreased lymphocyte count, All grades (45% to 51%), Decreased platelet count, All grades (21% to 45%)
- **Hepatic:** ALT/SGPT level raised (advanced renal cell cancer, 21%; subependymal giant cell astrocytoma, 46%; advanced pancreatic neuroendocrine tumor, 48%), AST/SGOT level raised (advanced renal cancer, 25%; advanced pancreatic neuroendocrine tumor, 56%; subependymal giant cell astrocytoma, 89%)
- **Immunologic:** Surgical wound finding (35%)
- **Neurologic:** Asthenia (33%)
- **Otic:** Otitis media (36%)
- **Renal:** Serum creatinine raised (advanced renal cancer, 50%; advanced pancreatic neuroendocrine tumor, 19%; subependymal giant cell astrocytoma, 11% ; kidney transplant recipients, 18%), Urinary tract infectious disease (advanced pancreatic neuroendocrine tumor, 16% ; kidney transplant recipients, 22%)
- **Respiratory:** Cough (advanced renal cancer, 30%; advanced pancreatic neuroendocrine tumor, 25%; subependymal giant cell astrocytoma, 21% ; kidney transplant recipients, 7%), Dyspnea (20% to 24%), Sinusitis (39%), Upper respiratory infection (kidney transplant recipients, 16% ; subependymal giant cell astrocytoma, 82%)

Other: Fatigue (advanced pancreatic neuroendocrine tumor, 45% advanced renal cancer, 31%; subependymal giant cell astrocytoma, 7% kidney transplant recipients, 9%), Fever (advanced renal cancer, 20%; advanced pancreatic neuroendocrine tumor, 31%; subependymal giant cell astrocytoma, 32% ; kidney transplant recipients, 19%)

FAMOTIDINE

Brand Name(s): **Fluxid ; Pepcid**

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome (very rare), Toxic epidermal necrolysis (very rare)
- **Gastrointestinal:** Necrotizing enterocolitis in fetus OR newborn
- **Immunologic:** Anaphylaxis (infrequent), Angioedema (infrequent)
- **Neurologic:** Seizure (rare)
- **Respiratory:** Interstitial pneumonia (infrequent), Nosocomial pneumonia

Common:

- **Gastrointestinal:** Constipation (1.2% to 1.4%), Diarrhea (1.7%)
- **Neurologic:** Dizziness (1.3%), Headache (1.3% to 4.7%)

Patient Information

- This drug may cause constipation, diarrhea, or dizziness.
- Advise patient to take at bedtime.
- Patient may take with antacids, if needed.

Contraindications

- hypersensitivity to famotidine or any component
- hypersensitivity to other H2-receptor antagonists, history

Precautions

- neonates, very low birth weight (401 to 1,500 g); increased risk of developing necrotizing enterocolitis
- renal insufficiency, moderate or severe; risk of prolonged QT interval and CNS adverse effects; dose adjustment recommended
- symptomatic response does not rule out gastric malignancy

Felbamate

Common	Serious
Photosensitivity Weight loss Abdominal pain Constipation Indigestion Loss of appetite Nausea Taste sense altered Vomiting Purpuric disorder Adnormal gait Dizziness Headache Insomnia Fever	Stevens-Johnson syndrome Agrnulocytosis Aplastic anemia Bone marrow depression Drug-induced eosinophilia Leukopenia Pancytopenia Thrombocytopenia Hepatic failure (acute) Anaphylactoid reaction Seizure

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause weight loss, abdominal pain, constipation, dyspepsia, loss of appetite, nausea, altered sense of taste, vomiting, purpuric disorder, abnormal gait, dizziness, headache, or insomnia.
- Instruct patient to report signs/symptoms of pancytopenia, hepatic failure, or Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering).
- Advise patient against sudden discontinuation of drug.
- Instruct patient to call healthcare provider for instructions if 2 or more doses are missed.

Felodipine

Common	Serious
Peripheral edema (2% to 17.4%) Flushing (1.6%) Drug-induced gingival hyperplasia (<0.5%) Dizziness (4.4%) Headache (10.3%)	Angina (<0.5%) Hypotension (rare) Myocardial infarction (<0.5%) Tachyarrhythmia (0.4% to 2.5%)

- Patient should avoid activities requiring coordination until drug effects are realized, as drug may cause dizziness.
- Warn patient that hypotension may occur, especially with the first dose and dosage changes.
- This drug may cause peripheral edema, flushing, headache, myocardial infarction, or tachyarrhythmia.
- Inform patient that mild gingival hyperplasia may occur. Incidence and severity can be minimized with good dental hygiene.
- Patient should report exacerbation in angina. This may occur more frequently with initial dose, dose changes, or during drug withdrawal.
- Patient may take drug without food or with a light meal.
- Advise patient against sudden discontinuation of drug.
- Patient should avoid eating grapefruit or drinking grapefruit juice while taking this drug.
- Patient should not drink alcohol while taking this drug.

Fenoprofen

Common	Serious
Edema Anemia Increased liver function test (up to 15%)	Hypertension Myocardial infarction (<2%) Thrombotic tendency observations Scaling eczema Stevens-Johnson syndrome (<0.1%) Gastrointestinal perforation (<2%) Inflammatory disorder of digestive tract Hepatitis (<2%) Jaundice Liver failure(<0.1%) Anajphylactoid reaction Cerebrovascular accident Acute renal failure Bronchospasm (<2%)

- This drug may cause edema.
- Tell patient to report signs/symptoms of liver dysfunction or anemia.
- Patients with a history of cardiac disease or on long-term therapy may be at an increased risk for adverse cardiovascular thrombotic events. Advise patient to report signs/symptoms of myocardial infarction or stroke.
- Instruct patients to report signs/symptoms of serious gastrointestinal events such as bleeding, ulceration, or perforation of stomach or intestines. Elderly and debilitated patients may be at an increased risk for this adverse effect.
- Patient may take drug with meals or milk to lessen or prevent gastric upset.

Fexofenadine

Common	rare

Nausea (1.6%) Dyspepsia (1.3%) Headache (31.2%) Drowsiness (1.3%) Fatigue (1.3%) Dizziness Otitis media Dysmenorrhea (1.5%)	Decreased bilirubin Flu-like symptoms Upper respiratory infection

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause dyspepsia, dizziness, headache, somnolence, dysmenorrhea, or fatigue.
- Take drug with water. Do not take with fruit juices (grapefruit, orange, apple).
- Patient should avoid administration of aluminum- or magnesium-containing antacids within 30 min before or after taking drug.

FLUCYTOSINE

Brand Name(s): **Ancobon**

Adverse Effects

Serious:

- **Cardiovascular:** Cardiotoxicity
- **Hematologic:** Leukopenia, Myelosuppression, Thrombocytopenia
- **Renal:** Renal failure

Common:

- **Gastrointestinal:** Abdominal pain, Diarrhea, Nausea, Vomiting
- **Neurologic:** Confusion, Headache
- **Psychiatric:** Hallucinations

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause diarrhea, nausea, vomiting, confusion, headache, somnolence, or hallucinations.
- Instruct patient to report signs/symptoms of infection or bleeding.
- Patient may administer a few capsules at a time over 15 min to minimize nausea and vomiting.

Contraindications

- hypersensitivity to flucytosine

Precautions

- bone marrow depression
- renal impairment

FLUDARABINE PHOSPHATE

Brand Name(s): **Fludara ; Oforta**

Adverse Effects

Serious:

- **Hematologic:** Decreased hemoglobin (14% to 60%), Hemolytic anemia, Neutropenia (37% to 59%), Pancytopenia, Thrombocytopenia (17% to 55%)
- **Neurologic:** Neurotoxicity, Progressive multifocal leukoencephalopathy
- **Respiratory:** Pulmonary toxicity
- **Other:** Graft versus host disease, Tumor lysis syndrome (0.33% to 1%)

Common:

- **Gastrointestinal:** Loss of appetite (0% to 34%), Nausea (1% to 5%), Vomiting
- **Neurologic:** Asthenia (9% to 65%), Paresthesia (4% to 12%)
- **Respiratory:** Cough (6% to 44%)
- **Other:** Fatigue (10% to 38%), Fever (11% to 69%), Infectious disease (12% to 44% .), Pain (5% to 22%), Shivering (11% to 19%)

Patient Information

- Instruct patient to avoid driving and other activities requiring mental alertness or coordination until drug effects are realized, as drug causes fatigue, weakness, visual disturbances, confusion, agitation, and seizures (rare).
- Advise patient to avoid live vaccines during therapy due to drug-induced immunosuppression.
- Counsel patient to avoid pregnancy during and for at least 6 months after completion of therapy.
- Drug may cause chills, loss of appetite, nausea, vomiting, diarrhea, cough, malaise, pneumonia, or fever.
- Instruct patient to report signs/symptoms of myelosuppression, neurotoxicity, or infections.
- Tell patient not to crush oral tablets and to avoid direct contact with skin and mucous membranes or inhalation.
- Fludarabine (Intravenous route, Powder for Solution, Solution)
- Fludarabine (Oral route, Tablet)

Contraindications

- hypersensitivity to fludarabine or to any product ingredient

Precautions

- autoimmune hemolytic anemia (fatal) has occurred; monitor for hemolysis; discontinue if hemolysis occurs
- autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evan's syndrome, and acquired hemophilia has occurred; monitor for hemolysis (intravenous); discontinue if hemolysis occurs
- neurotoxicity, severe; dose-dependent , delay or discontinue treatment if neurotoxicity occurs
- concomitant pentostatin; use not recommended
- bone marrow suppression, severe (anemia, thrombocytopenia and neutropenia), preexisting exacerbation or new onset; monitor blood counts before and during treatment
- infection (fatal), has occurred, monitor for signs and symptoms of infection
- impaired performance; risk of compromising ability to drive or operate machinery

- pregnancy, avoid during treatment and for 6 months after cessation of treatment due to the potential for fetal harm (fertile male patients must take contraceptive measures)
- mild to moderate renal impairment, creatinine clearance 30 to 70 mL/min/1.73 m(2) or less; dose reduction and monitoring required
- severe renal impairment, creatinine clearance less than 30 mL/min/1.73 m(2); use not recommended (intravenous); dose reduction and monitoring required (oral)
- transfusion-associated graft-versus-host disease, has occurred after transfusion with non-irrradiated blood; recommend use of irradiated blood products
- tumor lysis syndrome (may present as flank pain and hematuria); increased risk in patients with chronic lymphocytic leukemia (CLL) with large tumor burdens
- vaccination with live vaccines, during and after treatment, should be avoided
- adverse event reporting; Antisoma 1-866-949-7420 or Food and drug Administration 1-800-FDA-1088, or www.fda.gov/medwatch (oral)

Fludrocortisones

Common	Serious
Edema Bruising symptom Impaired would healing Petechiae Rash Urticaria Decreased body growth (children) Abnormal electrolytes Hypokalemia Hyperglycemia Abdominal distension Peptic ulcer disease Drug-induced myopath Muscle weakness Headache Vertigo Glycosuria Irregular periods	Cardiomegaly Congestive heart failure Hypertension Thrombophlebitis Secondary hypocortisolism Raised intracranial pressure seizure

- Advise patient to avoid vaccines during therapy unless approved by healthcare professional.
- Instruct patient to avoid exposure to chickenpox or measles. If exposure occurs, patient should notify healthcare professional.
- This drug may cause edema, bruising, impaired wound healing, petechiae, decreased body growth in children, abdominal distension, myopathy, muscle weakness, headache, vertigo, or irregular periods.
- Patient should report seizure activity or signs/symptoms of congestive heart failure.
- Advise patient against sudden discontinuation of drug.

FLUOXETINE HYDROCHLORIDE

Brand Name(s): **Prozac ; Sarafem ; Symbyax**

Adverse Effects

Serious:

- **Cardiovascular:** Prolonged QT interval
- **Endocrine metabolic:** Hyponatremia
- **Hematologic:** Bleeding (up to 1%)
- **Neurologic:** Seizure
- **Psychiatric:** Depression, worsening (rare), Mania (rare), Suicidal thoughts, Suicide
- **Other:** Serotonin syndrome

Common:

- **Dermatologic:** Diaphoresis, Rash (7%)
- **Gastrointestinal:** Loss of appetite (3.5% to 15%), Nausea (20% to 30% .), Xerostomia
- **Neurologic:** Asthenia (9% to 21%), Dizziness (2% to 11%), Insomnia (9% to 26%), Somnolence (13%), Tremor (12%)
- **Psychiatric:** Anxiety (3% to 9%), Feeling nervous (3% to 14%)
- **Respiratory:** Pharyngitis (6% to 10%), Rhinitis (16% to 23%)

Patient Information

- Instruct patient to report use of a MAO inhibitor within the last 14 days prior to starting therapy. Notify patient that at least 5 weeks should be allowed between discontinuation of fluoxetine and initiation of MAO inhibitor therapy.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause anticholinergic effects, sweating, weight loss, dyspepsia, loss of appetite, nausea, asthenia, insomnia, tremor, abnormal ejaculation, or impotence.
- Advise patient that symptomatic improvement may not be seen for a few weeks.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk for these effects during the first few months of therapy.
- Advise patient to report abnormal bleeding.
- Patient should report skin rash with or without systemic symptoms (fever, edema, pulmonary effects), as drug may cause serious cutaneous systemic illness.
- Instruct diabetic patients to monitor for signs/symptoms of hyper- or hypoglycemia and report any changes in glycemic control.
- Advise patient against sudden discontinuation of drug.
- Advise patient not to use thioridazine with fluoxetine or within 5 weeks of discontinuation. Pimozide should not be used with fluoxetine.
- Avoid NSAID or aspirin use during therapy.
- Patient should not drink alcohol while taking this drug.
- Instruct patients on a weekly dose to take a missed dose as soon as possible. Patient should then go back to regular schedule for the next week.

Contraindications

- concomitant use of monoamine oxidase inhibitors (MAOIs), pimozide, or thioridazine
- hypersensitivity to fluoxetine or any components of the product
- use of thioridazine or MAOIs within 5 weeks after fluoxetine discontinuation
- use of fluoxetine within 14 days of MAOI discontinuation

Precautions

- suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults with major depressive and other psychiatric disorders during the first few months of therapy or following changes in dosage
- abrupt withdrawal; serious discontinuation symptoms have been reported; gradual reduction in dose recommended
- acute narrow angle glaucoma or increased intraocular pressure; mydriasis has been reported
- allergic reactions, including anaphylaxis, angioedema, and urticaria have been reported; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy
- bipolar disorder; increased risk of precipitation of a mixed/manic episode with antidepressant treatment only
- concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation; abnormal bleeding, particularly the gastrointestinal tract, may occur; monitoring recommended
- concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); risk of serotonin syndrome, use is not recommended
- diabetes, history of; increased risk of hypoglycemia
- pulmonary events, including fibrosis, have been rarely reported
- seizures, history of
- serotonin syndrome and neuroleptic malignant syndrome-like reactions (serotonin syndrome in its most severe form), have been reported with fluoxetine therapy alone or in combination with other serotonergic drugs; monitoring recommended
- skin reactions, including serious cutaneous systemic illnesses (eg leukocytoclastic vasculitis, erythema multiforme, and lupus-like syndrome) with fatalities have been reported rarely; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy
- volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with fluoxetine

Fluvastatin

Common	Serious
Abdominal pain (3.7% to 4.9%) Diarrhea (3.3% to 7.9%) Nausea (2.5% to 3.2%) Headache	Pancreatitis (rare) Increased liver enzymes (1.1%) Disorder of muscle Rhabdomyolysis (rare) Tendon rupture

- This drug may cause abdominal pain, diarrhea, dyspepsia, nausea, or headache.
- Instruct patient to report signs/symptoms of renal failure or myopathy.
- Advise patients to administer capsule at least 2 h after taking a bile-acid resin (cholestyramine) if using concomitantly.
- Patient should not drink alcohol while taking this drug.
- Patient should avoid concomitant use of fibrates, niacin, cyclosporine, macrolides, or azole antifungals (eg, fluconazole, itraconazole), as combination may increase risk of myopathy.

FLUVOXAMINE MALEATE

Brand Name(s): **Luvox**

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Endocrine metabolic:** Hyponatremia
- **Hematologic:** Agranulocytosis, Bleeding, Abnormal
- **Immunologic:** Anaphylaxis
- **Neurologic:** Seizure (0.2%)
- **Psychiatric:** Depression, worsening, Suicidal thoughts, Suicide
- **Other:** Neuroleptic malignant syndrome, Serotonin syndrome

Common:

- **Dermatologic:** Sweating (immediate-release, 7%; extended-release, 7%)
- **Gastrointestinal:** Diarrhea (immediate-release, 11%; extended-release, 18%), Indigestion (immediate-release, 10%; extended-release, 8%), Loss of appetite (immediate-release, 6%; extended-release, 13%), Nausea (immediate-release, 40%; extended-release, 34%), Xerostomia (immediate-release, 14%; extended-release, 10%)
- **Neurologic:** Asthenia (immediate-release, 14%; extended-release, 26%), Dizziness (immediate-release, 11%; extended-release, 12%), Insomnia (immediate-release, 21%; extended-release, 35%), Somnolence (immediate-release, 22%; extended-release, 27%), Tremor (immediate-release, 5%; extended-release, 6%)
- **Psychiatric:** Anxiety (immediate-release, 5%; extended-release, 6%), Feeling nervous (immediate-release, 12%)
- **Reproductive:** Abnormal ejaculation (immediate-release, 8%; extended-release, 10%), Orgasm incapacity (immediate-release, 2%; extended-release, 5%)

Patient Information

- Instruct patient to report use of a MAO inhibitor within the last 14 days prior to initiation of drug therapy.
- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness or somnolence.
- This drug may cause anticholinergic effects, weight loss, diarrhea, dyspepsia, nausea, vomiting, asthenia, headache, insomnia, agitation, anxiety, nervousness, or abnormal ejaculation.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk for these effects during the first few months of therapy.
- Advise patient against sudden discontinuation of drug.
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).
- Patient should not drink alcohol while taking this drug.

Contraindications

- concomitant use with alosetron, pimozide, thioridazine, tizanidine , or ramelteon
- concomitant use of an MAOI or within 14 days (before or after) fluvoxamine therapy

Precautions

- suicidal ideation and behavior or worsening depression has been reported, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage; monitoring recommended
- abnormal bleeding, including potentially life-threatening hemorrhages; has been reported
- abrupt withdrawal; increased risk of serious discontinuation symptoms; monitoring and gradual dose reduction recommended
- bipolar disorder; increased risk of precipitation of a mixed/manic episode with antidepressant monotherapy; rule out disorder prior to initiating therapy
- concomitant use with alcohol should be avoided
- concomitant use with serotonergic drugs (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors), diazepam, or serotonin precursors (eg, tryptophan) is not recommended
- hepatic impairment; decreased fluvoxamine clearance; lower initial doses and monitoring recommended
- hyponatremia, primarily due to SIADH, has been reported, including serious cases (serum sodium less than 110 mmol/L); increased risk in elderly, volume-depleted patients, or with concomitant use of diuretics; discontinue if symptomatic hyponatremia occurs
- mania, history of; risk of activation of mania/hypomania
- seizure disorder, history of; seizures have been reported; avoid use in unstable epilepsy; monitoring recommended if controlled epilepsy
- serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic malignant syndrome; monitoring recommended
- report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/Medwatch

FOLIC ACID

Brand Name(s): **Folacin-800**

Adverse Effects

Serious:

- **Immunologic:** Allergy

Common:

- **Gastrointestinal:** Bad taste in mouth, Large doses, Loss of appetite, Nausea
- **Neurologic:** Confusion
- **Psychiatric:** Irritability, Sleep pattern disturbance

Patient Information

- his drug may cause loss of appetite, nausea, confusion, irritability, or sleep-pattern disturbance. Large doses of drug may cause bad taste in mouth.
- Patient should not drink alcohol while taking this drug.

Contraindications

- hypersensitivity to folic acid products

Precautions

- folic acid doses above 0.1 mg/day may obscure pernicious anemia (hematologic remission while neurological manifestations progress)
- pernicious anemia and other megaloblastic anemias caused by vitamin B12 deficiency

FUROSEMIDE

Brand Name(s): **Lasix**

Adverse Effects

Serious:

- **Cardiovascular:** Orthostatic hypotension
- **Dermatologic:** Erythema multiforme, Erythroderma, Stevens-Johnson syndrome, Toxic epidermal necrolysis due to drug
- **Gastrointestinal:** Pancreatitis
- **Hematologic:** Agranulocytosis, Aplastic anemia, Thrombocytopenia
- **Immunologic:** Anaphylaxis

Common:

- **Endocrine metabolic:** Hyperuricemia (40%), Hypomagnesemia
- **Gastrointestinal:** Loss of appetite
- **Renal:** Spasm of bladder

Patient Information

- Drug causes sun-sensitivity. Advise patient to use sunscreen and avoid tanning beds.
- Patient should avoid activities requiring coordination until drug effects are realized, as drug may cause dizziness, vertigo, or blurred vision.
- This drug may cause hyperglycemia, hyperuricemia, constipation, diarrhea, loss of appetite, nausea, vomiting, purpuric disorder, cramps, spasticity, asthenia, headache, paresthesia, or scaling eczema.
- Instruct patient to report unusual bleeding/bruising or signs/symptoms of hypotension, infection, pancreatitis, or ototoxicity (tinnitus, hearing impairment).
- Advise patient to report signs/symptoms of severe skin reactions (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering) or erythema multiforme.
- Instruct patient to eat high-potassium foods during drug therapy, as directed by healthcare professional.
- Patient should not drink alcohol while taking this drug

Contraindications

- anuria
- history of hypersensitivity to furosemide

Precautions

- diuresis, profound; may cause water and electrolyte depletion, dehydration, and blood volume reduction; monitoring recommended
- blood dyscrasias may occur; monitoring recommended
- blood glucose increases, alterations in glucose tolerance tests, or precipitation of diabetes have been reported
- concomitant use of aminoglycosides should be avoided
- concomitant use of ethacrynic acid not recommended
- elderly patients; increased risk of dehydration
- electrolyte depletion, preexisting; should be corrected prior to treatment
- electrolyte imbalance (eg, hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hypocalcemia) may occur, especially in patients receiving higher doses and a restricted salt intake; monitoring recommended

- hepatic cirrhosis and ascites, preexisting; may precipitate hepatic coma with sudden fluid or electrolyte alteration; monitoring recommended
- hepatic coma, preexisting; use not recommended until basic condition improved
- hepatic damage may occur; monitoring recommended allergy to sulfonamides; may also be allergic to furosemide
- hyperuricemia, asymptomatic or gout; may occur
- hypokalemia has been reported; especially with brisk diuresis, inadequate electrolyte intake, cirrhosis, or concomitant use with corticosteroids, ACTH, large amounts of licorice, or prolonged use of laxatives
- hypoproteinemia; reduced efficacy and increased risk of ototoxicity
- nephrocalcinosis/nephrolithiasis; increased risk in premature infants and children under 4 years without prematurity receiving chronic therapy
- ototoxicity (eg, tinnitus, reversible/irreversible hearing impairment, deafness) has been reported; especially with rapid injection (infusion rate not to exceed 4 mg/min in adults), severe renal impairment, higher than recommended doses, hypoproteinemia, or concomitant ototoxic drugs (eg, aminoglycosides, ethacrynic acid)
- patent ductus arteriosis, persistent; increased risk with administration to premature infants during first week of life
- radiocontrast nephropathy, high-risk; increased risk of renal deterioration
- renal damage may occur; monitoring recommended
- severe progressive renal disease, preexisting; discontinue use if increase in azotemia and oliguria occur
- sulfonamide allergy; increased risk of furosemide allergy
- systemic lupus erythematosus, preexisting; risk of exacerbation or activation
- urinary retention, severe; increased risk of acute urinary retention particularly during initial stages of treatment; monitoring recommended

GABAPENTIN

Brand Name(s): **Neurontin**

Adverse Effects

Serious:

- **Dermatologic:** Stevens-Johnson syndrome
- **Immunologic:** Drug hypersensitivity syndrome
- **Neurologic:** Drug-induced coma, Seizure (0.6%)
- **Psychiatric:** Suicidal thoughts

Common:

- **Cardiovascular:** Peripheral edema (1.7% to 8.3%)
- **Gastrointestinal:** Nausea (greater than 1%), Vomiting (3.3%)
- **Immunologic:** Viral disease (10.9%)
- **Neurologic:** Ataxia (3.3% to 12.5%), Dizziness (adults, 10.9% to 28%; pediatrics, 2.5%), Nystagmus (0.1% to 8.3%), Somnolence (4.5% to 21.4%)
- **Psychiatric:** Hostile behavior (1% to 7.6%)
- **Other:** Fatigue (3.4% to 11%), Fever (greater than 1%)

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.
- Drug may cause peripheral edema, myalgia, ataxia, nystagmus, tremor, or fatigue.
- Advise patient to immediately report a rash or other signs/symptoms of hypersensitivity (eg, fever, lymphadenopathy).
- Instruct patient or caregiver to report new or worsening depression, suicidal ideation, or unusual changes in behavior.
- Advise patient against sudden discontinuation of drug, as this may increase seizure frequency or precipitate status epilepticus.
- Gralise(R) should be taken with the evening meal .
- Counsel patient using an antacid containing aluminum hydroxide and magnesium hydroxide to wait 2 hours before taking gabapentin.
- This drug is available in multiple brand names with varying properties by brand. Instruct patients to follow dosing instructions specific to each brand. Gralise(R) specifically is not interchangeable with other gabapentin products.
- Patient should avoid alcohol and other CNS depressants while taking this drug.

Contraindications

- hypersensitivity to gabapentin or any component of the product

Precautions

- abrupt discontinuation; may increase seizure frequency or precipitate status epilepticus; discontinue gradually over a minimum of 1 week
- drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, including fatal cases, has been reported; evaluate early signs/symptoms and discontinue Neurontin(R) if confirmed
- gabapentin products are not interchangeable; differing pharmacokinetic profiles affect dosing frequency

- pediatric patients (age 3 to 12 years); neuropsychiatric adverse events, including emotional lability, hostility, thought disorder, and hyperkinesia, have been reported with Neurontin(R)
- renal impairment or hemodialysis; dose adjustment of Neurontin(R) is necessary
- renal impairment; dose adjustment may be required in mild to moderate impairment; do not administer Gralise(R) in patients with severe renal impairment (CrCl 15 to 30 mL/min) or on hemodialysis
- suicidality, worsening depression, and/or any unusual behavioral or mood changes (eg, anxiety, agitation, hostility, mania, and hypomania); monitoring recommended
- report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

Gefitinib

Common	Serious
Ance (25% to 33%) Dry skin (13% to 26%) Pruritus (8% to 9%) Rash (43% to 54%) Weight loss (3% to 5%) Diarrhea (48% to 67%) Loss of appetite (7% to 10%) Nausea (13% to 18%) Vomiting (9% to 12%) Asthenia (4% to 6%)	Tumor hemorrhage Hepatotoxicity Eye disorder New onset eye pain Aberrant eyelash Corneal erosion/ulcer Interstitial lung disease Interstitial pneumonia Pneumonitis (1%) Alveolitis (1%)

- This drug may cause acne, dry skin, loss of appetite, nausea, vomiting, or asthenia.
- Instruct patient to report diarrhea, skin rash, or signs/symptoms of hepatotoxicity or ocular toxicity (new onset eye pain, aberrant eyelash, corneal erosion/ulcer).
- Patient should also report signs/symptoms of myelosuppression.
- Advise patient to report respiratory issues such as signs/symptoms of interstitial pneumonia, pneumonitis, or pulmonary fibrosis.
- If patient vomits after taking drug, instruct patient to contact healthcare professional for instructions.

Gemcitabine

Gemcitabine

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, pain at the injection site, fluid build up in tissues causing swelling, flu-like symptoms, rash (L), mild diarrhea or	Unnatural drowsiness (L), difficulty breathing	Decreased blood pressure; a group of side effects: fever, decreased kidney function, low hemoglobin and platelets - which may result in death

	constipation		
Prompt: Within 2-3 weeks, prior to the next course	Decrease in the number of red and white blood cells and platelets made in the bone marrow, decreased liver function, protein in the urine, blood in the urine	Mouth sores, weakness (L)	Kidney toxicity, confusion, seizure (L), coma (L), fluid buildup in the lungs, - unrelated to heart function, which occurs very rarely but may be fatal
Delayed: Any time later during therapy, excluding the above conditions		Hair loss, numbness or tingling, itching	
Late: Any time after completion of treatment			

(L) Toxicity may also occur later.

GENTAMICIN SULFATE

Brand Name(s): **Gentak ; Gentasol**

Adverse Effects

Serious:

- **Neurologic:** Neuromuscular blockade finding
- **Otic:** Ototoxicity
- **Renal:** Nephrotoxicity
- **Respiratory:** Respiratory tract paralysis, Concomitant anesthesia, muscle relaxants

Common:

- **None indicated**

Patient Information

- Instruct patient to maintain adequate fluid intake and avoid dehydration during drug therapy, as this may increase risk for toxicity.
- Instruct patient to report signs/symptoms of ototoxicity or nephrotoxicity.
- Instruct patient on proper instillation technique for ophthalmic preparation.

Contraindications

- hypersensitivity to gentamicin/aminoglycosides

Precautions

- pre-existing renal, vestibular, or auditory impairment
- concomitant anesthesia or neuromuscular blockers; risk for neuromuscular blockade, respiratory paralysis
- concomitant neurotoxic, ototoxic, or nephrotoxic drugs, age (very young/very old), and dehydration; risk factor for toxicity

GRISEOFULVIN

Brand Name(s): **Grifulvin ; Gris-PEG**

Adverse Effects

Serious:

- **Neurologic:** Acroparesthesia (rare)

Common:

- **Dermatologic:** Photosensitivity, Rash, Urticaria
- **Gastrointestinal:** Diarrhea, Nausea, Vomiting
- **Neurologic:** Headache

Patient Information

- Drug may cause sun-sensitivity. Advise patient to use sunscreen and avoid tanning beds.
- Adverse effects to a fetus may be caused by either male or female patients receiving treatment with this drug. Emphasize the use of reliable contraception to patient. This applies during treatment and up to 1 month post therapy for women and 6 months post therapy for men.
- This drug may cause rash, urticaria, diarrhea, nausea, vomiting, or headache.

Contraindications

- hepatocellular failure
- hypersensitivity to griseofulvin
- porphyria
- pregnancy

Precautions

- alcohol use; griseofulvin may potentiate effects (eg, tachycardia, flush)
- hepatotoxicity (jaundice and elevation in ALT, AST, and bilirubin), including serious and fatal cases, has been reported; monitoring recommended; discontinuation may be necessary
- lupus erythematosus or lupus-like syndromes have been reported
- penicillin allergy; potential for cross-sensitivity with penicillin
- photosensitivity may occur; avoid excessive exposure to sunlight
- serious skin reactions (eg, Stevens-Johnson syndrome and toxic epidermal necrolysis) and erythema, including serious and fatal cases, have been reported; discontinuation if severe skin reactions occur

GUAIFENESIN

Brand Name(s): **Mucinex**

Adverse Effects

Serious:

- **None indicated**

Common:

- **Gastrointestinal:** Nausea, Vomiting

Patient Information

- This drug may cause nausea or vomiting.
- Patient should take drug with a full glass of water and maintain adequate hydration during drug therapy.
- Instruct patient that guaifenesin in combination with dextromethorphan should not be used in patients taking MAO inhibitors.
- Advise patients with history of cardiac disorder, diabetes, peripheral vascular disease, prostatic hypertrophy, or glaucoma to avoid guaifenesin in combination with phenylpropanolamine.

Contraindications

- hypersensitivity to guaifenesin products

Precautions

- cough accompanied by too much mucus
- guaifenesin in combination with dextromethorphan should not be used in patients taking MAOI's
- guaifenesin in combination with phenylpropanolamine should be used with caution in patients with hypertension, cardiac disorders, diabetes or peripheral vascular disease, prostatic hypertrophy and glaucoma
- persistent or chronic cough such as that which occurs with smoking, asthma, chronic bronchitis, or emphysema

GUANETHIDINE MONOSULFATE

Brand Name(s): **Intuniv ; Tenex**

Adverse Effects

Serious:

- **Cardiovascular:** Bradyarrhythmia (ADHD, 2% ; hypertension, 3% or less .), Hypotension (ADHD, 3% to 7%), Syncope (ADHD, 1% ; hypertension, less than 1%)
- **Dermatologic:** Peeling of skin
- **Neurologic:** Seizure

Common:

- **Cardiovascular:** Orthostatic hypotension (ADHD, 1% ; hypertension, 15%)
- **Gastrointestinal:** Abdominal pain (ADHD, 10% to 11%), Constipation (ADHD, 2% to 3%; hypertension, up to 15%), Xerostomia (ADHD, 2% to 4%; hypertension 5% to 54%)
- **Neurologic:** Dizziness (ADHD, 6% to 8% ; hypertension, 1% to 15%), Headache (ADHD, 21% to 24% ; hypertension, 1% to 13%), Insomnia (ADHD, 12% ; hypertension, 4%), Somnolence (ADHD, 18% to 38% ; hypertension, up to 39%)
- **Reproductive:** Impotence (hypertension, up to 7%)
- **Other:** Fatigue (ADHD, 10% to 14% ; hypertension 2% to 10%)

Patient Information

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness or somnolence.
- Advise patient to use caution with activities leading to an increased core temperature to avoid dehydration, orthostatic hypotension, and syncope.
- Drug may cause sedation, hypotension, dry mouth, headache, fatigue, constipation, or abdominal pain.
- Advise patient against sudden discontinuation of drug, as this may cause rebound hypertension.
- Patient should not drink alcohol or take CNS depressants with this drug.
- Tell patient to contact healthcare professional for instructions if more than 2 successive doses are missed as titration may be necessary.

Contraindications

- hypersensitivity to guanfacine or to any component of the product

Precautions

- abrupt withdrawal; risk of rebound hypertension
- blood pressure decreases have been reported; monitoring recommended
- bradycardia, history; risk of decreased blood pressure and heart rate
- cardiovascular disease, history; risk of decreased blood pressure and heart rate
- concomitant use of alcohol; should be avoided
- concomitant use of other guanfacine-containing products (eg, Tenex(R)); do not use
- dehydration or becoming overheated; risk of decreased blood pressure and heart rate
- heart block, history; risk of decreased blood pressure and heart rate
- heart rate decreases have been reported; monitoring recommended
- hypotension, history; risk of decreased blood pressure and heart rate
- sedation and somnolence have been reported; consider potential for additive effects before coadministering centrally active depressants (eg, phenothiazine, barbiturates, or benzodiazepines)
- syncope has been reported; increased risk in patients with history or predisposition (eg, hypotension, orthostatic hypotension, bradycardia, or dehydration)
- report suspected adverse reactions to Shire US Inc. at 1-800-828-2088 or to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

HYDROXYUREA

Brand Name(s): **Droxia ; Hydrea ; Mylocel**

Adverse Effects

Serious:

- **Dermatologic:** Gangrenous disorder, Skin cancer, Skin ulcer
- **Hematologic:** Genetic mutation, Long-term use, Secondary leukemia, Long-term use

Common:

- **Hematologic:** Myelosuppression

Patient Information

- Adverse effects to a fetus may be caused by either male or female patients receiving treatment with this drug. Emphasize the use of reliable contraception to patient. This applies during treatment and up to 6 months post-therapy.

- Instruct patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- Advise patient on the proper handling and disposal of chemotherapy drugs.
- This drug may cause skin ulcers.
- Counsel patient to report signs/symptoms of myelosuppression, especially in patients receiving radiotherapy or cancer chemotherapy.
- Advise HIV-infected patients receiving concomitant didanosine and/or stavudine to report signs/symptoms of pancreatitis and hepatotoxicity.

Contraindications

- hypersensitivity to hydroxyurea or any component of the product
- significant bone marrow depression, such as leukopenia, thrombocytopenia or severe anemia (Hydrea(R))

Precautions

- causes macrocytosis which may mask development of folic acid deficiency (prophylactic folic acid recommended with Droxia(R) therapy)
- correct severe anemia prior to initiating hydroxyurea therapy
- cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene; reported in patients with myeloproliferative disorders and receiving interferon therapy
- elderly patients; increased sensitivity to effects
- exacerbation of postirradiation erythema
- HIV-infected patients; hepatotoxicity, hepatic failure, pancreatitis, some fatal, and severe peripheral neuropathy have been reported; avoid combination of hydroxyurea, didanosine and stavudine
- hydroxyurea is mutagenic and clastogenic; secondary leukemias have occurred with long-term therapy for myeloproliferative disorders
- myelosuppression; especially in patients previously receiving radiotherapy or cancer chemotherapy
- renal impairment; initial dose reduction required

Ibuprofen

Common	Serious
Hypotension (intravenous, up to 10%) Rash (oral, 3% to 9%) Hypernatremia (intravenous, up to 10%) Hypoalbuminemia (intravenous, 3% to 10%) Hypoproteinemia (intravenous, up to 13%) Serum lactate dehydrogenase level elevated (intravenous, 3% to 10%) Flatulence (injection, 7% to 16%) Heartburn (oral, 3% to 9%) Nausea (oral, 3% to 9%; intravenous, 53% to 57%) Vomiting (oral, 1% to 3%; intravenous, 15% to 22%)	Congestive heart failure (oral, less than 1%), Hypertension (oral, less than 1%; intravenous, up to 10%), Myocardial infarction, Thrombotic tendency observations Erythema multiforme (oral, less than 1%.), Erythroderma, Stevens-Johnson syndrome (oral, less than 1%), Toxic epidermal necrolysis Gastrointestinal hemorrhage (oral, less than 1%), Gastrointestinal perforation (oral, less than 1%), Gastrointestinal ulcer, Inflammatory disorder of digestive tract,

Thrombocytosis (intravenous, 3% to 10%) Bacteremia (injection, 13%) Dizziness (oral, 3% to 9%; intravenous 4% to 6%) Headache (oral, 1% to 3%; intravenous, 9% to 11%) Serum blood urea nitrogen raised (intravenous, up to 10%) Urinary retention (intravenous, 3% to 5%) Bacterial pneumonia (intravenous, 3% to 10%)	Melena (oral, less than 1%), Pancreatitis (oral, less than 1%) Agranulocytosis (oral, less than 1%), Anemia (intravenous, 2% to 36%), Aplastic anemia (oral, less than 1%), Bleeding (intravenous, 4% to 10%), Hemolytic anemia (oral, less than 1%), Neutropenia (intravenous, 7% to 13%; oral, less than 1%), Thrombocytopenia (less than 1%), Wound hemorrhage (intravenous, 1% to 3%) Fulminant hepatitis (rare), Hepatic necrosis (rare), Hepatitis (oral, less than 1%), Hepatotoxicity (rare), Jaundice (oral, less than 1%), Liver failure (rare), Vanishing bile duct syndrome Anaphylactoid reaction (oral, less than 1%), Immune hypersensitivity reaction (oral, less than 1%) Aseptic meningitis (oral, less than 1%), Cerebrovascular accident Amblyopia (oral, less than 1%) Hearing loss (oral, less than 1%) Depression (oral, less than 1%) Acute renal failure (oral, less than 1%), Hematuria (oral, less than 1%), Renal azotemia (oral, less than 1%) Reye's syndrome

- Advise patient to avoid use of additional NSAIDs or aspirin during therapy, unless approved by doctor.
- Advise patient to avoid use in late pregnancy as drug may cause premature closure of ductus arteriosus.
- Drug may cause fluid retention, abdominal pain, constipation, diarrhea, dyspepsia, heartburn, nausea, vomiting, dizziness, headache and hemorrhage.
- Advise patient with previous cardiac history to report signs/symptoms of myocardial infarction or stroke, especially with long-term use.
- Instruct patient to report signs/symptoms of serious gastrointestinal events, such as bleeding, ulceration, or perforation. Elderly and debilitated patients may be at increased risk.
- Instruct patient to report signs/symptoms of hepatotoxicity (nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms).
- Patient should promptly report skin rash, blistering, or any symptoms of a serious skin reaction.
- Tell patient to take oral form with food or milk to minimize GI irritation.

- Patient should not drink alcohol or smoke while using this drug to reduce risk of GI bleeds.

Imatinib

Risks and side effects related to Gleevec (imatinib mesylate include):

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Heartburn, nausea/vomiting, headache, fluid buildup in the arms, legs, face, or around the eyes (L), weight gain	Fever,), increase in liver enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin indicating possible liver damage (L),, abdominal pain/cramping, muscle and joint pain (L)	Swelling of the brain, breakdown of bone (L), inflammation of the lung and/or damage to the lungs (L)
Prompt: Within 2-3 weeks, prior to the next course	Decrease in numbers of red and white blood cells and platelets made in bone marrow (L), fatigue	Decreased number of bone marrow cells (L), scaly and/or itchy rash, rash, muscle pain and cramping, loss of appetite	Dark, bloody bowel movements, diarrhea, difficulty swallowing, inflammation of the passage between the throat and stomach, pain during swallowing,widespread red itching rash , bleeding, vomiting blood
Delayed: Any time later during therapy, excluding the above condition		Skin color changes, usually lighter patches	Liver Damage (L)*
Late: Any time after the completion of treatment			

(L) Side effect may also occur later

* One patient with no known history of liver problems died on study due to liver failure. This patient was also taking acetaminophen (Tylenol®), also known as paracetamol in European countries. It is recommended you adhere carefully to the instructions and warnings on the acetaminophen package label. Additionally, it is recommended that over-the-counter medications be carefully reviewed, as these may possibly contain combinations of drugs, including acetaminophen or paracetamol.

Since there is an increased risk of bleeding when taking imatinib mesylate (Gleevec), the blood anticoagulant warfarin sodium must not be taken. Your doctor will discuss alternatives with you. However, even when alternative anti clotting drugs are used it will be necessary to closely watch for bleeding and to maintain platelet counts at a safe level with transfusion if necessary. Bleeding may occur into a tumor or a space near the tumor and may be dangerous.

Indomethacin

Common	Serious
Abdominal pain (1% to 3%), Constipation (1% to 3%), Diarrhea (1% to 3%), ndigestion (3% to 9%), Nausea (3% to 9%) Dizziness, Headache, Somnolence Tinnitus Depression Fatigue	Cardiac dysrhythmia (less than 1%), Chest pain (less than 1%), Congestive heart failure (less than 1%), Edema (less than 1%), Hypertension (less than 1%), Myocardial infarction Erythema multiforme (less than 1%), Rash (less than 1%), Scaling eczema, Stevens-Johnson syndrome (less than 1%), Toxic epidermal necrolysis (less than 1%) Hyponatremia, Transitory neonatal hyperkalemia (3-9%) Gastrointestinal hemorrhage (less than 1%), Gastrointestinal perforation (less than 1%), Gastrointestinal ulcer (less than 1%), Inflammatory disorder of digestive tract (less than 1%) Agranulocytosis (less than 1%), Anemia (less than 1%), Aplastic anemia, Leukopenia (less than 1%), Neutropenia, Thrombocytopenic purpura (less than 1%) Hepatitis (less than 1%), Jaundice (less than 1%), Liver failure IAnaphylactoid reaction (less than 1%) Cerebrovascular accident, Epilepsy, Aggravation, Parkinsonism, Aggravation (less than 1%), Peripheral neuropathy (less than 1%), Seizure (less than 1%) Blurred vision (less than 1%), Corneal deposit (less than 1%), Retinal disorder (less than 1%) Hearing loss (less than 1%) Psychic disease (less than 1%)

	Hematuria (less than 1%), Interstitial nephritis (less than 1%), Nephrotic syndrome (less than 1%), Newborn renal dysfunction (41%), Renal failure (less than 1%) Asthma (less than 1%), Bronchospasm (less than 1%), Dyspnea (less than 1%), Persistent pulmonary hypertension of the newborn (<3%), Pulmonary edema (less than 1%)

- Patient should avoid activities requiring mental alertness until drug effects are realized, as drug may cause somnolence.
- This drug may cause abdominal pain, anal irritation, constipation, diarrhea, dyspepsia, nausea, tenesmus, vomiting, dizziness, headache, tinnitus, depression, scaling eczema, or fatigue.
- Instruct patient to report signs/symptoms of a serious cardiovascular thrombotic event, such as myocardial infarction or stroke. Patients with cardiovascular disease or on prolonged therapy may be at increased risk for this adverse effect.
- Advise patients to report signs/symptoms of a serious gastrointestinal adverse event, such as bleeding, ulceration, or perforation of the stomach or intestines. Elderly or debilitated patients may be at increased risk for this adverse effect.
- Patient should take the oral formulations with food, immediately after meals, or with antacids.
- Patient should not use other NSAIDs concomitantly without approval by healthcare professional.

IRINOTECAN HYDROCHLORIDE

Brand Name(s): **Camptosar**

Adverse Effects

Serious:

- **Cardiovascular:** Disorder of cardiovascular system
- **Gastrointestinal:** Diarrhea, Grade 3 and 4 (4.9% to 31%), Gastrointestinal perforation
- **Hematologic:** Anemia, Grade 3 and 4 (2.1% to 8.4%), Febrile neutropenia (adults, 2% to 7.1%; pediatrics, 8.8%), Hemorrhage (1% to 5%), Infectious disease, Neutropenic (1% to 2.2%), Leukopenia, Grade 3 and 4 (17.4% to 37.8%), Neutropenia, Grade 3 or 4 (adults, 26% to 53.8%; pediatrics, 31.8%), Thrombocytopenia, Grade 3 and 4 (up to 4%), Thromboembolic disorder (5.4% to 11.7%)
- **Immunologic:** Hypersensitivity reaction
- **Respiratory:** Interstitial lung disease

Common:

- **Dermatologic:** Alopecia (43.1% to 60%)
- **Endocrine metabolic:** Weight decreased (30%)
- **Gastrointestinal:** Abdominal pain (all grade, 17.2% to 67.7%; grade 3 and 4, 2.1% to 14%), Constipation (all grade, 30% to 43.9%; grade 3 and 4, 0.4% to 10%), Diarrhea, All grade (early-onset, 43% to 51%; late-onset, 72.4% to 88%), Loss of appetite (all grade, 34.2% to 55%; grade 3 and 4, 2.1% to 7.2%), Nausea (all grade, 66.9% to 86%; grade 3 and 4, 2.1% to 17%), Vomiting (all grade, 44.8% to 67%; grade 3 and 4, 3.5% to 14%)

- **Hematologic:** Anemia, All grade (60% to 97.2%), Drug-induced eosinophilia, Leukopenia, All grade (63% to 96.9%), Neutropenia, All grade (54% to 96.9%), Thrombocytopenia, All grade (32.6% to 96%)
- **Hepatic:** Increased bilirubin level (19.1% to 87.6%)
- **Neurologic:** Asthenia (all grade, 57.9% to 76%; grade 3 and 4, 9% to 19.5%), Dizziness (15% to 23.1%)
- **Respiratory:** Cough (17% to 26.7%), Dyspnea (9.7% to 27.6%)
- **Other:** Fever (42.2% to 45%), Infectious disease (13.9% to 35.9%), Pain (all grade, 22.9% to 64.1%; grade 3 and 4, 2% to 19%), Poisoning by parasympathomimetic drug (28.3%)

Patient Information

- Drug may cause dizziness or visual disturbances, especially within 24 h after infusion. Patient should avoid driving or other activities requiring clear vision until drug effects are realized.
- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- This drug may cause alopecia, nausea, vomiting, or interstitial lung disease.
- Instruct patient to report diarrhea that occurs during or shortly after infusion. Inform patient that diarrhea may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, or abdominal cramping.
- Patient should also report diarrhea that occurs more than 24 h after drug infusion. Instruct patient to take anti-diarrheal medicine only as prescribed by healthcare professional.
- Patient should contact healthcare professional if diarrhea cannot be controlled within 24 h, nausea/vomiting precludes patient from taking liquids, or patient has signs/symptoms of dehydration or infection.

Contraindications

- hypersensitivity to irinotecan or any component of the product

Precautions

- diarrhea, early or late; may be life-threatening due to possible dehydration, electrolyte imbalance, and sepsis
- bilirubin levels, elevated serum (1 to 2 mg/dL); increased risk for first cycle, grade 3 or 4 neutropenia
- bone marrow failure, severe; potential for neutropenia, leucopenia, and anemia
- concomitant use with live vaccine; avoid use
- elderly patients, greater than 65 years of age; increased risk of late diarrhea
- hepatic insufficiency; deficient glucuronidation of bilirubin (Gilbert's syndrome), increased risk of myelosuppression
- hereditary fructose intolerance; Camptosar(R) contains sorbitol
- homozygous for UGT1A1*28 allele ; increased risk of neutropenia; testing of the UGT1A1 6/6, 6/7 and 7/7 genotypes may be considered
- interstitial pulmonary disease (IPD)-like events, including fatalities, have been reported; hold therapy for any suspicious symptoms pending diagnostic evaluation
- Mayo Clinic regimen (5-fluorouracil/leucovorin) concomitant use; especially in patients receiving treatment with pelvic/abdominal radiation, elderly with comorbidities; may result in increased risk of neutropenic fever, hospitalization, thromboembolism, first-cycle treatment discontinuation, early death, toxicity, including toxic death
- myelosuppression, severe
- neutropenia; may lead to sepsis and death; dose reduction may be necessary

- vomiting and/or severe diarrhea; leading to volume depletion and increased risk of renal impairment and acute renal failure

Ixabepilone

Ixabepilone has been tested in more than one thousand adults, and risks and side effects related to Ixabepilone in adults include:

Likely	Less Likely	Rare but Serious

• **A feeling of weakness and/or tiredness**
• **Loss of appetite or desire to eat**
• **Nausea, and/or vomiting**
• **Diarrhea**
• **Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)**
• **Hair loss**
• **Muscle and joint pains**
• **A problem in nerve function that may cause pain, numbness, tingling, and muscle weakness in various parts of the body.**
	• **Allergic reactions**
	• **Fever caused by the medication**
	• **Fewer white blood cells, red blood cells and platelets in the blood**
	  ○ **a low number of white blood cells can make it easier to get infections**
	  ○ **a low number of red blood cells can make you feel tired and weak**
	  ○ **a low number of platelets causes you to bruise and bleed more easily**
	• **Constipation**
	• **A slower than normal heart rate**
	• **Chest pain which may be caused by heart damage**
	• **Heart attack**
	• **An increased level of a protein in the blood which is found in heart muscle and when elevated may indicate a heart attack or heart damage that could lead to a heart attack**
	• **A decrease in blood pressure**
	• **Change in the ability of the blood to clot if you are on a drug called warfarin or coumadin. You will need to be closely followed if you are on this medication.**
	• **Weight loss**
	• **Reddening of the face with feelings of warmth**
	• **Dizziness or fainting**
	• **Difficulty sleeping or falling asleep**
	• **Damage to the skin if the medication leaks from the vein**
	• **Changes to your finger or toenails**
	• **Itching**
	• **Redness and burning at sites which have received radiation in the past**
		• **Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling**
		• **A condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure. Vascular or capillary leak syndrome may lead to multiple organ failure such as kidney, heart or liver failure and shock**
		• **Fluid build-up in the lungs that can make you feel short of breath.**
		• **A stoppage (or blockage) of the intestine which may require treatment**
		•

	• **Rash with peeling of the skin** • **Severe rash with redness and pain on the palms of the hand and soles of the feet** • **Excessive loss of water from the body** • **Difficulty or discomfort on swallowing** • **Inflammation and/or sores in the throat and/or esophagus (the tube between the mouth and the stomach) that may make swallowing difficult and are painful** • **Upset stomach (heartburn)** • **Things taste differently** • **Erosion (ulceration) of the lining of the intestines which can result in pain and/or bleeding** • **Bleeding from the intestines** • **Damage to the liver which could lead to liver failure** • **Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics** • **Infections including those caused by bacteria, virus, and fungus** • **Fluid build-up in the tissues of the head, neck, arms, legs, body, abdomen (belly), body and sex organs** • **Increased levels of a chemical (creatinine) in the blood which could mean kidney damage** • **Unsteadiness when walking** • **Inability to speak or difficulty with speaking or putting words together** • **Watery eyes (tearing)** • **Abdominal (belly) pain** • **Bone pain** • **Headache** • **Arm or leg pain** • **Tumor pain** • **Muscle weakness** • **Hiccoughs** • **Cough** • **Feeling short of breath or shortness of breath** • **Low levels of oxygen in the blood which may make you feel**	

	short of breath • **Inflammation of the lungs that can lead to fluid in the lungs and affect your ability to breathe and the levels of oxygen in your blood making you short of breath** • **Difficulty emptying the bladder which may be caused by nerve damage** • **Lowered amount of salt (sodium) in the blood**	

The side effects that occurred in the adult patients may or may not occur in children entered on this study.

Ketoprofen

Common	Serious
Edema	Congestive heart failure (<1%),
Rash	Hypertension (<1%),
Abdominal pain,	Myocardial infarction (<2%),
Constipation,	Thrombotic tendency observations
Diarrhea,	Scaling eczema,
Flatulence,	Stevens-Johnson syndrome (<0.1%)
Indigestion,	Gastrointestinal hemorrhage (<1%),
Nausea	Gastrointestinal perforation (<1%),
Dizziness,	Inflammatory disorder of digestive tract,
Headache,	Melena (<1%)
Insomnia	Agranulocytosis (<1%),
Tinnitus	Anemia (<1%),
	Thrombocytopenia (<1%)
	Hepatitis (<1%),
	Increased liver function test (up to 15%),
	Jaundice (<1%),
	Liver failure (<0.1%)
	Anaphylactoid reaction (<1%),
	Immune hypersensitivity reaction
	Cerebrovascular accident
	Impaired renal function disorder (3-9%),
	Interstitial nephritis (<1%),
	Renal failure (<1%)
	Bronchospasm (<2%)

- This drug may cause edema, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, dizziness, headache, insomnia, or tinnitus.

- Patients with a history of cardiac disease or on a long-term treatment regimen are at an increased risk for adverse cardiovascular thrombotic events. Advise patient to report signs/symptoms of myocardial infarction or stroke.
- Instruct patients to report signs/symptoms of serious gastrointestinal events such as bleeding, ulceration, or perforation of stomach or intestines. Elderly and debilitated patients may be at an increased risk for this adverse effect.
- Patient may take with food, milk, or antacids to minimize gastrointestinal irritation.
- Advise patient to avoid use of additional NSAIDs without healthcare professional approval.
- Patient should not drink alcohol while taking this drug.

Ketorolac

Common	Serious
Edema, Hypertension Injection site pain, Pruritus, Rash, Sweating Abdominal pain (13%), Diarrhea (7%), Indigestion (12%), Nausea (12%) Anemia Dizziness, Headache, Somnolence Burning sensation in eye, Transient, ophthalmic ketorolac (20% to 40%, ophthalmic), Corneal edema (1% and 10%, ophthalmic), Eye irritation, Iritis (1% and 10%, ophthalmic), Keratitis (1% and 10%, ophthalmic) Feeling nervous	Myocardial infarction, Thrombotic tendency observations Body pale (<1%), Erythema multiforme, Erythroderma, Stevens-Johnson syndrome, Toxic epidermal necrolysis Gastrointestinal hemorrhage, Gastrointestinal perforation, Gastrointestinal ulcer, Melena, Pancreatitis (rare (incidence less than 0.1%) **H**Bleeding, Blood coagulation disorder with prolonged bleeding time, Hematoma, Postoperative hemorrhage Hepatitis, Increased liver function test, Jaundice, Liver failure Anaphylactoid reaction Aseptic meningitis, Cerebrovascular accident Corneal epithelial degeneration, Corneal erosion, Corneal thinning, Perforation of cornea Hearing loss Hematuria, Hemolytic uremic syndrome, Interstitial nephritis, Nephrotic syndrome,

	Papillary necrosis, Proteinuria, Renal failure Asthma, Bronchospasm, Dyspnea, Pulmonary edema Angioedema

- This drug may cause edema, sweating, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, stomatitis, vomiting, anemia, dizziness, headache, or somnolence. The ophthalmic formulation may cause a burning sensation in the eye.
- Patients with a history of cardiac disease or on a long-term regimen are at an increased risk for adverse cardiovascular thrombotic events. Advise patient to report signs/symptoms of myocardial infarction or stroke.
- Instruct patients to report signs/symptoms of serious gastrointestinal events such as bleeding, ulceration, or perforation of stomach or intestines. Elderly and debilitated patients may be at an increased risk for this adverse effect.
- Advise patients using the ophthalmic formulation to remove contact lenses prior to instilling drug. Lenses may be reinserted 15 min following instillation.
- Advise patient to avoid use of additional NSAIDs without healthcare professional approval.
- Patients using the ophthalmic formulation should avoid concomitant use of topical steroids.

Lansoprazole

Common	Serious
Abdominal pain (up to 5%), Constipation (1% to 5%), Diarrhea (up to 7.4%), Nausea (1.3% to 3%) Vomiting Taste sense altered Dyspepsia Headache Fatigue	Fracture of bone, Osteoporosis-related, Hip fracture, Rhabdomyolysis

- This drug may cause abdominal pain, constipation, diarrhea, dyspepsia, loss of appetite, nausea, vomiting, altered taste, headache, or fatigue.
- Patient should take oral preparations before eating.

Lapatinib

Common	Serious
Hand-foot syndrome due to cytotoxic therapy (53%), Rash (28% to 31%)	Depression of left ventricular systolic function (1.3% to 2%), Prolonged QT interval

Diarrhea (42% to 65%), Indigestion (11%), Nausea (13% to 44%), Vomiting (26%) Anemia (56%), Thrombocytopenia (18%) ALT (SGPT) level raised (37%), AST/SGOT level raised (49%), Hyperbilirubinemia (45%) Backache (11%), Pain in limb (12%) Insomnia (10%) Dyspnea (12%)	Hepatotoxicity (less than 1%) Interstitial lung disease

- Advise patient on the proper handling and disposal of chemotherapy drugs.
- This drug may cause gastrointestinal (nausea and vomiting) and dermatological (palmar-plantar erythrodysesthesia and rash) adverse events and fatigue.
- Instruct patient to report severe diarrhea and consult a healthcare professional prior to taking antidiarrheal medicine.
- Patient should report signs/symptoms of interstitial lung disease, pneumonitis, or decreased left ventricular ejection fraction (eg, dyspnea, palpitation, and/or fatigue).
- Advise patient to take this drug at least one hour before or one hour after a meal. In contrast, capecitabine should be taken with food or within 30 minutes after food.
- Patient should not eat grapefruit or drink grapefruit juice while taking this drug.

Leflunomide

Common	Serious
Alopecia (10%), Rash (10%) Diarrhea (17%)	Hypertension (9% to 10%; new-onset, 1% to 2%) Stevens-Johnson syndrome (rare), Toxic epidermal necrolysis (rare) Agranulocytosis (rare), Pancytopenia (rare) Hepatic necrosis (rare), Hepatotoxicity (rare), Increased liver enzymes, Liver failure (rare) Anaphylaxis, Opportunistic infection, Sepsis Interstitial lung disease (rare)

- Adverse effects to a fetus may be caused by either male or female patients receiving treatment with this drug. Emphasize the use of reliable contraception to patient. If pregnancy is desired or suspected in females, or males wishing to father a child, a drug elimination procedure may be

employed in order to rapidly remove leflunomide from the body. Consult healthcare professional.

- Advise patient to avoid vaccines during therapy without healthcare professional approval.
- This drug may cause rash, alopecia, diarrhea, or hypertension.
- Instruct patient to report signs/symptoms of hepatotoxicity, especially if using concomitant methotrexate.
- Advise patient to report signs/symptoms of a severe skin reaction such as Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering) or toxic epidermal necrolysis (widespread peeling/blistering of skin).
- Tell patients with a history of or active hematological abnormalities to monitor for and report signs/symptoms of pancytopenia.

Lenalidomide (CC-5013)

- We know about the following side effects of CC-5013:
-
- The main side effects that were seen in adults taking this drug were low blood counts, itchiness, and rash. All the bad effects, both common and uncommon, that have been seen so far in people getting this drug are listed below. Some of these problems might not have been related to the drug.
-
- Risks and side effects related to CC-5013 include:
-
- Low blood counts: low number of red blood cells, increased or decreased levels of white blood cells which help fight infection, low number of platelets which help the blood to clot, breakdown of red blood cells.
-
- Heart-related: abnormal heart rhythm, unusually fast or slow heartbeat, changes in your heart tracing (EKG), chest pain, high or low blood pressure, blockage of blood vessels decreasing the blood supply to the heart. A 15 year old girl getting CC-5013 had chest pain and a heart attack. This might have been related to the CC-5013. She recovered, but people can die from heart attacks.
- CC-5013 can cause blood clots in veins. These clots could break off and block veins or arteries in other parts of the body, such as the heart or lungs. Blood clots may be more likely in patients who are getting certain medicines like corticosteroids (prednisone, dexamethasone), interferon, erythropoietin (a medicine to make the red blood cells increase) or chemotherapy. Patients who smoke or who do not move around very much may also be more likely to have blood clots. If you have pain or swelling in an arm or leg, or feel chest pain or have trouble breathing, you should call your doctor right away. You might need to come to the hospital for more tests.
-
- Eye-related: dry eyes, blurred vision, visual flashing, disease of the retina.
-
- Stomach/Intestine-related: bloated feeling, constipation (bowel movements that are difficult and less often than usual), diarrhea (watery bowel movements), dry mouth, difficulty swallowing, nausea (feeling as though you need to vomit), vomiting, stomach pain, pain in the gums, inflammation, dehydration, loss of appetite, excessive gas in the stomach, heartburn/indigestion, tearing of the colon, blockage in the intestine, gallbladder stones; irritation of the pancreas, the organ in the body that makes insulin.
-

- General: allergic reaction, sleepiness, fatigue, trouble sleeping, fever, weight loss, headache, general body pain; sweating, rigors/chills, infection, inflammation and swelling in the nose and sinus due to allergy and including sneezing, nasal stuffiness, and postnasal drip.
- Laboratory test-related: abnormal liver or kidney function, abnormalities in the balance of salts in the blood (magnesium, calcium, potassium, sodium), high blood sugar, low testosterone (a male hormone), abnormal thyroid function, high cholesterol.
- Muscle/ Joint-related: joint, muscle, or bone pain; back pain, muscle weakness, partial paralysis usually with loss of feeling on half of the body, arthritis, excessive buildup of fluids in the arms and legs.
- Nervous system-related: difficulty speaking or writing, difficulty understanding spoken or written words; feeling dizzy, confusion, change in the sense of taste; , fainting spells, ringing in the ears, shaking, disease of the brain, blockage of blood vessels decreasing the blood supply to the brain, changes in your mental, motor, and sensory abilities, inflammation of the spinal cord, hallucinations/delusions, seizures, bleeding which may be life-threatening.
- Mood-related: depression, anxiety, agitation.
- Kidney-related: bleeding, problems with urination, disease of the kidney, kidney failure.
- Breathing-related: problems with your sinuses, cough, difficulty breathing, fluid build-up in the chest, bleeding which may be life-threatening, lung collapse
- Skin-related: dry skin, severe itching, rash, hives, hair loss all over the body, pimples, a skin disease characterized by rash and bumps. You may be more sensitive than usual to severe sunburn and should use sunblock or cover your skin if outside in the sun.
- Vein-related: a disorder in which blood clots form throughout the body, problems with blood clotting.
- Tumor Lysis Syndrome: very rapid death of cancer cells releases chemicals which may lead to reduced kidney function. Accumulation of these chemicals may harm muscle or nerve function.
- Reproductive Risks: If a person gets pregnant while receiving CC-5013, it could be dangerous for the baby. CC-5013 is related to thalidomide. If pregnant women take thalidomide, their babies can be born with no arms or legs. We do not know if CC-5013 causes similar birth defects, but you should be sure not to get pregnant or father a baby while on this study. A pregnancy test will be done before each course of therapy for girls and women of childbearing age on this study. If at any time you think you might be pregnant, tell the study staff right away. You must not nurse (breast feed) a baby while on this study. You must NEVER donate blood or ova while on this study. CC-5013 does not cause abortion of the fetus and should never be used as a form of birth control. Men must NOT be sperm or blood donors while taking CC-5013.

Lovastatin

Common	Serious
Abdominal pain Constipation Diarrhea Nausea Headache	Dermatomyositis Hepatotoxicity Drug-induced myopathy Myalgia Rhabdomyolysis Rupture of Tendon

ADVERSE EFFECTS: Diarrhea is the most common reported adverse effect. Hyperkalemia, peripheral neuropathy, myopathy, myalgias, acute renal failure, rhabdomyolysis, elevated liver enzymes, hepatitis, behavioral changes, CNS depression also reported. One patient developed compartment syndrome resulting in a four-compartment fasciotomy from statin-induced myositis.

- This drug may cause abdominal pain, constipation, diarrhea, nausea, or headache.
- Instruct patient to report myalgias or signs/symptoms of myopathy or renal failure.
- Patient should take tablets with evening meal and extended-release tablets at bedtime.
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).
- Patient should not drink large amounts of grapefruit juice (greater than 1 quart/day) while taking this drug.
- Instruct patient to avoid alcohol during drug therapy.

MEGESTROL ACETATE

Brand Name(s): **Megace**

Adverse Effects

Serious:

- **Endocrine metabolic:** Adrenal insufficiency
- **Hematologic:** Anemia, Deep venous thrombosis, Thrombophlebitis
- **Respiratory:** Pulmonary embolism

Common:

- **Cardiovascular:** Hypertension
- **Dermatologic:** Rash, Sweating symptom
- **Endocrine metabolic:** Hot sweats, Weight gain
- **Gastrointestinal:** Diarrhea, Flatulence, Indigestion, Nausea, Vomiting
- **Neurologic:** Insomnia
- **Psychiatric:** Mood swings
- **Reproductive:** Impotence

Patient Information

- This drug may cause sweating, hot flashes, weight gain, diarrhea, dyspepsia, flatulence, nausea, vomiting, insomnia, mood swings, impotence, anemia, deep venous thrombosis, thrombophlebitis, or pulmonary embolism.
- Instruct patient to report signs/symptoms of adrenal insufficiency, as drug may suppress the hypothalamic-pituitary-adrenal axis.

- Inform patient that drug may need to be taken for at least 2 months before effectiveness can be determined.

Contraindications

- history of hypersensitivity to megestrol acetate or any component of the formulation
- known or suspected pregnancy

Precautions

- diabetes
- history of thromboembolic disease
- megestrol acetate is not intended for prophylactic use to avoid weight loss
- possibility of adrenal insufficiency in patients receiving or being withdrawn from chronic megestrol acetate therapy
- use of megestrol in other types of neoplastic disease is not recommended

Mercaptopurine

Risks and side effects related to mercaptopurine include those which are:

Likely	Less Likely	Rare But Serious
• Fewer white blood cells, red blood cells and platelets in the blood ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets cause you to bruise and bleed more easily	• Loss of appetite • Nausea and/or vomiting • Diarrhea • Inflammation an/or sores in the mouth which may look like thrush • Red itchy rash and/or hives which may even occur a few weeks after treatment stops • Darkening of the skin (L) • Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean liver irritation or damage • Hair loss • High levels of uric acid in the blood which could damage the kidneys • A feeling of extreme tiredness or weakness or not feeling well • Absence or decrease in the number of sperm which may decrease the ability to have children	• Inflammation of the pancreas which can cause severe abdominal pain • Inflammation or scarring of the lungs which could lead to chest pain or discomfort and shortness of breath • Damage to the liver which can lead to inflammation and or scarring which could lead to a yellow appearing skin, and fluid collection in the stomach which makes it look larger • A new cancer or leukemia resulting from this treatment

MESALAMINE

Brand Name(s): **Apriso ; Asacol ; Canasa ; Lialda ; Pentasa ; Rowasa ; sfRowasa**

Adverse Effects

Serious:

- **Cardiovascular:** Pericarditis (rare)
- **Gastrointestinal:** Pancreatitis (less than 1%), Rectal hemorrhage (less than 3%)
- **Hematologic:** Agranulocytosis (rare), Aplastic anemia (rare), Leukopenia (rare), Neutropenia (rare), Pancytopenia (rare), Thrombocytopenia (rare)
- **Hepatic:** Cholestatic hepatitis (less than 3%), Hepatotoxicity (rare), Liver failure

- **Immunologic:** Hypersensitivity reaction
- **Renal:** Renal impairment
- **Other:** Drug intolerance, Syndrome

Common:

- **Gastrointestinal:** Abdominal pain (2.2% to 2.3%), Diarrhea (up to 8%), Flatulence (up to 4%), Nausea (up to 4%), Ulcerative colitis (2.3% to 5.8%), Upper abdominal pain (1.2% to 5%)
- **Hepatic:** Liver function tests abnormal (2.3%)
- **Neurologic:** Headache (2.9% to 11%)
- **Respiratory:** Nasopharyngitis (1.4% to 4%)

Patient Information

- Instruct patient to stop drug and report signs/symptoms of acute intolerance syndrome (cramping, acute abdominal pain, bloody diarrhea, fever, headache, or rash).
- Warn patient with phenylketonuria that Apriso(TM) extended-release capsules contain aspartame.
- Advise patient with sulfite sensitivity that Rowasa(R) enema contains metabisulfite.
- Drug may cause abdominal pain, constipation, diarrhea, nausea, vomiting, arthralgia, asthenia, dizziness, or headaches.
- Oral formulations may cause blood dyscrasias, especially in the elderly (65 years and older).
- Advise patient to report signs/symptoms of renal failure (eg, nausea, vomiting, reduced urine output, drowsiness, headache, or back pain).
- For rectal formulations, advise patient on proper administration technique and timing (use at bedtime) for maximum retention of drug.
- Advise patient to avoid antacids with Apriso(TM) extended-release capsules.

Contraindications

- hypersensitivity to mesalamine, other salicylates (including aspirin), or to any component

Precautions

- acute intolerance syndrome, similar to exacerbation of inflammatory bowel disease or colitis, has been reported; discontinue treatment if this occurs
- cardiac hypersensitivity reactions (myocarditis or pericarditis) have been reported; use cautiously in conditions predisposing patient to myocarditis or pericarditis (Lialda(R), rectal suspension, and enema)
- concomitant use with antacids should be avoided (extended-release capsules (Apriso(TM))
- concurrent oral products which contain or release mesalamine; increased risk of renal abnormalities (rectal suppositories and enema)
- elderly (65 years and older); greater risk of blood dyscrasias; monitoring recommended (extended-release capsules and delayed-release tablets)
- inflammatory bowel disease; exacerbation of symptoms including melena and hematochezia may occur (enema)
- liver disease; hepatic failure has been reported (extended-release capsules and delayed-release tablets)
- pancolitis has been reported (rectal suppositories and enema)
- phenylketonuria; contains aspartame (extended-release capsule)

- pyloric stenosis; possibility of prolonged gastric retention of mesalamine (delayed-release tablets)
- renal dysfunction or history of renal disease; increased risk of renal toxicity; monitoring recommended
- renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and rarely renal failure have been reported; increased risk in those with renal disease; monitoring recommended
- sulfasalazine hypersensitivity, history; possibility of similar hypersensitivity reaction
- sulfite hypersensitivity; contains metabisulfite (enema)
- report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

Metformin

Common	Serious
Cobalamin deficiency Diarrhea Flatulence Indigestion Nausea Vomitting Asthenia	Lactic acidosis (generally associated with underlying conditions such as renal insufficiency, hepatic disease, sepsis, etc)

- Drug may cause diarrhea, dyspepsia, flatulence, nausea, vomiting, hyper- or hypoglycemia, or asthenia.
- Instruct patient to report signs/symptoms of lactic acidosis (nausea, vomiting, abdominal pain, tachypnea). Elderly patients (80 years and older) are at increased risk.
- Patient should take tablets with meals and extended-release tablets with the evening meal.
- Tell patient to maintain adequate hydration to prevent renal dysfunction.
- Tell patients to notify healthcare provider of metformin use before having radiologic studies using IV dye.
- Patient should not drink alcohol while taking this drug.

Methimazole

Common	Serious
Skin rash Uriticaria Nausesa Vomiting Epigastric distress Arthralgia Paresthesia Loss of taste	Agranulocytosis Aplastic anemia Hepatotoxicity Drug fever Lupus-like syndrome Insulin autoimmune syndrome Periartheritis Hypoprothrombinemia

Abnormal loss of hair Myalgia Headache Pruritus Drowsiness Neuritis Edema Vertigo Skin pigmentation Jaundice Sialadenopathy Lymphadenopathy	Nephritis (very rarely)

Advise patient to report signs/symptoms of hepatotoxicity, aplastic anemia, or infection (fever, headache, malaise, skin eruptions, sore throat).

Methotrexate

Risks and side effects related to methotrexate (when given by mouth or vein) include those which are:

Likely	Less Likely	Rare But Serious
• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea • Vomiting • Loss of appetite • Diarrhea • Chills and/or fever • Inflammation and/or sores in the mouth, gums, throat and/or esophagus • Inflammation of the intestines which may cause bleeding • Sensitivity to sunlight and increased risk of sunburn • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak. ○ A low number of white blood cells can make it easier to get infections. ○ A low number of platelets causes you to bruise and bleed • Learning disability • Dizziness • Sense of not feeling well or tiredness • Drowsiness • Blurred vision • Rashes with itching and hives • Hair loss, inflammation of the	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys. • Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet • Damage, inflammation and/or scarring of lung tissue which may make you short of breath and cough • Seizures • Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes • Temporary loss of function or feeling in the lower part of the body (partial paralysis) • Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or

	hair follicles • Acne • Tearing and inflammation of the eyes • Darkening of the fingernails	could lead to a coma. • Inflammation and scarring of the liver • Damage to the bone which could lead to arthritis pain and weakness of the bone • Inflammation of the heart • Fluid buildup around the heart • Damage to the kidney

Methyl CCNU

ADVERSE REACTIONS (Reported to be the same as BiCNU) Need to change drug name as listed below

Common	Serious
Nausea Vomiting Burning at injection site Suffusion of the conjunctiva Chest pain Headache	Pulmonary infiltrates (late effect) Pulmonary fibrosis (late effect) Delayed myelosuppression Delayed leucopenia Delayed thrombocytopenia Anemia Neutropenia Hepatic toxicity Renal damage Nephrotoxicity Decreased kidney size Renal failure Allergic reaction Neuroretinitis Hypotention tachycardia

Minocycline

Risks and Discomforts

If you agree to enroll in this study, there may be some risks to your health and well-being. Known side effects associated with minocycline use are: sensitivity to sunlight (frequent; greater than 20%); dizziness; constipation; nausea; vomiting; and loss of appetite (occasional; 2 to 20%). To avoid sunlight sensitivity, you can use sunscreen, wear clothing with long sleeves and long pants, and try to stay out of direct sun as much as possible. In rare cases (less than 2%), staining of the outer layer of teeth, kidney disease, anemia (low iron and red blood cells which may cause tiredness and shortness of breath), and liver disease have been reported.

Rare instances of inflammation of the esophagus (or food pipe) and ulcers in the esophagus have also been reported with minocycline. To reduce the risk of irritation of the esophagus, your study medication, if taken by mouth, should be taken with a full glass of water (8 ounces). If you

experience pain when swallowing, you must report this to your study doctor immediately. The study medication can be taken with or without food.

Other side effects of minocycline include rash, hives, headache, joint pain, and allergic reactions (rare; 1-3%).

Serious allergic reactions that can be life-threatening may occur with minocycline use.

You should be very careful when driving or using machinery until you know how the study drug(s) will affect you. This is because the study medication(s) may cause drowsiness, dizziness, lack of coordination, or slow your reaction time.

There may be other risks which are not known at this time and which we cannot predict.

Minocycline may not be as effective if taken with any antacids, calcium supplements, iron products, and laxatives containing magnesium. None of these medications may be taken within 2 hours before or after taking Minocycline.
In addition, minocycline may interfere with the effectiveness of oral contraceptives. Therefore, for female subjects of childbearing potential, the addition of a barrier method of contraception (condom or diaphragm) will be required during the study. Minocycline may be dangerous to an unborn child (fetus or embryo). If, at any time during the study, you suspect that you are pregnant, you must immediately notify your study doctor.

MITOXANTRONE

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea, fever, anorexia, green blue discoloration of the urine and/or sclera	Abdominal pain, back pain, headache, phlebitis, constipation	Anaphylaxis, angioedema, cardiac arrhythmias1 (bradycardia), seizures, extravasation reactions rare but if occur can lead to: (erythema, swelling, pain, burning and/or blue discoloration of the skin and rarely tissue necrosis), tumor lysis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L), mucositis /stomatitis, immunosuppression, alopecia, fatigue	Transient elevation of LFTs, pruritis with desquamation of the skin due to progressive dryness	Rash, conjunctivitis, (GI) hemorrhage, interstitial pneumonitis

Delayed: Any time later during therapy	Amenorrhea, menstrual disorders, temporary reduction in sperm count	Cardiotoxicity (decreased LVEF)2 (L)	CHF, hepatotoxicity
Late: Any time after completion of treatment			Secondary malignancy
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mitoxantrone have been noted in animals. Toxicities include: low birth weight and prematurity. Mitoxantrone is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration.		

1 Rarely clinically significant.
2 Risk increases with chest radiation and prior anthracycline dosage
(L) Toxicity may also occur later.

Nabumetone

Common	Serious
Edema Pruritus Skin Rash Abdominal pain Constipation Diarrhea Flatulence Indigestion Nausea Occult blood in stools Dizziness Headache Insomnia tinnitus	Hypertension Myocardial infarction (<2%) Thrombotic tendency observation Erythema multiforme (rare) Scaling eczema Stevens-Johnson syndrome Toxic epidermal necrolysis (<0.1%) Gastrointestinal hemorrhage (<1%) Gastrointestinal perforation (<1%) Inflammatory disorder of digestive tract Melena (<1%) Anemia Thrombocytopenia (<1%) Hepatitis Increased liver function test (up to 15%) Jaundice Liver failure (rare) Immune Hypersensitivitiy reaction (<1%) Cerebrovascular accident Albuminuria (<1%) Interstitial nephritis (rare) Renal azotemia (<1%) Renal failure (rare) Bronchospasm (<2%)

- Advise patient to immediately report signs/symptoms of Stevens-Johnson syndrome (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering).
- Patients with a cardiac history or on a long-term regimen are at an increased risk for adverse cardiovascular thrombotic events. Advise patient to report signs/symptoms of myocardial infarction or stroke.
- Instruct patients to report signs/symptoms of serious gastrointestinal events such as bleeding, ulceration, or perforation of stomach or intestines. Tell patient drug is best taken with food or milk.
- Patient should not drink alcohol while taking this drug.
- Advise patient to avoid concomitant use of oral corticosteroids, as this may increase the risk for serious gastrointestinal effects.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may be increased in patients with cardiovascular disease or risk factors for cardiovascular disease. Nabumetone is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs can also cause an increased risk of serious gastrointestinal adverse events especially in the elderly, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Naproxen

Common (>3 %)	Serious (1-3%)	Rare (<1%)
Edema Pruritus Skin Rash Abdominal Pain Constipation Diarrhea Heartburn Indigestion Nausea Stomatitis Dizziness Headache Somnolence Tinnitus Dyspnea	Lightheadedness Vertigo Scaling eczema Inflammatory disorder of digestive tract Anemia Thrombotic tendency observations Increased liver function	Congestive Heart Failure Myocardial Infarction Pulmonary Edema Vasculitis Steven-Johnson syndrome Toxic epidermal necrolysis Gastrointestinal hemorrhage Gastrointestinal perforation Pancreatitis Agranulocytosis Granulocytopenic disorder Thrombocytopenia Hepatitis Jaundice Liver failure Anaphylactoid reaction Aspectic meningitis Cerebrovascular accident Seizure Interstitial nephritis Nephrotic syndrome Papillary necrosis Renal failure Serum creatinine raised

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness or somnolence.
- This drug may cause edema, abdominal pain, constipation, diarrhea, dyspepsia, heartburn, nausea, stomatitis, anemia, headache, tinnitus, dyspnea, scaling eczema, or liver failure.
- Patients with a cardiac history or on a long-term regimen are at an increased risk for adverse cardiovascular thrombotic events. Advise patient to report signs/symptoms of myocardial infarction or stroke.
- Instruct patients to report signs/symptoms of serious gastrointestinal events such as bleeding, ulceration, or perforation of stomach or intestines. Elderly and debilitated patients may be at an increased risk for this adverse effect.
- Tell patient drug is best taken with food or milk.
- Patient should not drink alcohol while taking this drug.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may be increased in patients with cardiovascular disease or risk factors for cardiovascular disease. Naproxen is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs can also cause an increased risk of serious gastrointestinal adverse events especially in the elderly, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

VINORELBINE TARTRATE

Brand Name(s): **Navelbine**

Adverse Effects

Serious:

- **Cardiovascular:** Non-ST segment elevation myocardial infarction, acute
- **Gastrointestinal:** Bowel obstruction, Constipation, Pancreatitis, Paralytic ileus, Perforation of intestine
- **Hematologic:** Granulocytopenic disorder (Severe), Significantly greater in combination with cisplatin, Myelosuppression, Significantly greater in combination with cisplatin
- **Hepatic:** AST/SGOT level raised (frequent)
- **Respiratory:** Acute respiratory distress syndrome, Bronchospasm, Interstitial lung disease
- **Other:** Sepsis

Common:

- **Dermatologic:** Alopecia (grades 1 and 2, up to 35%; grades 3 and 4, 4% to 12%), Injection site reaction
- **Gastrointestinal:** Diarrhea, Nausea, Vomiting
- **Neurologic:** Asthenia, Neuromyopathy

Patient Information

- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- This drug may cause alopecia, tissue necrosis, diarrhea, nausea, vomiting, constipation, asthenia, and neuromyopathy.
- Drug may also cause significant adverse effects including bowel obstruction, pancreatitis, paralytic ileus, and perforation of intestine.
- Instruct patient to report signs/symptoms of myelosuppression.

- Advise patient to report signs/symptoms of respiratory adverse effects such as acute respiratory distress syndrome, bronchospasm, and dyspnea.

Contraindications

- granulocytopenia, granulocyte counts less than 1,000 cells/mm(3); withhold administration
- intrathecal administration; can be fatal

Precautions

- extravasation causing local tissue necrosis and/or thrombophlebitis can occur
- granulocytopenia, granulocyte counts from 1,000 to 1,499 cells/mm(3); dose adjustments according to complete blood counts with differentials obtained on the day of treatment
- compromised bone marrow reserve
- concomitant mitomycin, cisplatin, CYP3A inhibitors
- concomitant or sequential treatment with paclitaxel
- prior history or pre-existing neuropathy
- prior radiation therapy- radiation recall
- severe hepatic injury or impairment
- use proper procedures for handling and disposal of chemotherapy

Nitisinone

Adverse Events

Common ≥ 1%	Rare < 1%
Exfoliative Dermatitis	Diarrhea
Dry Skin	Abdominal pin
Cutaneous pruritus	Gastroenteritis
Alopecia	Gastrointestinal hemorrhage
Maculopapular rashes	Liver failure
Leukopenia	Neoplasm of liver
Thrombocytopenia	
Conjunctivitis	
Corneal opacity	
Keratitis	
Light sensitivity	

- Patient should report development of a rash or signs/symptoms of leukopenia, thrombocytopenia, or hepatic failure.
- Advise patient to report ocular symptoms (photophobia, eye pain, burning, redness, or swelling).
- Patient should take drug on an empty stomach at least 1 h before a meal.
- Instruct patient on any dietary tyrosine restrictions. Foods high in tyrosine include dairy products, meat, fish, eggs, pumpkin or sesame seeds, almonds, avocados, and soy.

Omeprazole

Common ≥ 1%	Rare < 1%
Abdominal pain (2.4% to 5.4%), Diarrhea (3% to 3.7%) Diarrhea (3% to 3.7%) Constipation (1.1% to 1.5%) Flatulence (2.7%) Nausea (2.2% to 4%) Vomiting (1.5% to 3.2%) Headache (2.9% to 6.9%) Back pain (1.1%) Asthenia (1.2%) Dizziness (1.5%) Cough (1.1%)	Pancreatitis Hepatotoxicity Bone fracture Joint pain Muscle cramps Osteroporosis-related bone fracture Hip fracture Rhabdomyolysis Myalgia Myositis Leg pain Throat pain Interstital nephrisis Visual disturbances Ringing in the ear Urinary Tract infection Epistaxis

- This drug may cause constipation, diarrhea, nausea, and headache.
- Tell patients on long-term therapy to report signs/symptoms of atrophic gastritis.
- Advise patient to take drug before a meal.

Orlistat

Common ≥ 5%	Rare < 1%
Abdominal discomfort Abdominal pain Defecation urgency Increased frequency of defecation Steatorrhea	Cholelithiasis (2.9)

- This drug may cause abdominal discomfort or pain, urgency or increased frequency of defecation, and steatorrhea.
- If using concurrently with orlistat, patient should take multivitamins or cyclosporine at least 2 h before or 2 h after an orlistat dose.
- Advise patient to take this drug during or up to 1 h after meals containing fat. Patient should omit dose if a meal is missed or contains no fat.
- Instruct patient to take a missed dose as soon as possible up to 1 h after meal. If missed dose is more than 1 h overdue, skip the missed dose.

Oxaliplatin

Risks and side effects related to oxaliplatin include those which are:

Likely

- Numbness or tingling sensation of mouth, throat, arms, legs, fingers and toes which may become worse with cold temperatures and which may affect the ability to perform tasks that require fine muscle coordination
- Nausea and vomiting
- Stomach cramps or pain
- Diarrhea or constipation

Less Likely

- Headache
- Runny nose
- Feeling of "heartburn"
- Change in taste
- Dehydration (fluid loss)
- Dizziness and/or loss of coordination
- Feeling of extreme tiredness not relieved by rest or sleep
- Reddening and cracking of the skin on the hand palms and soles of the feet, associated with pain and possibly infection
- Sudden reddening of face and neck
- Rash
- Difficulty sleeping
- Loss of appetite or desire to eat
- Allergic reaction that may be life threatening
- Shaking chills
- Blood in the urine
- Painful or difficulty urinating
- Inflammation of the vein through which the drug was given
- Fewer white blood cells, red blood cells and platelets in the blood*
    - A low number of white blood cells can make it easier to get infections
    - A low number of red blood cells can make you feel tired and weak
    - A low number of platelets causes you to bruise and bleed more easily
- Nose bleed
- Loss of weight
- Soreness or ulcers inside the mouth and throat
- Hair loss
- Swelling of the hands, arms, feet and legs
- Joint pain
- Lung infections
- Sore throat
- Fever
- Increased levels of creatinine in the blood which could mean kidney damage
- Lower levels of a salt (potassium) which is measured in the blood
- Too much acid in the blood
- Hiccups
- Too much gas produced in the intestines

- Difficulty swallowing
- Mild increases in liver enzymes without symptoms and usually returning to normal
- Increase in blood pressure
- Inflammation of the ear
- Inflammation of the small bowel which may cause pain and discomfort
- A feeling of depression
- Cough
- Bone Pain
- Inability to urinate
- Damage to the surface of the eye which might lead to pain and tearing
- Restless movements that are not under your control (involuntary)

Rare but some of these can be serious

- Shortness of breath
- Sudden, temporary feeling of difficulty in swallowing or breathing which can occur during or shortly after the infusion and may be caused by swallowing a cold drink
- Infections
- Irregular or rapid heart beat
- Rare but serious damage to the liver which can lead to an enlarged liver and spleen, bleeding from the veins in the esophagus, a yellow appearing skin, and fluid collection in the abdomen which makes your abdomen look larger
- Tissue irritation or damage which may be severe if drug leaks from the injection site – this may cause pain, redness and swelling
- Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
- Blood clots
- Blurred vision or blind spots in vision
- Damage to lung tissue
- Damage to kidney which may be permanent
- Loss of some hearing
- A bleeding disorder that can cause bleeding from many areas of the body including the nose, the rectum and the urine
- A blockage of the intestine that may require treatment
- Inflammation of the pancreas which can cause severe abdominal pain

Oxaprozin

Common ≥ 1%	Rare < 1%
%) Rash	Edema
Abdominal pain	Hypertension
Constipation	Palpitations
Diarrhea	Thrombotic tendency observations
Indigestion	Erythema multiforme
Nausea	Scaling eczema
Vomittin	Stevens-Johnson Syndrome
Tinnitus	Toxic epidermal necrolysis

Dysuria Increased frequency of urination Myocardial infaraction	Cerebrovascular accident Gastrointestingal hemorrhage Gastrointestinal perforation Inflammatory disorder of digestive tract Pancreatitis Agranulocytosis Anemia Leucopenia Thrombocytopenia Hepatitis Increased liver function test Jaundice Liver failure Anaphylactoid reaction Amblyopia Hearing loss Acute renal failure Hematuria Interstitial nephritis Bronchospasm Serum sickness due to drug

- This drug may cause abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, tinnitus, dysuria, photosensitivity, increased urinary frequency, or bronchospasm.
- Advise patient to report signs/symptoms of serious cardiovascular thrombotic events, myocardial infarction, and stroke.
- Patient should also report signs/symptoms of bleeding, ulceration, or perforation of the stomach or intestines. Elderly and debilitated patients are at higher risk while taking this drug.
- Tell patient to avoid concurrent use of other NSAIDs unless approved by healthcare professional.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may be increased in patients with cardiovascular disease or risk factors for cardiovascular disease. Oxaprozin is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs can also cause an increased risk of serious gastrointestinal adverse events especially in the elderly, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Paclitaxel

Risks and side effects related to Paclitaxel include those which are:

Likely	Less Likely	Rare but serious
• Nausea • Reddening of the face or skin with feelings of	• Vomiting • Diarrhea • Shortness of breath	• Severe allergic reaction which can be life threatening with shortness

warmth • Temporary changes on a test called an EKG that measures the activity of your heart • A feeling of weakness and/or tiredness • Aches and pains in the muscles or joints • Loss of appetite • Temporary hair loss • Fewer white blood cells and red blood cells in the blood o a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make you feel tired and weak • A problem in nerve function that may cause pain, numbness, tingling, and muscle weakness in various parts of the body • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores) • Elevation in the blood of certain enzymes or chemicals found in the liver which might indicate liver irritation or damage	• Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight • Cough • Rash with itching or hives • Low or high blood pressure • Fainting • Infections including those caused by bacteria, virus, and fungus • Elevation in the blood of bilirubin (a substance that comes from the liver breaking down waste products) found in the liver • found in the liver • Fewer platelets in the blood o a low number of platelets causes you to bruise and bleed more easily • Back or chest pain • Pain, redness, inflammation and skin damage in the vein through which the drug was given • Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics • Unsteadiness when walking • Inflammation, pain and reddening of the eye with watery eyes • Inflammation of the nerves to the eye which could lead to blurred vision or other vision changes • Damage to the ear causing hearing loss, which maybe temporary or permanent, balance problems (dizziness) and ringing in the ears • The finger or toe nails may darken in color	of breath, low blood pressure, rapid heart rate, chest pain, chills and fever • Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath. • Clotting of blood vessels which can lead to pain and swelling in the area of the clot. Such clots make break loose and cause damage or be life-threatening depending on where they go. • Abnormal heart rate which may be life-threatening • Heart attack • Bleeding which can occur in the head, stools, the nose, urine and other parts of the body • Seizures • Severe damage to the brain which may lead to difficulty carrying out normal daily tasks and to coma • A stoppage (or blockage) of the intestine which may require treatment • Severe rashes which can result in loss of skin and damage to mucous membranes and which may be life-threatening • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid • Inflammation, infection or scarring of the lungs that can lead to fluid in the lungs and affect your

	• Chills	ability to breathe and the levels of oxygen in your blood making you short of breath • Damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger

PAMIDRONATE DISODIUM

Brand Name(s): **Aredia**

Adverse Effects

Serious:

- **Musculoskeletal:** Arthralgia (13.6%), Aseptic necrosis of bone of jaw, Bone pain (at least 10% to 15%), Myalgia (26%)
- **Neurologic:** Seizure (2%)
- **Renal:** Focal segmental glomerulosclerosis

Common:

- **Dermatologic:** Injection site reaction
- **Endocrine metabolic:** Hypocalcemia (12%), Hypokalemia (18%), Hypomagnesemia (12%), Hypophosphatemia (18%)
- **Gastrointestinal:** Loss of appetite, Nausea, Vomiting
- **Hematologic:** Anemia (42.5%)
- **Renal:** Urinary tract infectious disease (18.5%)
- **Other:** Fever

Patient Information

- This drug may cause anorexia, nausea, vomiting, or fever.
- Advise patient to report incapacitating or severe bone, joint, and/or muscle pain .
- Patient should report signs/symptoms of renal impairment or anemia.
- Tell patients with concomitant risk factors for osteonecrosis of the jaw to report signs/symptoms of this condition (gum loss, numbness, or pain, swelling, infection of jaw/gums). Risk factors for osteonecrosis of the jaw include cancer, chemotherapy, corticosteroids, or poor oral hygiene.

Contraindications

- hypersensitivity to pamidronate or other bisphosphonates

Precautions

- anemia, leukopenia, or thrombocytopenia, preexisting; monitoring recommended
- focal segmental glomerulosclerosis (including the collapsing variant); has been reported, especially when treating multiple myeloma and breast cancer

- metabolic abnormalities (eg, calcium, phospate, magnesium, potassium levels) may occur; monitoring recommended
- musculoskeletal pain, severe; has been reported within days, months, or years following therapy initiation; consider discontinuing bisphosphonates if symptoms occur
- osteonecrosis of the jaw has been reported; risk factors include: cancer (advanced breast cancer, multiple myeloma), chemotherapy, corticosteroids, local infections, and dental status (dental extraction, periodontal disease, local trauma including poor fitting dentures); a dental examination with appropriate preventive dentistry should be considered prior to bisphosphonate treatment; invasive dental procedures should be avoided during bisphosphonate treatment
- renal function deterioration, progression to renal failure, and dialysis have been reported following initial or single doses; patients with multiple myeloma also receiving thalidomide may be at increased risk; single doses should not exceed 90 mg; monitoring recommended; withhold therapy for renal deterioration in patients with bone metastases
- renal impairment, preexisting; increased risk of renal adverse events; monitoring recommended; treatment of bone metastases in severe impairment is not recommended
- thyroid surgery, history of; may predispose to hypoparathyroidism and increase risk of hypocalcemia

Pazopanib

Risks and side effects related to the pazopanib include the following:

Likely:

- **Lack of enough red blood cells (anemia)**
- **Diarrhea**
- **Nausea or the urge to vomit**
- **Fatigue or tiredness**
- **Increased blood level of a liver enzyme (ALT/SGPT)**
- **Increased blood level of a liver enzyme (AST/SGOT)**
- **Increased blood level of a liver pigment (bilirubin) often a sign of liver problems**
- **Decreased number of a type of white blood cell (lymphocyte)**
- **Decreased number of a type of white blood cell (neutrophil/granulocyte)**
- **Decrease in the total number of white blood cells (leukocytes)**
- **Increased blood sugar level**
- **Changes in hair color**
- **High blood pressure**

Less Likely:

- **Belly pain**
- **Constipation**
- **Vomiting**
- **Test that shows a problem in blood clotting**
- **Increased blood level of a liver or bone enzyme (alkaline phosphatase)**

- **Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)**
- **Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding**
- **Increased blood level of fat-digesting enzyme (lipase)**
- **Decreased number of a type of blood cell that helps to clot blood (platelet)**
- **Increased blood level of a digestive enzyme level (amylase)**
- **Loss of appetite**
- **Dehydration (when your body does not have as much water and fluid as it should)**
- **Increased blood level of potassium**
- **Increased blood level of magnesium**
- **Increased blood level of sodium**
- **Decreased blood level of calcium**
- **Decreased blood sugar level**
- **Decreased blood level of potassium**
- **Decreased blood level of magnesium**
- **Decreased blood level of sodium**
- **Decreased blood level of phosphate**
- **Joint pain**
- **Back pain**
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)**
- **Taste changes**
- **Headache or head pain**
- **More protein leaking into the urine than usual, often a sign of kidney disease**
- **Bleeding in some organ(s) of the respiratory tract**
- **Hair loss**
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)**
- **Lightening of the skin**

Rare but Serious:

- **Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)**
- **Heart attack caused by a blockage or decreased blood supply to the heart**
- **Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue**
- **Bleeding in some organ(s) of the digestive tract**
- **Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair**
- **Abnormal electrical conduction within the heart that may result in sudden death**
- **Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)**

- **Abnormal hole between part of the urinary system and another organ or tissue**
- **Abnormal hole between a female reproductive organ and another organ**
- **Abnormal hole between the uterus (womb) and another organ**
- **Abnormal hole between the vagina and another organ or tissue**
- **Swelling and redness of the skin on the palms of the hands and soles of the feet**
- **Formation of a blood clot in a vein that breaks loose and is carried by the blood stream to plug another blood vessel**
- **Formation of a blood clot in an artery that breaks loose and is carried by the blood stream to plug another blood vessel**
- **Bleeding into the tumor or organs which may be life threatening**

Reproductive risks: **You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.** Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. The effect of pazopanib on your ability to have children in the future is unknown.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

Peg-asparaginase

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea	Allergic reactions (total likelihood of local, and or systemic reaction if **no** previous hypersensitivity reaction to native asparaginase), rash	Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia
Prompt: Within 2-3 weeks, prior to	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT	Hyperglycemia, abnormal liver function tests, pancreatitis (L),	Hemorrhage (L), DIC, thrombosis, anorexia, weight loss, CNS

the next course	and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	increased serum lipase/amylase	ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis [SBE], URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain
Delayed: Any time later during therapy			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure
Unknown Frequency and Timing:	Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

L)Toxicity may also occur later.

Pemetrexed

Risks and side effects related to pemetrexed include:

Likely	Less Likely	Rare but Serious

• Shortness of breath
• A feeling of extreme tiredness not relieved by sleep
• Fewer red blood cells in the blood
  ○ A low number of red blood cells can make you feel tired and weak
• Fever
• Nausea and/or vomiting
	• Chest pain, pain in the abdomen (belly) or pain in other parts of the body
	• Fewer platelets in the blood
	  ○ A low number of platelets causes you to bruise and bleed more
	• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
		• Allergic reactions
		• Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly) which can be severe and may increase the blood sugar.
		• Damage to the lungs that can

• Loss of appetite • Fewer white blood cells in the blood which can make it easier to get infections • Infection • Cough	• Headache • Dizziness • Inflammation and/or sores in the mouth or throat and/or the esophagus (the tube that carries food from the mouth to the stomach) that may make swallowing difficult and are painful • Inflammation of the lining of the stomach • A feeling of weakness • Aches and pains in the muscles and joints • Rashes with itching and which may cause loss of skin • Fluid build-up under the skin • Hair loss • Constipation or diarrhea • Difficulty sleeping or falling asleep • Weight loss • Things taste differently • Chills • Hiccoughs • Excessive sweating • Inflammation and clotting of blood vessels which can lead to pain and swelling in the area of the clot; this may occur where the IV is placed. • Irritation to the skin if the medication leaks from the vein • Irritation to the skin at the site of the injection • Blurred vision, runny or red eyes • Reddening of the face or skin with feelings of warmth (flushing) • Low or high blood pressure • Excessive loss of water from the body (dehydration) • Low or High levels of certain salts in the body	lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in the blood. • Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics • Severe kidney damage (which may be permanent) • Severe liver damage (which may be permanent) • Clotting of blood vessels which can lead to pain and swelling in the area of the clot. Such clots may break loose and cause damage or be life-threatening depending on where they go. • Blockage of the intestines or bleeding in the intestines • Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools and abdominal (belly) pain • Heart attack • Swelling and tightening of the throat (voice box) which can cause difficulty with breathing

	like sodium, magnesium and potassium • Increase in heart rate • Acid or upset stomach (heartburn) • Too much gas produced in the intestines • Depression, anxiety or a feeling of confusion • Feeling the urgency to urinate or pain on urination • Increased levels of a chemical (creatinine) in the blood which could mean kidney irritation or damage • High levels of sugar in the blood that may require treatment • A problem in nerve function that may cause pain, numbness, tingling, and muscle weakness in various parts of the body • Inflammation or infection of the skin which will require treatment with antibiotics • Lung infection • Bladder or kidney infection • Redness or burning at the sites which have received radiation in the past	

Pentamidine

Common ≥ 5%	Rare < 1%
Rash Loss of appetite Nausea Increased liver function test Nephrotoxicity Bronchospasm Cough Dyspnea (Inhalation form only) Hypotension Injection site pain Hypoglycemia Leukopenia (<1% with Inhalation form) Thrombocytopenia	Cardiac dysrhythmia Skin necrosis Skin ulcer Tissue necrosis Acute pancreatitis Anemia (1.2%)

- This drug may cause nausea. Inhaled form may also cause bronchospasm, cough, and dyspnea.
- Tell patient to report unusual bleeding/bruising or signs/symptoms of new or worsening infection (fever, chills, night sweats, fatigue, anorexia), nephrotoxicity, pancreatitis, or cardiac dysrhythmia.
- This drug may cause severe hypoglycemia. Patient should be counseled on appropriate action to take during a hypoglycemic event.
- Advise patients using inhaled form on proper nebulizer technique.
- Patient should not mix other drugs with pentamidine in the nebulizer. Tell patient to avoid using nebulizer to give any other drugs.
- Instruct patient to lie supine while receiving intravenous form. Patient should rise slowly after administration to avoid dizziness and other potentially severe hypotensive effects.
- Patients using intravenous form should monitor IV insertion site closely during pentamidine infusion. Advise patient to immediately report signs/symptoms of extravasation, as drug is caustic.

PENTOSTATIN

Brand Name(s): **Nipent**

Adverse Effects

Serious:

- **Dermatologic:** Rash (26% to 43%)
- **Endocrine metabolic:** Hyponatremia (less than 3%)
- **Hematologic:** Microangiopathic hemolytic anemia, Neutropenia, Thrombotic thrombocytopenic purpura
- **Immunologic:** Immune hypersensitivity reaction (2% to 11%)
- **Neurologic:** Neurotoxicity (1% to 11%)
- **Renal:** Renal failure (less than 3%)

Common:

- **Dermatologic:** Disorder of skin (4% to 17%), Pruritus (10% to 21%)
- **Gastrointestinal:** Abdominal pain (4% to 16%), Diarrhea (15% to 17%), Loss of appetite (13% to 16%), Nausea and vomiting (53%), Stomatitis (5% to 12%)
- **Hematologic:** Anemia (8% to 35%), Hemorrhage (3% to 10%), Leukopenia (22% to 60%), Thrombocytopenia (6% to 32%)
- **Hepatic:** Increased liver function test (2% to 19%)
- **Immunologic:** Infectious disease (7% to 36%)
- **Musculoskeletal:** Myalgia (11% to 19%)
- **Neurologic:** Asthenia (10% to 12%), Headache (13% to 17%)
- **Renal:** Disorder of the genitourinary system (15%)
- **Respiratory:** Cough (17% to 20%), Disorder of lung (12%), Dyspnea (8% to 11%), Rhinitis (10% to 11%), Upper respiratory infection (13% to 16%)
- **Other:** Fatigue (29% to 42%), Fever (42% to 46%), Pain (8% to 20%), Shivering (11% to 19%)

Patient Information

- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- This drug may cause shivering, nausea, vomiting, myalgia, headache, cough, fatigue, or fever.

- Patient should report signs/symptoms of hepatotoxicity, neurotoxicity, nephrotoxicity, or pulmonary toxicity. Patients receiving high dosages are at higher risk for these effects.
- Advise patient to report angina, or signs/symptoms of cardiac dysrhythmia, heart failure or myelosuppression

Contraindications

- hypersensitivity to pentostatin or any component of the product

Precautions

- concomitant use with fludarabine phosphate is not recommended due to an increased risk of fatal pulmonary toxicity
- higher than recommended doses; may increase the risk of severe renal, liver, pulmonary, and CNS toxicity
- acute pulmonary edema and hypotension, some cases fatal, have been reported in bone marrow transplant patients who received pentostatin in combination with carmustine, etoposide, and high-dose cyclophosphamide (unapproved use)
- infection, active; use caution in patients with preexisting infection; withhold pentostatin if active infection develops during therapy
- nervous system toxicity may occur; withhold or discontinue therapy if nervous system toxicity occurs
- neutropenia, severe or worsening of, has occurred; monitoring recommended; temporarily withhold therapy for severe neutropenia
- rash, severe, has been reported; withhold therapy if severe rash occurs
- renal impairment
- renal toxicity (eg, elevated serum creatinine) has been reported; monitoring recommended; withhold therapy for elevated serum creatine

PHENTOLAMINE MESYLATE

Brand Name(s): **OraVerse**

Adverse Effects

- **SeriousCardiovascular:** Cardiac dysrhythmia, Chest pain, Hypotension, Myocardial infarction
- **Neurologic:** CVA - cerebrovascular accident due to cerebral artery occlusion

Common:

- **Dermatologic:** Injection site pain (4% to 6%)
- **Gastrointestinal:** Diarrhea (less than 3%)
- **Respiratory:** Nasal congestion (10%)
- **Other:** Posttreatment pain (up to 10%)

Patient Information

- This drug may cause nasal congestion, flushing, orthostatic hypotension, and arrhythmias.
- Submucosal injection may cause pain at injection site.
- Advise patient to report tachyarrhythmia or other signs/symptoms of cardiac dysfunction with parenteral forms.

Contraindications

- angina
- coronary artery disease, other evidence suggestive of
- coronary insufficiency
- hypersensitivity to phentolamine or related compounds
- myocardial infarction, history or recent
- specific contraindications have not been determined when used for soft-tissue anesthesia reversal in dental procedures (ORAVERSE(TM))

Precautions

- cardiovascular disease, history; increased risk of tachycardia and cardiac arrhythmias (ORAVERSE(TM))
- cerebrovascular spasm and occlusion have been reported, usually in association with marked hypotensive episodes following parenteral administration
- myocardial infarction has been reported, usually in association with marked hypotensive episodes following parenteral administration

Piperazine (Estropipate)

Common	Serious
Swelling of the limbs	Heart disease
Chloasma	Hypertension
Hisutism	Myocardial infarction
Bloating	Body fluid retention
Nausea	Breast cancer
Stomach cramps	Hypercalcemia
Vomiting	Gallbladder disorder
Headache	Pancreatitis
Migraine	Deep venous thrombosis
Depression	Venous thromboembolism
Mood changes	Anaphylaxis
Breast tenderness, pain, and/or swelling	Cerebrovascular accident
Disorder of menstruation	Dementia
Withdrawal bleeding	Impaired cognition
	Thrombosis of retinal vein
	Malignat neoplasm of endometrium of corpus uteri
	Ocarian cancer
	Pulmonary embolism
	Breast cancer

PIROXICAM

Brand Name(s): **Feldene**

Adverse Effects

Serious:

- **None indicated**

Common:

- **Dermatologic:** Injection site reaction (34%)

- **Gastrointestinal:** Diarrhea (37%), Nausea (34%), Vomiting (10%)
- **Musculoskeletal:** Arthralgia (13%)
- **Neurologic:** Dizziness (11%), Headache (22%)
- **Other:** Fatigue (27%)

Patient Information

- Drug may cause splenic rupture. Advise patient to report left upper abdominal, scapular, or shoulder pain.
- Drug may cause injection site reactions, headache, arthralgia, dizziness, vomiting, diarrhea, nausea, and fatigue.
- Instruct patient to report signs and symptoms of systemic reaction (urticaria, periorbital swelling, dyspnea, hypoxia).
- Instruct patient to report signs and symptoms of vasovagal reaction (orthostatic hypotension, syncope).

Contraindications

- specific contraindications have not been determined

Precautions

- leukemia; may mobilize leukemic cells and contaminate the apheresis product; use not recommended
- peripheral blood neutrophil counts above 50,000/mcL; monitoring recommended
- renal impairment, moderate and severe (CrCl 50 mL/min or less); dose reduction recommended
- thrombocytopenia has been reported
- women of childbearing potential; risk of fetal harm; avoid pregnancy using effective contraceptive measures
- report suspected adverse reactions to the Genzyme Corporation at 1-877-4MOZOBIL or to the US Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch

Pravastatin Sodium

Common ≥ 2%	Rare <1%
Diarrhea (2%) Flatulence (1.2%) Heartburn (2%) Nausea (1.6%) Vomiting (1.6%) Rhabdomyolysis (11.8%)	Pancreatitis Hepatotoxicity Rupture of tendon

- This drug should be discontinued 4 to 7 days before major surgery, as patient is at higher risk for occurrence of rhabdomyolysis.
- This drug may cause nausea, vomiting, diarrhea, abdominal pain, asthenia, headache, and flu-like symptoms.
- Tell patient to report signs/symptoms of rhabdomyolysis (myalgias, dark urine, arthralgias, fatigue) or myopathy (unexplained muscle aches, tenderness, or weakness).

- Patient should take this drug at least 1 h before or 4 h after cholestyramine, colestipol or other bile-acid-binding resins.
- Patient should not drink large amounts of alcohol taking this drug.

Prazosin Hydrochloride

Common ≥ 1%	Rare <1%
Orthostatic hypotension (1-4%) Palpitation (5.3%) Syncope (1-4%) Nausea (4.9%) Asthenia (6.5%) Dizziness (10.3%) Headache (7.8%) Lethargy (6.9%) Somnolence (7.6%)	Pancreatitis

- Tell patient to avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.
- Instruct patient to rise slowly from a sitting/lying position, as this drug may cause orthostatic hypotension.
- Patient may experience syncope or loss of consciousness, especially within 24 h of first dose.
- This drug may cause angina, palpitations, tachyarrhythmia, nausea, and asthenia.
- Advise patient against sudden discontinuation of drug, as this may cause rebound hypertension.
- Patient should not drink alcohol while taking this drug.

Prednisolone

Common	Serious
Body fluid retention Hypertension Acne Ecchymosis Skin superinfection Decreased body growth Hyperglycemia Abnormal lipids Gastrointestinal superinfection Muscle weakness Osteroporosis Headache Cararact Glaucoma Raised intraocular pressure Euphoria Psychotic disorder	Congestive heart failure Kaposi's sarcoma Diabetes mellitus with hyperosmolar coma Diabetic ketoacidosis Latrogenic Cushing's disease Secondary hypocortisolism Gastrointestinal perforation Pancreatitis Drug-induced myopathy Pseudotumor cerebri Seizure Pulmonary tuberculosis

General superinfection	

Prochlorperazine

Common	Rare <1%
Hypotension	Prolonged QT interval
Orthostatic hypotension	Torsades de pointes
Diminished sweating	Obstipation
Light sensitivity	Paralytic ileus
Constipation	Agranulocytosis
Xerostomia	Disorder of hematopoietic structure
Akathisia	Leucopenia
Dizziness	Thrombocytopenia
Drug-induced tardive dystonia	Cholestatic jaundice syndrome
Dystonia	Drug-induced lupus erythematosus, systemic
Extrapyramidal disease	Ineffective thermoregulation
Parkinsonian	Heatstroke or hypothermia
Somnolence	Neuroleptic malignant syndrome
Tardive dyskinesia	Seizure
Blurred vision	Priapism
Epithelial keratopathy	Death
Eye/vision findings	
Retinitis pigmentosa	
Nasal congestion	

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.
- Advise patient to rise slowly from a sitting/lying position, as drug may cause orthostatic hypotension.
- This drug may cause false readings on some types of pregnancy tests.
- Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- This drug may cause anticholinergic effects, eye dryness, extrapyramidal signs, and progressive loss of peripheral vision.
- Tell patient to report signs/symptoms of tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities) or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Patients using intravenous form should maintain adequate hydration to prevent volume depletion and hypotensive effects. Parents or caretaker of pediatric patients should report recent illness or dehydration before next dose is given.

- Advise patient to avoid drinking alcohol or taking other central nervous system depressants during prochlorperazine therapy.
- Patient taking oral form should not take calcium- and magnesium-based antacids concomitantly with this drug.
- For patients taking multiple oral doses per day, instruct patient to take a missed dose if within 1 h of regular dosage time, otherwise skip the missed dose and continue with regular schedule.

Propylthiouracil

Common	Serious
Rash Leukopenia Fever Skin rash Headache Sore throat	Hepatic Necrosis (<1%) Liver failure Nephritis (<1%)

- Tell patient that symptomatic improvement may not be seen for a few weeks.
- Patient should immediately report, fever, skin rash, sore throat, or headache.
- Advise patient to report signs/symptoms of hepatic dysfunction, such as anorexia, pruritus, right upper quadrant pain, fatigue, weakness, abdominal pain that is vague, loss of appetite, itching, bruising, and yellowing of the eyes.
- Advise patient of importance of taking this drug regularly and at evenly spaced intervals as prescribed.
- If a dose is missed and it is almost time for the next dose, instruct patient to use two doses together and then return to the regular dosing schedule.
- Patient should contact healthcare professional if more than one dose is missed.

Pyridostigmine Bromide

Common	Serious
Diaphoresis Diarrhea Excessive salivation Increased peristalsis Nausea Vomiting Stomach cramps Muscle cramps Muscle fasciculation Asthenia Miosis Excessive bronchial secretion	Bradyarrhythmia Cholinergic crisis

- Patient should avoid activities requiring visual clarity until drug effects are realized.
- This drug may cause diaphoresis, diarrhea, excessive salivation, nausea, vomiting, stomach cramps, muscle cramps/fasciculation, asthenia, or excessive bronchial secretions.

- Patient should report increasing muscle weakness, as this could be a sign of underdosage or cholinergic crisis (overdosage).
- Advise patient to also report signs/symptoms of bradyarrhythmia.
- Tell patient to take drug with food or milk to minimize gastric irritation.
- Patient should not drink alcohol while taking this drug.

Rabeprazole Sodium

Common	Serious
Headache Swelling of the limbs Abdominal pain Diarrhea Nausea Dizziness Sleeplessness	Stevens-Johnson syndrome Bone fracture (Osteoporosis-related) Hip fracture Rhabdomyolysis

- This drug may cause edema, abdominal pain, diarrhea, nausea, dizziness, headache, and insomnia.
- Advise patients being treated for duodenal ulcer to take drug after the morning meal.

Raloxifene Hydrochloride

Common	Serious
Hot sweats Leg cramps	Deep venous thrombosis Venous thromboemoblism (1%) Verebrovascular accident Thrombosis of tetinal vein (<1%) Pulmonary embolism

- Advise patient to avoid sitting for prolonged periods of time, as drug increases risk of venous thromboembolic disorders, especially during first 4 months of therapy.
- This drug may cause leg cramps and hot flashes (especially during the first 6 months of therapy).
- Instruct patient to report signs/symptoms of cerebrovascular accident, pulmonary embolism, and deep vein thrombosis.
- Patient should not use cholestyramine, colestipol, or an estrogen pill, patch, or injection while taking this drug.

Ramipril

Common	Serious
Hypotension Hyperkalemia Nausea Vomiting Dizziness Cough fatigue	Intestinal angioedema Liver failure (starting with cholestatic jaundice) (<1%) Angioedema (face, lips, throat)

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness.
- Advise patient to rise slowly from a sitting or lying position.
- This drug may cause nausea, vomiting, persistent cough, and fatigue.
- Tell patient to report signs/symptoms of angioedema (deep swelling around eyes and lips and sometimes hands and feet), intestinal angioedema (abdominal pain), unusual bleeding, or infection.
- Instruct patient to maintain adequate hydration to prevent volume depletion and symptomatic hypotension.
- Patient should avoid using potassium-containing supplements or salts while taking this drug.

Reserpine

Common	Serious
Dizziness Lethargy Depression Nasal congestion Chest pain	Cardia dysrhythmia Gastrointestinal hemorrhage Thrombocytopenia (<1%) Vivid dreams Dream anxiety disorder Impotence

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- This drug may cause dizziness, lethargy, nasal congestion, vivid dreams, dream anxiety disorder, or impotence.
- Advise patient to report depression, chest pain, or signs/symptoms of gastrointestinal hemorrhage or cardiac dysrhythmia.
- Tell patient to avoid abrupt discontinuation of drug.
- Patient should not drink alcohol while taking this drug.
- If a dose of reserpine is missed, advise patient to skip the missed dose and return to regular dosing schedule.

Rifampin (Rifamycin)

Common	Serious
Abnormal color Sweat Heartburn Loss of appetite Nausea Saliva discoloration Increased liver function test Tear discoloration Discolored urine Flu-like illness	Thrombocytopenia (high-dose therapy_ Hepatotoxcity

- This drug may decrease effectiveness of oral contraceptives with concurrent use. Recommend additional form of birth control.
- Warn patient that drug may permanently discolor soft contact lenses.
- Tell patient that drug causes red-orange discoloration of urine, feces, saliva, sweat, and tears.
- This drug may cause flu-like symptoms, heartburn, or anorexia.
- Advise patient to report signs/symptoms of hepatotoxicity or thrombocytopenia.
- Patient should take drug in combination with other antibiotics exactly as prescribed, as resistance to this drug may occur rapidly.
- Tell patient to take drug 1 h before or 2 h after a meal with a full glass of water.
- Patient should not drink alcohol while taking this drug.

Rituximab

Common	Serious
Pruritus Nausea Vomiting Asthenia Dizziness Headache Fever (all grades, 53%; grades 3 & 4, 1%) Shivering (all grades, 33%; grades 3 & 4, 3%	Angina Cardia dysrhythmia Drug-induced pemphigus Lichenoid dermatitis Stevens-Johnson syndrome Toxic epidermal necrolysis Bowel obstruction Gastrointestinal perforation Anemia (all grades, 8%; grades 3 & 4, 3%) Aplastic anemia (transient) Cytopenia (grade 3 & 4, 48%) Hemolytic anemia Leukopenia (all grades 14%; grade 3 & 4, 4%) Lymphocytopenia (grade 3 & 4, 40%) Neurtropenia (all grades, 14%; grade 3 & 4, 6%) Thrombocytopenia (all grades, 12%; grade 3 & 4, 2 %) Relapsing type B viral hepatitis Complication of infusion (1st infusion, 77%; subsequent infusions, 14-30%)

	Allergic reaction Progressive multifocal leukoencephalopathy Nephrooxicity Obliterative bronchiolitis Pneumonitis Infection (all grades 31%; grades 3 & $, 4%) Tumor lysis syndrome

Intravenous (Solution)

- Fatal infusion reactions may occur within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue rituximab infusion for severe reactions. Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of Tumor Lysis Syndrome following treatment in patients with non-Hodgkin's lymphoma. Severe and potentially fatal mucocutaneous reactions can occur. JC virus infection resulting in Progressive Multifocal Leukoencephalopathy (PML) and death can also occur.

- Advise patient to avoid vaccines during therapy due to drug-induced immunosuppression.
- Recommend women of childbearing potential use reliable contraception to avoid pregnancy during therapy and at least 12 months post-treatment.
- This drug may cause nausea, vomiting, asthenia, dizziness, headache, or pruritus.
- Tell patient to immediately report signs/symptoms of allergic reaction or severe mucocutaneous reaction such as dermatitis, Stevens-Johnson syndrome, or toxic epidermal necrolysis (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering).
- Patients with a history of hepatitis B should report signs/symptoms of an active infection, as drug may cause a relapse of hepatitis B.
- Patient should also report signs/symptoms of myelosuppression, renal failure, hypotension, angina/cardiac dysrhythmia, or bronchiolitis/pneumonitis.

Romidepsin

Adverse Effects

Serious:

- **Cardiovascular:** Supraventricular arrhythmia (6%), Ventricular arrhythmia (4%), Hypotension (7-23%)
- **Hematologic:** Anemia, Grades 3/4 (3% to 28%), Leukopenia, Grades 3/4 (Up to 45%), Neutropenia, Grades 3/4 (4% to 47%), Thrombocytopenia, Grades 3/4 (up to 36%)
- **Immunologic:** Sepsis (5%)
- **Other:** Tumor lysis syndrome (1% to 2%)

Common:

- **Cardiovascular:** EKG ST segment changes (2% to 63%)
- **Dermatologic:** Pruritis (7-31%)
- **Endocrine metabolic:** Weight decreased (10% to 15%); Hyperglycemia (2-51%); Hypermagnesemia (up to 27%); Hyperuricemia (up to 33%), Hypoalbuminemia (3-48%),

Hypocalcemia (4-52%), Hypokalemia (6-20%), Hypomagnesemia (22-28%), Hyponatremia (up to 20%), Hypophosphatemia (up to 27%),

- **Gastrointestinal:** Loss of appetite (23% to 54%), Nausea (56% to 86%), Vomiting (34% to 52%), Constipation (12-40%), Diarrhea (20-36%), Altered taste sense (15-40%),
- **Hematologic:** Anemia, All grades (19% to 72%), Leukopenia, All grades (4% to 55%), Neutropenia, All grades (11% to 66%), Thrombocytopenia, All grades (17% to 72%)
- **Hepatic:** ALT/SGPT raised (3-22%), AST/SGOT raised (3-28%),
- **Immunologic:** Infectious disease (19% to 54%), Lymphocytopenia (4% to 57%)
- **Neurologic:** Asthenia, Headache (15% to 34%)
- **Respiratory:** Cough (18% to 21%), Dyspnea (13-21%),Pneumonia (5%)
- **Other:** Fatigue, Shivering (11% to 17%), Fever (20-47%)

Rosiglitazone Maleate

Common	Serious
Edema (4.8 to 14.7%) Weight gain	Angina Congestive heart failure Myocardial infarction Myocardial ischemia Cholestatic hepatitis Hepatotoxicity (<1%) Diabetic macular edema (<1%) Pleural effusion Pulmonary edema

- Premenopausal, anovulatory patients should use reliable contraception, as drug may stimulate ovulation.
- This drug may cause edema and weight gain.
- Advise patient to report signs/symptoms of congestive heart failure or pulmonary edema.
- Tell patient that symptomatic improvement may not be seen for a few weeks and full effect of drug may not be realized until after 2 to 3 months of therapy.
- Advise diabetic patients to monitor for signs/symptoms of hyper- or hypoglycemia and to report difficulties with glucose control, especially patients on concomitant hypoglycemic agents.

Rosuvastatin Calcium

Common ≥ 2%	Rare < 2%
Abdominal pain Constipation Nausea Arthralgia Myalgia Asthenia Headache Urinary tract infection Pharyngitis Flu-like illness	Abnormal liver enzymes Muscle disorders Rhabdomyolysis Backache

Rupture of tendon tendinitis	

- This drug may cause headache and pharyngitis.
- Patient should report signs/symptoms of myopathy or rhabdomyolysis (myalgias, dark urine, arthralgias, fatigue).
- Patient should not use any aluminum- or magnesium-containing antacids for at least 2 h after taking this drug.
- Advise patient to avoid using gemfibrozil while taking this drug.

Saha

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking SAHA. In some cases, side effects can be serious, long lasting, or may never go away. The combination of SAHA and 13-cis RA (for those children who will take both) may result in an unexpected toxicity.

You should talk to your study doctor about any side effects that you have while taking part in the study.

A child getting SAHA had blood clotting in his blood vessels, and this may be related to the SAHA.

There have been reports of changes in blood clotting ability in patients who received both coumadin
and SAHA. If you are receiving coumadin, you will be monitored carefully for signs related to increased risk of bleeding (such as easy bruising, bleeding from nose, gums etc.) In addition, the ability of your blood to clot will be watched more closely (at least monthly).

Risks and side effects that adults who have been given SAHA had included those which are:

Likely

- Low Blood Counts: decreased red blood cells (anemia), lower numbers of white blood cells (infection fighting cells) which may increase your risk of infection, decrease in the type of blood cells that act to help stop bleeding when you are cut.
- feeling tired
- weight loss
- decreased appetite
- diarrhea (watery bowel movements)
- nausea
- vomiting

- weak kidney function
- high levels of sugar in the blood
- bleeding of the upper digestive tract

Less Likely:

Low Blood Counts: decreased number of a type of white blood cells, fever with dangerously low white blood cell count, infection that occurs when the white blood cell count is low.

Heart-related: abnormal electrical conduction within the heart

General: fever, chills, shivering, hair loss, infection, dehydration, dry mouth, swelling of the arms and legs, head pain

Stomach/Intestine-related: constipation, heartburn, abnormal sense of taste, pain in the stomach

Laboratory test-related: low levels of a blood protein called albumin, abnormal bone enzyme level,
abnormal liver enzyme level, abnormal level of bilirubin in the blood (Bilirubin is a bile pigment found in the liver), low levels of potassium, sodium, phosphate, and calcium in the blood, increased blood magnesium level

Nervous system-related: muscle spasms, muscle weakness, dizziness, condition of the nervous system that causes numbness, tingling, burning

Breathing-related: cough, shortness of breath

Vein-related: formation or presence of a blood clot inside a blood vessel, a blood test to check blood clotting ability

Rare but Serious:

- Death of skin cells

The following side effects have been experienced by adults treated on SAHA studies, but it is not certain yet if they are related to taking the drug SAHA

Heart-related: change in the regular beat of the heart, abnormally high or low blood pressure, changes in the heart rhythm which may affect blood flow, heart attack.

General: sleeplessness, infection, sweating, pain throughout different parts of the body.

Laboratory-test related: abnormalities in the balance of salts, proteins, sugars, and acids in the blood

Muscle/Joint related: changes in the way you walk

Nervous-system related: confusion

Skin-related: hair loss, bruising, itching and rash, nail changes, tiny broken blood vessels under the skin.

Stomach/Intestine related: difficulty swallowing, gas, inflammation, bleeding, acid from the stomach flowing back up which may cause damage to the throat tissues.

Breathing related:, sinus congestion, coughing up of blood from the lungs indicating possible lung damage.

Kidney-related: retaining urine in the body, inability to control bladder, blood in urine.

Vein-related: changes to the way the blood clots, blood clot within a blood vessel.

Death

Patients receiving SAHA also experienced the following side effects and these may be related to the SAHA:

- a decrease in blood flowing to the brain which led to a stroke
- painful mouth sores
- decrease in memory function,
- bleeding of the respiratory tract
- kidney failure
- liver failure
- Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking

Simvastatin

Common	Serious
Constipation Stomach and bowel irritation Headache Upper respiratory infection	Liver toxicity (<1%) Compartment Syndrome of lower leg Muscle disorder Rhabdomyolysis (<1%) Tendon rupture

- This drug may cause constipation, gastrointestinal irritation, headache, and upper respiratory infection.
- Patient should not drink alcohol while taking this drug.
- Patient should not eat grapefruit or drink grapefruit juice while using this drug.

Sirolimus (rapamycin)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Headache (L), hypertension (L), nausea, immunosuppression (L), diarrhea, constipation,	Chest pain, insomnia, dyspepsia, vomiting, dyspnea	Hypotension, asthma, increased cough, flu like syndrome, tachycardia, anorexia, sensitivity reactions

	fever		
Prompt: Within 2-3 weeks, prior to next course	Tremor (L), renal dysfunction, elevated creatinine/BUN anemia, asthenia, pain (abdominal, back, pain), hyperlipidemia, hypercholesteremia, hypertrigylceridema, hyperglycemia, peripheral edema, weight gain, arthralgia	Elevated LFT's, UTI, URI's, mild thrombocytopenia, leukopenia, hyper/hypokalemia (L), hypophosphatemia, rash, hives, pruritis, hyperuricemia, delayed wound healing, hypomagnesaemia (L)	Gastritis, esophagitis, flatulence, CNS abnormalities: (Confusion (L), somnolence (L), depression (L), anxiety, anxiousness, paresthesias, emotional lability, hypo/ hypertonia, dizziness, neuropathy, hypesthesia, nervousness), infections (bacterial, fungal, viral sepsis, cellulitis, herpes simplex & zoster, EBV, mycobacterial, sinusitis, pharyngitis, abscess, pneumonia, bronchitis, peritonitis), pleural effusions, pleural edema, hypoxia thrombosis, thrombophlebitis, myalgia, delayed wound healing,
Delayed: Anytime later during therapy, excluding the above conditions	Acne		Skin ulcer, hirsutism (hypertrichosis) (L), gingival hyperplasia, abnormal vision, ear pain, cataracts, otitis, tinnitus, hemorrhage, ileus, chronic renal dysfunction, renal tubular necrosis, post transplant diabetes mellitus (L), CHF, ascites, thrombocytopenic purpura (hemolyticuremic syndrome), arthrosis, bone necrosis, osteoporosis
Late:			Lymphoproliferative

Anytime after completion of therapy			disorders, skin malignancies

(L) Toxicity may also occur later.

Unknown Frequency and Timing: Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk.

Sodium Phenylbutyrate

Common ≥4%	Rare < 4%
Lower limb swelling	Arrythmias
Skin rash	Syncope
Hypoalbuminemia	Hyperuricemia
Metabolic acidosis	Hypokalemia
Alkalosis	Hypothosphatemia
Hyperchloremia	Hypernatremia
Anorexia	Weight gain
Epigastric discomfort	Taste aversion
Abnormal menstration	Abdominal pain
	Nausea
	Vomiting
	Gastritis
	Peptic ulcer
	Retal bleeding
	Constipation
	Pancreatitis
	Aplastic anemia
	Anemia
	Leukopenia
	Leukocytosis
	Thrombocytopenia
	Thrombocytosis
	Headache
	Depression
	Fatigue
	Somnolence
	Lightheadedness
	Disorientation
	Memory impairment
	Renal tubular acidosis
	Offensive body odor

Sorafenib

Risks and side effects related to Sorafenib include those which are:

Likely:

- Hair loss
- Inflammation of the skin on the palms of the hands or soles of the feet
- Rash / flaking or shedding of outer layer of skin
- Fatigue or tiredness
- Loss of appetite
- Diarrhea
- Nausea
- Low levels of a blood protein called albumin
- Low blood phosphate level
- Stomach ache

Less Likely:

Low blood counts: decrease in a red blood cell protein that carries oxygen in the body, decreased total number of white blood cells, decreased number of a type of white blood cell, decreased number of blood cells that help clot blood.

Stomach / Intestine Related: bleeding in the digestive tract, constipation, painful inflammation and ulceration of the lining of the mouth and digestive tract, vomiting.

Laboratory test-related: increased liver enzymes, abnormal liver or bone enzyme level, abnormal digestive enzyme level, high blood levels of a liver pigment indicative of abnormal liver function, low blood calcium level, high blood sugar, low blood sugar, abnormal level of fat-digesting enzyme, high blood potassium level, low blood potassium level, low blood sodium level.

Breathing-related: shortness of breath, cough, fluid accumulation around the lungs (pleural effusion), voice changes (for example hoarseness, loss or change in voice), bleeding of the respiratory tract or lungs

Skin-related: dry skin, itching.

General: allergic reaction, dizziness, fever (with or without a dangerously low white blood cell count), weight loss, infection (with or without a low white blood cell count), pain throughout the body (such as back pain, chest pain, leg pain, headache, joint pain, muscle pain), difficulty sleeping or falling asleep.

High blood pressure

Bleeding in the reproductive organs or urinary system (such as the bladder or kidney)

Swelling of the arms and legs

Nerve damage causing numbness, tingling, or burning

Hoarseness, laryngitis, loss or change in voice

Kidney failure

Formation or presence of a blood clot inside a blood vessel

Rare but Serious:

Heart-related: decreased blood supply to the heart, heart attack, decrease in the ability of the heart to pump blood.

Nervous system-related: bleeding into the brain or spinal cord, Syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings.

Stomach / Intestine-related: A hole somewhere in the intestinal tract from the esophagus to the anus.

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Abstinence is an acceptable method of birth control.

Sulfasalazine

Common ≥ 3%	Serious
Rash (3-13%)	Leukopenia (3.7%)
Pruritus (3-4%)	Macrocytic anemia (<1%)
Abdominal pain (8%)	Neutropenia (2%)
Indigestion (13-33%)	Stevens-Johnson syndrome (<1%)
Loss of appetite (33%)	Agranulocytosis (1%)
Nausea (19-33%)	Aplastic anemia (<1%)
Vomiting (8-33%)	Leukopenia (<3%)
Stomatitis (4%)	**Hemolytic anemia (<3%)**
Headache (9-33%)	Pure red cell aplasia (<1%)
Dizziness (4%)	Thrombocytopenia (1%)
Oligozoospermia (reversible) (33%)	Fulminant hepatic failure (<1%)
Macrocytosis (9%)	Liver toxicity (<1%)
Fever (3-5%)	Hypersensitivity reaction (<1%)
Discolored urine	Systemic lupus erythematosus (<1%)
urticaria (3%)	Central nervous system disorder (<1%)
abnormal liver function test (4%)	Myoneural disorder (<1%)

Hypogammaglobulinemia (10%)	Kidney disease (<1%) Male infertility (<1%) Diffuse interstitial pulmonary fibrosis (<1%)

- Inform patient that drug may cause urine/skin to turn yellow-orange color.
- This drug may cause anorexia, nausea, vomiting, and headache.
- Advise patient to report signs/symptoms of nephrotoxicity/hepatoxicity.
- Patient should maintain adequate hydration during therapy to prevent renal stone formation.
- Tell patients being treated for arthritis that symptomatic improvement may not be seen for 4 to 12 weeks.
- Patient should take drug after meals.

Sulindac

Risks and side effects related to Sulindac include those which are:

Likely	Less Likely	Rare but serious (see next page)
• You may be unaware of an infection when the white count is low (neutropenia) because you may not develop a fever while taking Sulindac • A decrease in the ability of the platelets to clot the blood which may lead to bruising and to bleeding more easily	• Acid or upset Stomach (heartburn) • Stomach or abdominal (belly) pain • Nausea and/or vomiting • Diarrhea or constipation • Headache • Drowsiness • Fluid retention which could lead to weight gain and puffiness • Ringing in the ears or a decrease in the ability to hear • Too much gas produced in the intestines • Cramping and discomfort in the intestines • Dry mouth and/or a metallic or bitter taste in the mouth • Itching and/or a rash • Sweating • Loss of appetite • Anxiety or depression • Sleepiness or inability to sleep (insomnia) • A feeling of weakness and/or tiredness • Numbness and tingling in the fingers and toes • Fainting • Blurred vision • Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores) • Inflammation of the stomach • Increased tendency to sun burn	

Rare but serious side effects of Sulindac		
• Severe allergic reactions which can be life threatening or fatal with may include shortness of breath, low blood pressure, rapid heart rate, chills and fever, aches and pains in the muscles or joints, and abnormal laboratory values in blood tests • Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath. • Irritation of the small airways of your lungs that can make you cough and wheeze • Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools and abdominal (belly) pain • Severe rashes which can affect the skin and mucous membranes and be life-threatening • Bleeding due to irritation of the gastrointestinal tract and/or from erosion of the lining of the stomach (an ulcer) which if untreated could rupture and may be fatal • Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver, a yellow appearing skin, and fluid collection in the abdomen which makes it look larger. • Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly)which can be severe and may increase the blood sugar • Severe damage to the kidney which may be irreversible and lead to kidney failure • Drugs of this type called non-steroidal anti-inflammatory drugs (NSAIDS) have been associated with severe cardiovascular events such as heart attack, high blood pressure or stroke. This is more likely to occur in patients who are older, who have had coronary artery surgery or who have diseases that make them more susceptible to events of this type. • Seizures • Changes in mood which may include severe depression, feelings of suicide, and feelings of aggressiveness • Temporary inflammation of the brain which could lead to a stiff neck and severe headaches. • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid • Fewer white blood cells, red blood cells and platelets in the blood -a low number of white blood cells can make it easier to get infections -a low number of red blood cells can make you feel tired and weak -a low number of platelets causes you to bruise and bleed more easily		

Sunitinib Malate

Common	Serious
Discoloration of skin, yellow (19-30%)	Porlonged QT interval (<0.1%)
Dry skin (18%)	Severe hypothyroidism
Rash (14-27%)	Gastrointestinal perforation (<1%)
Hypothyroidism (3-36%)	Pancreatitis (1%)
Abdominal pain (22%)	Tumor hemorrhage (3%)
Constipation (16-20%)	Throbotic microangiopathy
Diarrhea (40-58%)	Liver failure (<1%)
Increased serum lipase level (25-52%)	Posterior leukoencephalopathy syndrome,
Indigestion (28%)	reversible (<1%)
Inflammatory disease of mucous membrane (29-	Pulmonary embolism (1%)

43%) Loss of appetite (33-38%) Nausea (49%) Mouth/tooth pain (6-10%) Taste aversion (21-44%) Vomiting (28%) Anemia (26-71%) Bleeding (18-30%) Leukopenia (78%) Lymphocytopenia (38-59%) Neutropenic disorder (53-72%) Abnormal liver function test Asthenia (22%) Increased uric acid level (41%) Hypertension (15-30%) Left ventricular cardiac dysfunction (11-21%) Thrombocytopenia (38-65%)	Pulmonary hemorrhage Infection

- This drug may cause yellow discoloration of skin, diarrhea, mucositis, anorexia, stomatitis, dyspepsia, nausea, vomiting, altered taste sense, hypertension, or asthenia.
- Tell patient to report signs/symptoms of left ventricular dysfunction or congestive heart failure.
- Patient should also report signs/symptoms of hemorrhagic events including pulmonary hemorrhage.
- Patient should avoid eating grapefruit or drinking grapefruit juice while taking this drug.

Sunitinib

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the Sunitinib. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Possible Risks of Heart Damage: As of December 2007, two of 12 patients treated on this study developed a probable side effect involving their heart function, with both patients experiencing a decrease in how well their hearts were able to pump blood. These effects on the heart seemed to improve once sunitinib was stopped. In larger studies performed in adult patients with cancer, between 1 in 10 and 1 in 100 patients developed heart problems. In some cases the heart problems improved when treatment with sunitinib was stopped, but in other cases the problems did not improve when sunitinib was stopped. For children, we do not yet know how common this side effect actually is, and also do not know if it goes away completely once a patient stops taking sunitinib. However, you are only being offered to participate in this study because you have not previously been treated with medicines or radiation that could weaken the heart. All patients will have their heart function closely watched, and we will stop sunitinib if we find that it may be affecting your heart.

Other risks and side effects related to Sunitinib include those which are:

Likely:

- Fatigue
- Loss of appetite
- Diarrhea
- Irritation or sores in the lining of the gastrointestinal tract
- Nausea
- Changes in taste
- Vomiting
- Stomach (belly) pain

Less Likely:

- Decrease in blood protein that carries oxygen
- Decrease in the total number of white blood cells
- Decrease number of a type of white blood cell
- Decrease number of blood cells that help blood to clot
- High blood pressure
- Fever
- Difficulty in sleeping or falling to sleep
- Chills
- Weight loss
- Change in hair color
- Dry skin
- Hair loss
- Lightening of the skin
- Rash/flaking or shedding of outer layer of skin
- Inflammation or blistering of the skin on the palms of the hands or soles of the feet
- Low thyroid function
- Constipation
- Dehydration
- Feeling of fullness
- Dry mouth
- Excess passing of gas
- Irritation of the stomach lining
- Heartburn
- Nose bleed
- Swelling of the arms and/or legs
- Increased liver enzymes
- Low levels of a blood protein called albumin
- Abnormal liver or bone enzyme level
- Abnormal digestive enzyme level
- Increased liver pigment in blood indicative of abnormal liver function
- Increased blood level of a substance normally eliminated by the kidneys into the urine
- Abnormal level of fat-digesting enzyme
- Decreased blood phosphate level
- Increased blood levels of uric acid (a waste material from food digestion)

Less Likely (cont):

- Swelling of the nerve in the back of the eye responsible for vision
- Back pain
- Chest pain
- Leg pain
- Headache
- Joint pain
- Muscle pain
- Mouth pain
- Cough

Rare but serious:

- Abnormal electrical conduction within the heart
- Decrease in the ability of the heart to pump blood
- Abnormal clotting of blood in small blood vessels
- Swelling of a part of the eye
- Decrease in vision

Sunitinib may interact with other medications that you may be taking, including prescription medication, over-the-counter (non-prescription) medications, and herbal remedies or supplements. These interactions may increase your risk of having a bad reaction to sunitinib. Be sure to discuss all medications you are taking with your study doctor.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. The long-term effects of sunitinib on fertility are unknown. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Pregnancy tests will be obtained in women interested in participating in this study.

Tacrolimus

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Headache (L), hypertension (L), nausea,vomiting, anorexia, immunosuppression (L), diarrhea, constipation, fever	Chest pain	Anaphylaxis with the injection, allergic reaction, hypotension, asthma, dyspnea, increased cough, flu like syndrome, pleural effusion, seizure (L), tachycardia, angina
Prompt: Within 2-3 weeks,	Tremor (L),), renal dysfunction (acute	Alopecia, dizziness,	Dyspepsia, dysphagia, gastritis, esophagitis, flatulence, CNS

prior to the next course	with decrease in GFR, impaired urinary concentrating ability, and sodium retention), elevated creatinine/BUN, anemia, insomnia, asthenia, pain (abdominal, back, pain), hyperglycemia, hypomagnesemia (L), hyper/hypokalemia (L), hypophosphatemia, paresthesia	elevated LFTs, UTI, peripheral edema, rash, pruritis, hyperlipidemia, hypercholesteremia	abnormalities (confusion (L), somnolence (L), depression (L), anxiety, anxiousness, abnormal dreams, emotional labiality, hallucinations, psychosis, hypertonia, incoordination, neuropathy, nervousness encephalopathy), coagulation disorder, leukopenia (L), thrombocytopenia, polycythemia, anemia, leukocytosis, infections (bacterial, fungal, viral –sepsis, cellulites, fungal dermatitis, herpes simplex, sinusitis, pharyngitis, abscess, pneumonia, bronchitis, peritonitis), hyperbilirubinemia (L), thrombosis, phlebitis, arthralgia, myalgia, electrolyte abnormalities
Delayed: Any time later during therapy, excluding the above conditions			Acne, exfoliative dermatitis, skin discoloration, photosensitivity reaction, skin ulcer, delayed wound healing, hirsutism (hypertrichosis) (L), gingival hyperplasia, abnormal vision, amblyopia, ear pain, otitis, tinnitus, GI hemorrhage, GI perforation, cholelithiasis, cholestatic jaundice, chronic renal dysfunction, renal failure, post-transplant diabetes mellitus (L), myocardial hypertrophy, elevated liver function tests, liver damage, ascites
Late: Any time after completion of treatment			Lymphoproliferative disorders, skin malignancies
Unknown Frequency and Timing:	Fetal toxic effects of tacrolimus have been noted in animals. Tacrolimus is transported across the placenta and its use during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus is excreted in human milk, nursing should be avoided.		

(L) Toxicity may also occur later

Tamoxifen

Risks and side effects related to Tamoxifen [reported side effects seen mainly in women treated for breast cancer at standard doses] include those which are:

Likely	Less Likely	Rare but serious
• Hot flashes • Reddening of the face	• Nausea and/or vomiting • Bone pain	• Severe rashes which can result in loss of skin and damage to

with feelings of warmth • Absence of menstrual flow or changes in menstrual flow (periods) • Weight gain or loss • A decrease in the sexual drive	• Fluid retention • Vaginal discharge, dryness or itching • Fewer platelets in the blood o a low number of platelets causes you to bruise and bleed more easily • Cough • Lightheadedness or dizziness • Headache • Skin changes or rashes • Thinning of the hair or partial loss of hair • High levels of a certain salt in the body calcium which may require treatment • Elevation in the blood of certain enzymes or bilirubin found in the liver which could mean mild liver damage • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Increase in the level of thyroxin (T_4) which is hormone produced by the thyroid • An increase in the levels of lipids (fats) in your blood which if prolonged could lead to heart problems later in life • Changes on a test called an EKG that measures the activity of your hear	mucous membranes and which may be life-threatening • Clotting of blood vessels which can lead to pain and swelling in the area of the clot. Such clots make break loose and cause damage or be life-threatening depending on where they go. • Fewer white blood cells and red blood cells in the blood o a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make you feel tired and weak • Damage to your eye which could lead to a decrease in vision • Allergic reactions • A cyst (fluid filled sac) may form on the ovaries which are found in the abdomen (belly) and may be associated with pain • An increased risk of cancer of the lining of the uterus (womb)

Tarceva (OSI-774)

We know about the following side effects of OSI-774:

	Common (happens in 21-100 patients out of 100)	Occasional (happens in 5-20 patients out of 100)	Rare (happens in less than 5 patients out of 100)
The timing of these side effects (how soon they happen after taking OSI-774) is not known.	Acne-like skin rash, diarrhea, nausea, vomiting, tiredness, weariness, ill feeling	Dry skin, dry mouth, decreased appetite, mouth sores, heartburn	Peeling of the skin, hives and itching, elevation in liver function tests, redness/inflammation of the eye/damage to the cornea, dry eye, inward growth of eyelashes, tearing, kidney damage, headache, inflammation of the lungs, lung tissue changes and damage and scarring of lung tissues, blurry vision, allergic reaction, changes to taste, increase in bilirubin

Allergic reactions may occur with any medicine.

Also reported on OSI-774 trials but with the relationship to OSI-774 unknown: low levels of red blood cells, low levels of white blood cells, increased numbers of white blood cells in the blood, low number of platelets in the blood which may increase the risk of bleeding, poor blood supply to an area of bone causing bone death, blockage of the pulmonary artery (1 case), a clot blocking a vein, shaking chills, fever, hair loss, sore throat, burning or painful sensation in the tongue, inflammation and cracking of the skin of the lips, constipation, abdominal pain or cramping, sores in the stomach, too much gas produced in the intestines, difficulty swallowing, decreased blood flow to the intestines, inflammation of the pancreas, blood in the urine, nose bleed, dark, bloody bowel movement, blood in sputum or spit, bleeding in the intestines, elevated liver enzyme levels, inflammation of the lungs, urinary tract infection, infection with or without decrease in a type of white blood cell called a neutrophil, low levels of potassium and sodium in the blood, dryness in the nose, runny nose, depression, anxiety, sleeplessness, a skin sensation, such as burning, prickling, itching, or tingling, with no apparent cause, dizziness, blockage of the blood vessels of the brain (1 case), back pain, cough, difficulty breathing, too much protein in the urine, kidney failure, inflammation of the lining of the uterus, confusion, dehydration and increased levels of urea in the blood which is likely directly related to diarrhea, changes in blood clotting in patients also taking Coumadin, inflammation of the cornea causing watery painful eyes and blurred vision, inflammation of the eye, inflammation of the pancreas, the presence of air or gas in abnormal places in the body, and secondary skin infection from rash.

If a person gets pregnant while receiving OSI-774, it could be dangerous for the baby. You should not become pregnant or father a baby while on this study. You should not nurse (breast feed) a baby while on this study. Ask about counseling and more information about preventing pregnancy. Women of child-bearing potential and males must agree to use an adequate form of birth control while on this protocol.

Temsirolimus

Risks and side effects related to temsirolimus include those which are:

Likely

- *Low Blood Counts:* low hemoglobin which means low red cell count (anemia), low number of platelets which help the blood to clot.
- Fatigue which is a feeling of extreme tiredness not relieved by sleep
- Rash including rash with peeling of the skin
- Loss of desire to eat or appetite
- Diarrhea
- Inflammation or sores in the mouth, throat, or esophagus (the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)
- Nausea
- Increase in a fat in the blood (cholesterol) which if continued for long periods of time could lead to heart or blood vessel problems

Less Likely

- Allergic reactions
- Runny nose

- *Low Blood Counts:* low number of white blood cells which help fight infection.
- An increase or decrease in blood pressure
- A change in the amount of a protein that helps your blood to clot
- Fever (high body temperature)
- Difficulty sleeping or falling asleep
- Chills and shaking chills
- Weight loss
- Dry Skin
- Nail changes
- Itching of the skin
- Rash and acne (pimples)
- Hives
- Wound complication
- Low levels of testosterone, a hormone found in the body
- Diabetes, a condition which causes an inability to tolerate glucose (sugar) in the body
- Constipation
- Feeling bloated, tightness or pain in the belly
- Mouth sores
- Taste alteration where things taste differently
- Vomiting
- Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
- Risk of bleeding
- Risk of infection
- Fluid build-up in the arms, legs, head or neck.
- Acidosis that is metabolic (through your body's system) or respiratory (in the lungs).
- Abnormal amounts of liver enzymes
- Low amounts of calcium
- High levels of glucose (sugar) in the blood which may require treatment
- An increase in the levels of lipids (fats) in your blood which if prolonged could lead to heart problems later in life
- Low levels of certain salts in your body (such as potassium and phosphate)
- Increase of triglycerides in the blood which could lead to heart problems later in life
- Depression
- Somnolence which is a feeling of sleepiness, an inability to stay awake or aware
- Pain (such as belly, back, chest, head, joint, or muscle pain)
- Cough
- Shortness of breath
- Nose or sinus reactions
- Inflammation of the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood making you short of breath
- Erectile dysfunction
- Decreased libido, which means a decrease in sexual desire
- Flu type symptoms with fever, tiredness, aches and pains

Rare but serious

- Holes or tears in the gastrointestinal tract (including the stomach, intestine and colon).
- Severe kidney damage (which may be permanent)
- Clotting of blood vessels which can lead to pain and swelling in the area of the clot. Such clots may break loose and cause damage or be life-threatening depending on where they go.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. These precautions should be in place for the whole duration of the study therapy and for at least 3 months after the last dose of temsirolimus due to the long half lives of these drugs. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Temozolomide

Risks and side effects related to temozolomide include those which are:

Likely	Less Likely	Rare but can be Serious

• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Nausea
• Vomiting
• Constipation
• Loss of appetite
	• Diarrhea
	• Headache
	• Tiredness
	• Difficulty swallowing
	• Dizziness
	• Anxiety or depression
	• Difficulty sleeping
	• Rash
	• Itching
	• Increased need to urinate
	• Urinary Tract Infections
	• Mouth sores
	• Fluid Build up in legs and arms
	• Hair loss
	• Elevation in the blood of certain enzymes found in the liver
	• Visual disturbances that may cause double vision
	• Forgetfulness or confusion
	• Aches and pains in muscles and joints
	• Pain in the abdomen
		• Convulsions
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening
		• Partial paralysis or weakness of one side of the body
		• Blood clots which may be life-threatening
		• A new cancer or leukemia resulting from this treatment

(L) Toxicity may also occur later.

Thalidomide

Common	Serious
Swelling of the limbs (4.2% to 56.9%)	Stevens-Johnson syndrome
Rash (30.4%)	Toxic epidermal necrolysis
Hypocalcemia (71.6%)	Teratogenesis
Hypokalemia (22.5%)	Pulmonary embolism
Hyponatremia (43.1%)	Seizure (rare)
Hypothyroidism (20%)	Loss of menstruation (<0.1%)
Increased appetite (21.6%)	
Weight loss (22.5%)	
Constipation (54.9%)	
Nausea (28.4%)	
Leukopenia (35.3%)	
Confusion (28.4%)	
Somnolence (37.5%)	
Tremor (4.2% to 25.5%)	
Neutropenia (31.4%)	
Thrombosis (22.5%)	
Peripheral neuropathy (21.6% to 53.9%)	
Increased liver function test (24.5%)	
Increased serum bilirubin (13.7%)	
Joint pain (12.7%)	
Bone pain (30.4%)	
Muscle pain (16.7%)	
Muscle weakness (40.2%)	
Headache (12.5% to 19.6%)	
Sleeplessness (22.5%)	
Dizziness/lightheadedness (4.2% to 19.6%)	
Anxiety (25.5%)	
Fatigue (79.4%)	

Oral (Capsule)

- Thalidomide can cause severe birth defects or death to an unborn baby if taken during pregnancy. Women of childbearing potential should have a pregnancy test before starting therapy, then weekly for first month, and monthly thereafter. Effective contraception must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks following discontinuation of thalidomide therapy. Males must always use a latex condom during any sexual contact with women of childbearing potential. Only prescribers and pharmacists registered with the S.T.E.P.S.(R) distribution program can prescribe and dispense thalidomide. The use of thalidomide in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep vein thrombosis and pulmonary embolus.

- This drug may decrease effectiveness of oral contraceptives with concurrent use. Instruct patient to use 2 forms of reliable contraception to avoid pregnancy during therapy and at least 4 weeks before and after therapy.
- Male patients must use a latex condom during intercourse during any sexual contact with women of childbearing potential, even if patient has had a vasectomy.

- Tell patient to avoid activities requiring mental alertness until drug effects are realized, as this drug may cause dizziness and somnolence.
- Patient should rise slowly from a sitting/lying down position.
- This drug may cause edema, constipation, nausea, confusional state, and tremors.
- Advise patient to immediately report signs/symptoms of Stevens-Johnson syndrome/toxic epidermal necrolysis (flu-like symptoms, spreading red rash, or skin/mucous membrane blistering), thromboembolism (shortness of breath, chest pain, or arm/leg swelling), or pregnancy.
- Patient should also report signs/symptoms of infection, bleeding, or peripheral neuropathy (numbness, tingling, pain, or burning in hands/feet).
- Advise patient to closely follow healthcare professional's instructions regarding frequency of taking pregnancy test.
- Tell patient to take drug at bedtime at least 1 h after evening meal.
- Patient should not drink alcohol while taking drug.

Theophylline

Common	Serious
Nausea Vomiting Headache Insomnia Tremor Irritability Restlessness	Attial fibrillation Trachyarrhythmia Stevens-Johnson syndrome Intracranial hemorrhage Seizure

- Advise patient that this drug is not indicated for acute asthma attacks or other respiratory flare-ups.
- This drug may cause nausea, headache, insomnia, tremors, and restlessness.
- Patient should immediately report signs/symptoms of theophylline toxicity (vomiting, arrhythmia, seizures).
- Advise patient to report signs/symptoms of infection or any changes in ongoing health, as healthcare professional may need to make dose adjustments.
- Serious toxicity is not necessarily preceded by mild/moderate side effects. Inform patient that regular blood work is important to ensure therapeutic drug level.
- Instruct patient to take drug the same way every dose. Patient should choose to take drug always with food or always without food, as this influences drug level.
- Counsel patient to avoid abruptly discontinuing or changing dosage without supervision by healthcare professional.
- Patient should inform provider of significant changes in diet (such as "low carb" diet, increased caffeine) and smoking habits (start/stop smoking tobacco or marijuana, increased exposure to second-hand smoke).
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).

Thioguanine

Common	Serious
Loss of appetite Nausea Stomatitis Vomiting	Hyperuricemia Gastrointestinal necrosis (with combination regimens) Perforation of intestine Myelosuppression Hepatotoxicity Jaundice Abnormal liver function test Infection

- Patient should avoid vaccines during therapy due to drug-induced immunosuppression.
- Advise patient on the proper handling and disposal of chemotherapy drugs.
- This drug may cause anorexia, nausea, stomatitis, and vomiting.
- Advise patient to immediately report signs/symptoms of bleeding (unexplained bruising, black tarry stools, hematuria, purpura) or infection.
- Instruct to report signs/symptoms of gastrointestinal toxicity or hepatotoxicity (jaundice, right upper quadrant pain, weight gain, ascites).
- Encourage patient to maintain adequate hydration to prevent hyperuricemia.
- Patient should not drink alcohol while taking this drug.

Thioguanine Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Anorexia, nausea, vomiting, diarrhea, malaise	Urticaria, rash, hyperuricemia
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression		Toxic hepatitis (L), increased SGOT (AST)/SGPT (ALT), ataxia, mucositis
Delayed: Anytime later during therapy			Hepatic fibrosis(L), sinusoidal obstruction syndrome (SOS, formerly VOD) (L), hyperbilirubinemia
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of thioguanine have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

- ***(L) Toxicity may also occur later.***

Thioridazine Hydrochloride

Common	Serious
Hypotension	Porlonged QT interval (rare)
Orthostatic hypotension	Sudden cardiac death
Diminished sweating	Torsades de pointes (rare)
Light sensitivity (rare)	Obstipation (rare)
constipation	Paralytic ileus (rare)
Xerostomia	Agranulocytosis (rare)
Akathisia	Disorder of hematopoietic structure (rare)
Dizziness	Leukopenia (rare)
Drug-induced tardive dystonia	Thrombocytopenia (rare)
Systonia	Cholestatic jaundice syndrome (rare)
Extrapyramidal disease	Drug-induced lupus erythematosus (rare)
Parkinsonian	Systemic (rare)
Somnolence	Ineffective thermoregulation,
Tardive dyskinesia	heatstroke/hypothermia (rare)
Blurred vision	Neuroleptic malignant syndrome (rare)
Epithelial keratopathy	Seizure (rare)
Eye/vision change	Priapism (rare)
Retinitis pigmentosa	Death
Urinary retention	
Nasal congestion	

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness or somnolence.
- Instruct patient to rise slowly from a sitting/supine position, as drug may cause orthostatic hypotension.
- This drug may cause hypotension, anticholinergic effects, akathisia, dystonia, epithelial keratopathy, retinitis pigmentosa, or nasal congestion.
- Tell patient to report signs/symptoms of arrhythmia or tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities).
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).
- Patient should avoid drinking alcohol while taking this drug.

Thiotepa

Risks and side effects related to the Thiotepa are listed below:

Likely	Less Likely	Rare but serious
• Nausea • Vomiting • Loss of appetite • A feeling of extreme tiredness or weakness • Fewer white blood cells, red blood cells	• Pain at the injection site • Dizziness • Headache • Blurred vision • Hives, skin rash • Wheezing	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a

and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak. ○ A low number of white blood cells can make it easier to get infections. ○ A low number of platelets causes you to bruise and bleed • Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children • Absence or decrease in monthly periods and could affect your ability to become pregnant With High Doses used before marrow transplants: • Inflammation and/or sores in the mouth, throat and/or esophagus (the passage between the throat and stomach)	• Sudden high fever • Pain in the abdomen • Difficulty emptying the bladder • Feeling the urgency to urinate or pain on urination • Hair loss • Inflammation and reddening of the eye • Inflammation of the skin where the drug comes into contact with the skin With High Doses used before marrow transplants: • inappropriate behavior • confusion • drowsiness • Elevation in the blood of certain enzymes and/or bilirubin found in the liver • Bronze discoloration or darkening of the skin	rapid heart rate • Swelling and tightening of the throat which can cause difficulty with breathing • A new cancer or leukemia resulting from this treatment

Tolbutamide

Common	Serious
Cutaneous hypersensitivity Hypoglycemia Hyperglycemia Heartburn Nausea	Death (cardiovascular, reported in University group diabetes program) Severe hypoglycemia (0.35%)

- This drug may cause heartburn or nausea.
- Drug may cause hypo- or hyperglycemia. Instruct patient to monitor for and report problems with glycemic control.
- Tell patient to report stress due to infection, fever, trauma, or surgery, as dosing adjustments may need to be made.
- Advise patient to avoid drinking alcohol while taking this drug.

Tolcapone

Common	Serious
Constipation Diarrhea Loss of appetite Nausea Xerostomia Dream disorder Sleep disorder	Orthostatic hypotension Hyperpyrexia Fulminant hepatic failure (rare) Rhabdomyolysis Confusion Dyskinesia Dystonia Hallucinations

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and drowsiness.
- Advise patient to rise slowly from a lying/sitting position, as this drug may cause orthostatic hypotension.
- This drug may cause diarrhea, loss of appetite, nausea, anticholinergic effects, dystonia, dyskinesia, and hyperpyrexia (very high fever).
- Drug may also cause hallucinations and dream/sleep disorders.
- Advise patient to report signs/symptoms of acute renal failure or hepatic dysfunction (persistent nausea, fatigue, dark urine, pruritus, right upper quadrant tenderness, jaundice, clay-colored stools).
- May take with food to minimize gastric irritation.
- Advise patient against sudden discontinuation of drug.

Tolmetin

Common	Serious
Swelling of the limbs	Congestive heart failure (<1%)
Weight gain	Hypertension (3-9%)
Weight loss	Myocardial infarction (<2%)
Abdominal pain	Thrombotic tendency observations
Diarrhea	Erythema multiforme (<1%)
Flatulence	Scaling eczema
Indigestion	Stevens-Johnson syndrome
Nausea	Toxic epidermal necrolysis (<1%)
Vomiting	Gastrointestinal hemorrhage (<1%)
Asthenia	Gastrointestinal perforation
Dizziness	Digestive tract inflammation
Headache	Agranuloscytosis (<1%)
	Anemia (<3%)
	Neutropenia (<1%)
	Thrombocyutopenia (<1%)
	Hepatitis (<1%)
	Increased liver function test (increased up to15%)
	Jaundice (<1%)
	Liver failure (<0.1%)
	Allergic reaction (<1%)
	Cerebrovascular accident
	Acute kidney failure (<1%)
	Hematuria (<1%)
	Proteinuria (<1%)
	Brochospasm

- Elderly and debilitated patients may be at higher risk for serious gastrointestinal adverse effects while taking this drug.
- This drug may cause edema, weight gain or loss, abdominal pain, diarrhea, dyspepsia, flatulence, nausea, vomiting, asthenia, dizziness, and headache.
- Advise patient to report signs/symptoms of thrombotic events, myocardial infarction, or stroke.
- Instruct patient to report signs/symptoms of gastrointestinal bleeding or ulceration.

Topiramate

Common	Serious
Diarrhea (5-11%)	Erythema mutiforme
Loss of appetite (4-24%)	Stevens-Johnson syndrome
Nausea (6-14%)	Toxic epidermal necrolysis
Altered sense of taste (3-15%)	Increased body temperature
Weight loss (6-21%)	Hperammonemia (with or without encephalopathy)
Confusion (3-14%)	Hypohidrosis
Language disorder (6-10%)	Metabolic acidosis (7% to 67%)
Dizziness (8-32%)	Liver failure
Nervous feelings (7-14%)	

Headache Impaired psychomotor performance (3-21%) Memory impairment (5-14%) Paresthesia (2-51%) Reduced concentration span (4-14%) Somnolence (9-29%) Speech and language disorder Abnormal vision (2% to 13%) Diplopia (1% to 10%) Nystagmus (10% to 11%) Fatigue (14% to 30%)	Glaucoma Myopia Depression (3% to 13%) Mood disorder (2% to 11%) Suicidal thoughts Nephrolithiasis (1% to 3%)

- Patient should avoid activities requiring mental alertness and coordination until drug effects are realized, as drug may cause dizziness, somnolence, and motor retardation.
- Drug may impair heat regulation, especially in pediatric patients. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- Drug may decrease effectiveness of estrogen-containing oral contraceptives with concurrent use. Recommend additional form of birth control with oral contraceptives.
- Drug may cause nausea, diplopia, nervousness, dysmenorrhea, breast pain, and fatigue.
- Drug may cause asthenia, ataxia, confusion, speech and language problems, memory impairment, nystagmus, paresthesias, tremors, and inability to concentrate.
- Advise patient to report signs/symptoms of acute myopia associated with angle-closure glaucoma (sudden decreased visual acuity, ocular pain).
- Advise patient against sudden discontinuation of drug, as this may cause increased seizure activity.
- Patient should avoid concomitant use of valproic acid. Hyperammonemia with encephalopathy is possible.

<u>TOPOTECAN</u>:

	Common	Occasional	Rare
Immediate:		Nausea, vomiting, diarrhea (L), mouth sores (L), flu-like symptoms (L), headache, rashes (L), increased liver enzymes in the blood	Stomach pain, shaking chills
Within 2-3 wks:	Decrease in the number of red and white blood cells and platelets made in the bone marrow, hair loss		
Delayed:		Loss of strength or energy	Tiny amounts of blood in the urine
Late:			

-
- ***(L) Toxicity may also occur later.***

Torsemide

Common	Serious
Orthostatic hypotension Electrolyte imbalance (2-4%) Hyperuricemia Constipation (2%) Diarrhea (2%) Indigestion (2%) Nausea (2%) Muscle cramp Dizziness (3%) Fatigue Headache (7%) Insomnia (1%) Nervous feeling (1%) Excessive urination (7%) Cough (2%) Rhinitis (3%)	Ototoxicity (rare)

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized.
- Advise patient to rise slowly from a lying/sitting position, as this drug may cause orthostatic hypotension.
- This drug may cause headache and excessive urination.
- Instruct patient to report signs/symptoms of ototoxicity (tinnitus, hearing loss).

Tranylcypromine

Common	Serious
Edema Orthostatic hypotension Weight gain Constipation Diarrhea Loss of appetite Nausea Xerostomia Asthenia Dizziness Headache Insomnia Somnolence Impotence	Hypertensive crisis Agranulocytosis (rare) Anemia (rare) Leucopenia (rare) Thrombocytopenia (rare) Hepatitis (rare) Worsening depression (rare) Suicidal thoughts (rare) Suicide (rare)

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness or somnolence.
- Instruct patient to rise slowly from a sitting/supine position, as drug may cause orthostatic hypotension.
- This drug may cause edema, weight gain, anticholinergic effects, diarrhea, anorexia, nausea, asthenia, headache, insomnia, agitation, anxiety, manic behavior, or impotence.

- Advise patient that full symptomatic improvement may not be seen for up to 3 weeks.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk for these effects during the first few months of therapy.
- Advise patient against sudden discontinuation of drug.
- Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter and herbal drugs).
- Patient should not drink alcohol while taking this drug.
- Tell patient to limit amount of caffeine during therapy.
- Patient should avoid eating foods high in tyramine while taking this drug, as this may cause extremely high blood pressure. High tyramine foods include dried or very ripe fruits, liver, sausage, and other meats, and aged or fermented foods/drinks such as wine, cheese or pickles.

Trastuzumab

Risks and side effects related to trastuzumab include those which are:

Likely	Less Likely	Rare but serious
• Diarrhea The following reactions are more common with the first dose of tratuzumab but could occur with any infusion of the drug • Nausea and vomiting • Headache • Rash during the infusion • Fever and chills including shaking chills. • Feeling short of breath • Pain in the abdomen, the back or at the tumor site • A feeling of tiredness or weakness • A decrease or an increase in blood pressure	• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid* • A feeling of tiredness • Muscle and joint aches and pains • Bone, chest and nerve pain • Numbness and tingling in the fingers and toes • Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight • Inflammation of the sinuses, the throat and nose which could lead to pain or pressure, runny nose or change in your voice • Infections including bladder or kidney infections and skin infections • Wheezing and/or shortness of breath • Rash, hives or itchiness • Acne • Rash with skin sores • Fast or irregular heart beat during the infusion • Mouth Sores with inflammation and pain	• Allergic reactions during the infusion that can be severe and life-threatening and may lead to difficulty in breathing, a drop in blood pressure, irregular heart beat, a sudden stopping of the heart (cardiac arrest), fluid in the lungs or damage to the lungs and shock.** • Fewer white blood cells, red blood cells and platelets in the blood o a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make you feel tired and weak o a low number of platelets causes you to bruise and bleed more easily • Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath. • Sudden, temporary feeling of chest tightness, wheezing or coughing making it difficult to breath which can occur during or

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	• Loss of desire to eat • Dizziness or fainting • Cough • Depression • Difficulty sleeping • Elevation in the blood of certain enzymes found in the liver • Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics	shortly after the infusion • Inflammation and scarring of the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood. • Damage to the heart which can lead to inflammation of the heart muscle and a build-up of fluid around the heart which may be painful and affect the ability of the heart to work normally • Damage to the kidneys that causes protein to be lost from the blood by leaking from the kidneys into the urine and causing swelling usually in the legs and ankles from fluid build-up in body tissues.

** Trastuzumab rarely causes decreases in heart function when administered by itself. When Trastuzumab is given alone, these changes in heart function are usually reversible. When Trastuzumab is given in combination with chemotherapy drugs called anthracyclines (for example doxorubicin) or cyclophosphamide, there is a much greater risk of heart damage, though this complication is still uncommon. Such damage can result in a rapid heart beat, decreased pumping strength of the heart, and accumulation of fluid in the lungs which may rarely interfere with breathing.*

***Some patients may have a severe of life-threatening reaction during or after treatment with Trastuzumab. These reactions can involve a drop in blood pressure and shortness of breath, and have resulted in death in several patients. These severe reactions may be more common in patients who already have breathing difficulties or lung disease. If you develop any clear discomfort during or after a treatment with Trastuzumab, you should contact your physician immediately or go to the nearest Emergency Care facility.*

Trazodone

Common	Serious
Sweating symptom	Cardiac diysrhythmia (rare)
Weight change	Hypertension (rare)
Constipation	Hypotension (rare)
Diarrhea	Hemolytic anemia (rare)
Loss of appetite	Leukocytosis (rare)
Nausea	Methemoglobinemia (rare)
Vomiting	Seizure (rare)
Xerostomia	Worsening depression (rare)
Dizziness	Suicidal thoughts (rare)
Headache	Suicide (rare)
Insomnia	Priapism (rare)
Lethargy	
Memory impairment	

Somnolence Blurred vision	

- Patient should avoid driving and other activities requiring mental alertness or coordination until drug effects are realized, as this medicine may cause dizziness or somnolence.
- This drug may cause sweating, weight change, anticholinergic effects, diarrhea, anorexia, nausea, vomiting, headache, insomnia, lethargy, and memory impairment.
- Advise patient that symptomatic improvement may not be seen for 2 to 4 weeks.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk for these effects during the first few months of therapy.
- Patient should take with food or milk.
- Advise patient against sudden discontinuation of drug.
- Patient should not drink alcohol while taking this drug.

Valproic acid

Risks and side effects related to the valproic acid include those which are:
Likely:

- nausea
- vomiting
- abdominal pain
- diarrhea
- headache
- sleepiness
- tremor
- loss of strength and energy
- dizziness
- hair loss
- rash
- dry skin
- itching of the skin
- numbness and tingling of your hands and/or feet
- short-term weakness of your hands and/or feet

Less Likely:

- loss of appetite
- heartburns
- flu-like syndromes
- double vision
- blurred vision
- unsteadiness
- unsteady eye movement
- sleeplessness
- loss of memory

- moodiness
- anxiety or nervousness
- ringing in the ear
- pneumonia
- weight gain or loss
- abnormal thyroid function
- low platelet count, which may cause easy bruising or bleeding
- abnormal blood clotting which can lead to excessive bleeding during and after surgery

Rare but can be serious:

- sores in the mouth or on the tongue
- hyperactivity
- confusion
- coma
- severe reactions involving skin, mouth, and eyes, including blisters
- redness, swelling, and/or peeling of your skin, resulting in pain and infection
- eye pain and irritation
- low white and/or red blood cell count
- abnormal effects on unborn babies (see "Risks of Pregnancy", below)
- severe to life-threatening inflammation of the pancreas and liver
- hearing loss
- abnormal sodium level in the blood
- fast and/or irregular heart beats, high blood pressure
- peeing frequently, vaginal yeast infection
- inflammation of the kidney
- irregularities in your periods, including complete stoppage of your periods
- gum bleeding or swelling, infection around your teeth
- abnormal change in the bone marrow leading to chronic transfusions, and possibly leading to a pre-leukemia condition called myelodysplastic syndrome.
- abnormal clotting tests and possibly increased risk of bleeding

Vandetanib

Adverse Effects

Serious:

- **Cardiovascular:** Heart failure (0.9%), Prolonged QT interval (all Grades, 14%; Grade 3-4, 8%)
- **Dermatologic:** Stevens-Johnson syndrome
- **Gastrointestinal:** Pancreatitis (0.4%)
- **Hematologic:** Hemorrhage, Decreased platelet count (9%), Neutropenia (10%)
- **Immunologic:** Sepsis
- **Neurologic:** Ischemic stroke (1.3%), Reversible posterior leukoencephalopathy syndrome
- **Respiratory:** Aspiration pneumonia, Interstitial lung disease, Respiratory arrest, Respiratory failure

Common:

- **Cardiovascular:** Hypertension (all Grades, 33%; Grade 3-4, 5%)
- **Dermatologic:** Acne (all Grades, 35%; Grade 3-4, 1%), Rash (all Grades, 53%; Grade 3-4, 5%), Dry Skin (15%), Photosensitivity (13%), Pruritis (11%)
- **Endocrine metabolic:** Decreased calcium level (all Grades, 57%; Grade 3-4, 6%), Decreased glucose level (24%), Hypomagnesemia (7%), Decreased weight (10%)
- **Gastrointestinal:** Abdominal pain (all Grades, 21%; Grade 3-4, 3%), Colitis, Diarrhea, Loss of appetite (all Grades, 21%; Grade 3-4, 4%), Nausea (all Grades, 33%; Grade 3-4, 1%)
- **Hepatic:** ALT/SGPT level raised (all Grades, 51%; Grade 3-4, 2%)
- **Neurologic:** Headache (all Grades, 26%; Grade 3-4, 1%), Asthenia (15%)
- **Opthalmic:** Blurred vision (9%)
- **Psychiatirc:** Depression (10%)
- **Renal:** Proteinuria (10%), Serum creatinine raised (16%)
- **Respiratory:** Cough (11%),Nasopharyngitis (11%)
- **Other:** Fatigue (all Grades, 24%; Grade 3-4, 6%)

Verapamil

Common	Serious
Edema Hypotension Constipation Nausea Dizziness Headache	Angina (rare) Myocardial infarction (rare) Syncope (rare)

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as this medicine may cause dizziness and light-headedness.
- This drug may cause edema, constipation, nausea, and headache.
- Patient should watch for signs/symptoms of hypotension with initial dosing and dose changes.
- Advise patient against sudden discontinuation of drug, as this may precipitate hypertensive rebound/crisis.
- Patient should not drink alcohol while taking this drug.

Vinblastine

Risks and side effects related to Vinblastine include those which are:

Likely	Less Likely	Rare but serious

• Hair loss
• Fewer white blood cells, red blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
	• Constipation
	• Diarrhea
	• Nausea and /or vomiting
	• Loss of Appetite
	• Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes (Numbness and tingling) or may make you feel weak
	• A hoarse voice
	• Mouth sores
	• Depression
	• Jaw pain
	• Bone pain
	• Headache
	• A feeling or tiredness or not well
	• Rash and a tendency to burn more easily in the sun (very rarely reported)
	• Inflammation and discomfort in the vein through which the medicine was given
	• A sore throat
	• Pain and bloating in your abdomen
	• Drooping eyelids
	• Double vision
	• Rapid, jerky movements of the eye which are not under your control and can alter your vision
	• Difficulty with urination or increase desire to urinate
	• Abnormal hormone function which may lower the level of salt in the blood
	• Damage to the ear causing hearing loss which maybe temporary or permanent, balance problems (dizziness) and ringing in the ears
	• Absence or decrease in the number of sperm and/or damage to the testis which may be temporary or permanent which may decrease the ability to have children in the future
	• Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have
		• Complete stoppage of your intestinal activity which can result in intestinal blockage
		• If the drug leaks out of the vein when being administered it will cause damage to nearby tissue
		• The rapid death of large numbers of tumor cells which can cause the uric acid in the blood to rise quickly and this could lead to damage to the kidneys.
		• Seizures
		• A sudden onset of shortness of breath which may be accompanied by wheezing and/or coughing and a feeling of tightness in the chest
		• Fluid build up in the lungs
		• A heart attack or an abnormal heart rhythm
		• Bleeding from the gastrointestinal tract including from a stomach ulcer, the colon or the rectum

	children in the future • Temporary inflammation of the liver leading to an elevation in the blood of certain enzymes found in the liver • High blood pressure • Blanching (whiteness) of the fingers or toes when they are exposed to cold or when you are under stress, that may make them feel cold or throb and ache	

Vinorelbine

Likely Happens to 10-30 patients out of every 100	**Less Likely** Happens to 3-10 patients out of every 100	**Rare But Serious** Happens to less than 3 patients out of every 100

• Injection site reactions including redness, pain and vein discoloration
• Nausea
• Vomiting
• A drop in white blood cells and red blood cells in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
• Tiredness
• Constipation
• Increased liver enzyme levels
	• Diarrhea
	• Hair loss
	• Fever
	• A drop in platelets in the blood
	  ○ a low number of platelets causes you to bruise and bleed more easily
	• Muscle weakness
	• Inflammation of the vein through which the drug was given
	• Decreased appetite
	• Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes, the likelihood of which increases with the number of doses
	• Pain in your abdomen
	• Mouth sores
	• Rash
	• Increased bilirubin which may result in a yellow appearance
	• Increased or decreased blood pressure
	• Muscle aches
	• Redness and peeling skin on the palms and soles
	• Hearing loss
	• Headache
	• Jaw pain
	• Bleeding of the bladder
	• A return of redness and inflammation at a site of previous radiation therapy
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• Complete stoppage of your intestinal activity which can result in intestinal blockage and damage
		• Fluid buildup in the lungs
		• Difficult breathing or shortness of breath
		• Chest pain or heart attack
		• If the drug leaks out of the vein when being administered it may cause damage to nearby tissue
		• Liver damage
		• Inflammation of the pancreas
		• Clots in veins such as the ones in the legs or lungs
		• Severe shortness of breath and respiratory failure due to injured lungs that can be fatal

Vorinostat

Risks and side effects related to the vorinostat include those which are:

Likely

- Low Blood Counts: decreased red blood cells that carry oxygen in the body (anemia), decrease in a type of white blood cell called neutrophils, decreased total numbers of white blood cells (infection fighting cells) which may increase your risk of infection, decrease in the type of blood cells called platelets that help to clot blood.
- fatigue
- weight loss
- loss of appetite
- diarrhea
- nausea
- vomiting
- high blood level of creatinine, a substance normally eliminated by the kidneys into the urine
- high level of sugar in the blood

Less Likely

- Low Blood Counts: decreased number of a type of white blood cell called lymphocytes
- changes in heart rhythm
- abnormal levels of blood protein in a blood test to check blood clotting ability
- fever
- chills
- hair loss
- constipation
- dehydration
- dry mouth
- heartburn
- taste alteration
- fever with dangerously low white blood cell count
- infection
- swelling of the limbs such as the arms or legs
- low levels of a blood protein called albumin
- abnormal liver or bone enzyme level
- abnormal liver enzyme level
- abnormal level of bilirubin in the blood. Bilirubin is a bile pigment found in the liver.
- decreased blood calcium level
- increased blood magnesium level
- decreased blood phosphate level
- decreased blood potassium level

- decreased blood sodium level
- muscle spasms
- muscle weakness
- dizziness
- Condition of the nervous system that causes numbness, tingling, burning.
- pain in the abdomen or belly
- headache
- cough
- shortness of breath
- formation or presence of a blood clot inside a blood vessel.

Rare but serious

- death of the skin tissue called tissue necrosis

Zolendronic acid

Likely Happens to 10-30 patients out of every 100	**Less Likely** Happens to 3-10 patients out of every 100	**Rare But Serious** Happens to less than 3 patients out of every 100
• Fatigue (tiredness) • Flu-like symptoms including fever, chills, and joint and muscle aches, which are generally seen after the first infusion • Low levels of calcium in the blood which may cause muscle cramps • Anorexia (loss of appetite)	• Headaches • Insomnia • Anxiety • Stomach irritation • Bone, back, muscle, and joint pain • Tachycardia (rapid heart rate) • Abnormal kidney function tests • Diarrhea • Tingling in the fingers and toes • Nausea, vomiting, constipation, and /or abdominal pain • Low red blood cell counts which may cause tiredness, shortness of breath or fatigue • Allergic reactions, which include itching, flushing, rash, and shortness of breath • Low levels of potassium, magnesium, and/or phosphate in the blood. In almost all cases, you would not experience symptoms from these effects. If these levels fall to extremely low levels, possible side effects could include muscle twitching, muscle weakness, and abnormal heart rhythm. • A reaction at the injection site, which might include pain, redness, tenderness, swelling, and/or bruising.	• Kidney failure • Severe allergic reactions • Permanent damage to the jawbone that may be painful and might require surgery to remove the damaged area. There is more information about this below.* This might be more likely to happen in patients who have certain dental procedures. If you see a dentist, you should inform them that you are receiving zoledronic acid. • Serious eye problems. If you suspect you are having an eye side effect after receiving the study drug, you should call the study doctor. • Chest pain • Red puffy eyes (conjunctivitis) • Low platelets (increased risk for bleeding) • Low white blood count (increased risk of infection) • Low blood pressure

*A condition called osteonecrosis of the jaw (ONJ) has been seen in patients taking zoledronic acid or other bisphosphonates. This happens in less than 1% of patients. ONJ can show up as a non-healing wound in the gum tissue covering the jaw bone, or roof of the mouth, that exposes the bone. The wound can be painful, can worsen over time and often involves an infection in the area with ONJ. This means a portion of the jawbone becomes permanently damaged, may be

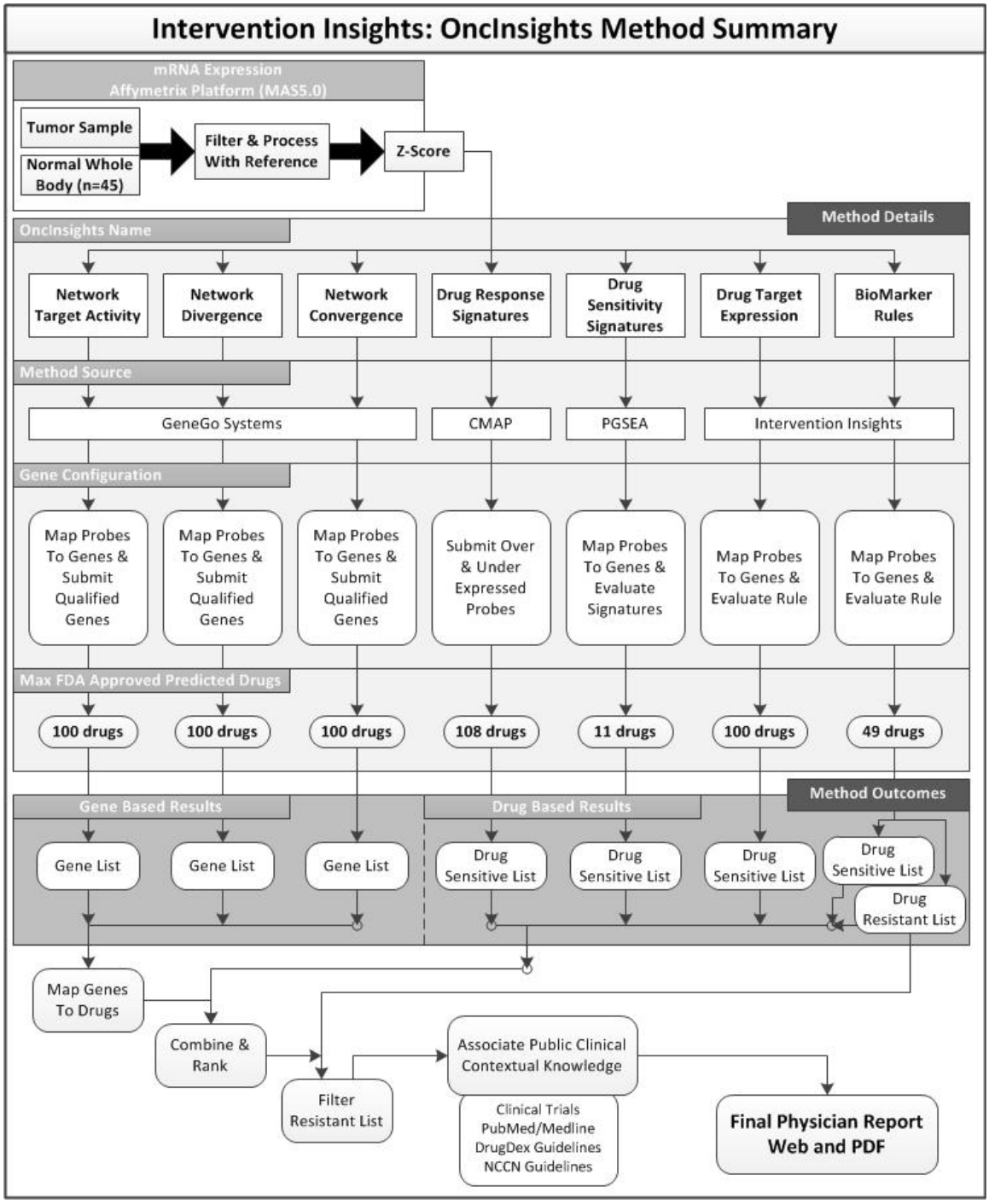
painful, and may require dental treatment or removal of the damaged area. Little is known about how the wound develops. Based on available evidence, a causal relationship between ONJ and bisphosphonates, including zoledronic acid, has not been established. Most of the patients who got ONJ had cancer and were receiving repeated monthly doses of bisphosphonates and most were also receiving chemotherapy and corticosteroids. Other risk factors for ONJ include radiotherapy and concurrent medical conditions (for example, anemia, a defect in the blood clotting mechanism, infection and pre-existing oral disease). In most cases, the patient also had surgery in the mouth or a tooth removed. ONJ has been much less frequently reported in non-cancer patients taking bisphosphonates. For patients requiring oral surgery, there are no data available to suggest whether stopping bisphosphonate treatment reduces the risk of ONJ. In patients who develop ONJ, surgery at the affected area may make the condition worse. If you think you have this condition see your Study Doctor and dentist immediately.

Appendix IV: Intervention Insights Whole Body Reference Set

Tissue	Tissue Sub Detail
Brain	Amygdala
Esophagus	
Brain	Corpus Callosum
Large Intestine	Cecum
Small Intestine	Jejunum
Prostate Gland	
Tonsil	
Salivary Gland	Submandibular Gland
Brain	Amygdala
Nipple	
Lymph Node	
Testis	
Prostate Gland	
Corpus Uteri	
Brain	Temporal Lobe L
Brain	Accumbens
Skeletal Muscle	Quadriceps Femoris
Brain	Accumbens
Brain	Putamen
Brain	Entorhinal Cortex
Brain	Putamen
Adrenal Gland	
Corpus Uteri	Myometrium
Corpus Uteri	Myometrium
Liver	
Uterus	Endometrium
Uterus	Endometrium
Brain	Substantia Nigra
Heart	
Brain	Hippocampus
Kidney	Medulla
Corpus Uteri	Endometrium
Skin	
Bronchus	
Brain	Frontal Lobe NOS
Brain	Hippocampus
Corpus uteri	Myometrium
Skin	

Spleen	
Small Intestine	Ileum
Brain	Brain, Subthalamic Nucleus
Brain	Thalamus
Brain	Accumbens
Brain	Occipital Cortex
Gland	Pituitary Gland

Appendix V: OncInsights Method Summary Diagram



The total number of drugs that can be selected by the OncInsights service is 327. The diagram represents the total number of drugs which can be selected by each method. Because one or more drugs can be selected by one or more methods the sum of drugs listed in the figure will not equal the unique drug count.