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Department	Stem Cell Transplantation and Cellular Therapy
IND Sponsor	MD Anderson Cancer Center
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Immunotherapy with Ex Vivo-expanded Cord Blood-derived NK Cells Combined with Rituximab High-dose Chemotherapy and Autologous Stem Cell Transplant for B-cell Non-Hodgkin's Lymphoma

Institution Study Number: **2015-0751**

IND Sponsor: The University of Texas MD Anderson Cancer Center

IND Number: 17314

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Table of Contents

Protocol Body

1.0 Objectives

Primary endpoint:
To establish the safety of this treatment by determining its treatment-related mortality (TRM) within 30 days.

Secondary endpoints:
To estimate the relapse-free survival (RFS).
To estimate the overall survival (OS).
To quantify duration of infused allogeneic UCB-derived NK cells in the recipient.

2.0 Background

High-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) is an established treatment for relapsed B lymphomas. The antitumor effect of ASCT results from the cytotoxic effect of HDC. Although ASCT is clearly safe (TRM <5%), tumor relapse constitutes a major cause of treatment failure. For example, the recent Coral trial in modern diffuse large B-cell lymphoma (DLBCL) patients who relapse after 1st line therapy with R-CHOP shows that up to 80% of patients who subsequently respond to salvage therapy and are thus become candidates to ASCT will still relapse after transplant.[1] Ways to improve ASCT results include the improvement of the efficacy of the HDC regimen, as well as the combination of HDC with immune therapies to increase tumor cell kill.

Natural killer (NK) cells are part of the innate immune system and have been implicated in tumor immunity and defense.[2] Importantly, NK cells do not require prior exposure or sensitization to kill a specific target. While the exact mechanism of NK cells anti-tumor immunity remains unclear, a complex interplay between activating and inhibitory receptors determines cytotoxicity against a specific target.[3] This includes possible disinhibition of the killer immunoglobulin like receptor due to absence of HLA class I molecules on target cells ("missing self hypothesis"), as well as death receptor-induced apoptosis via Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL).[4]

Robust NK reconstitution has been associated with improved outcomes for non-Hodgkin lymphoma after AHSCT.[5, 6, 7]. Unfortunately, autologous NK cells from patients with lymphoma appear to be dysfunctional, due to, among other causes, an unfavorable balance between activating and inhibitory receptors.[8, 9] While immunomodulatory drugs, such as lenalidomide, or cytokines, such as IL-12, may augment NK cell function after ASCT,[10] clinical experience has shown that this is not sufficient to prevent disease progression. Therefore, successful NK immunotherapy activity against lymphoma probably requires an allogeneic source. Because of these limitations of autologous NK cell function, we have been interested in the application of allogeneic NK cells as an adoptive cellular therapy to treat patients receiving an ASCT.

The clinical safety of peripheral blood-derived allogeneic NK cell infusions has been

demonstrated.[11, 12] This requires collection of peripheral blood from a normal donor to generate NK cells, which can be logistically cumbersome. To minimize obstacles to collection we have been interested in NK cells derived from cryopreserved umbilical cord blood (CB), a known source of hematopoietic progenitor cells and an “off-the-shelf” product. Our group has previously published a good manufacturing production (GMP)-grade method of NK cell expansion from thawed CB mononuclear cells based on artificial antigen-presenting cells (Fig. 1). This method yields a >1000-fold expansion of NK cells with in vitro and in vivo antitumor activity.[13]

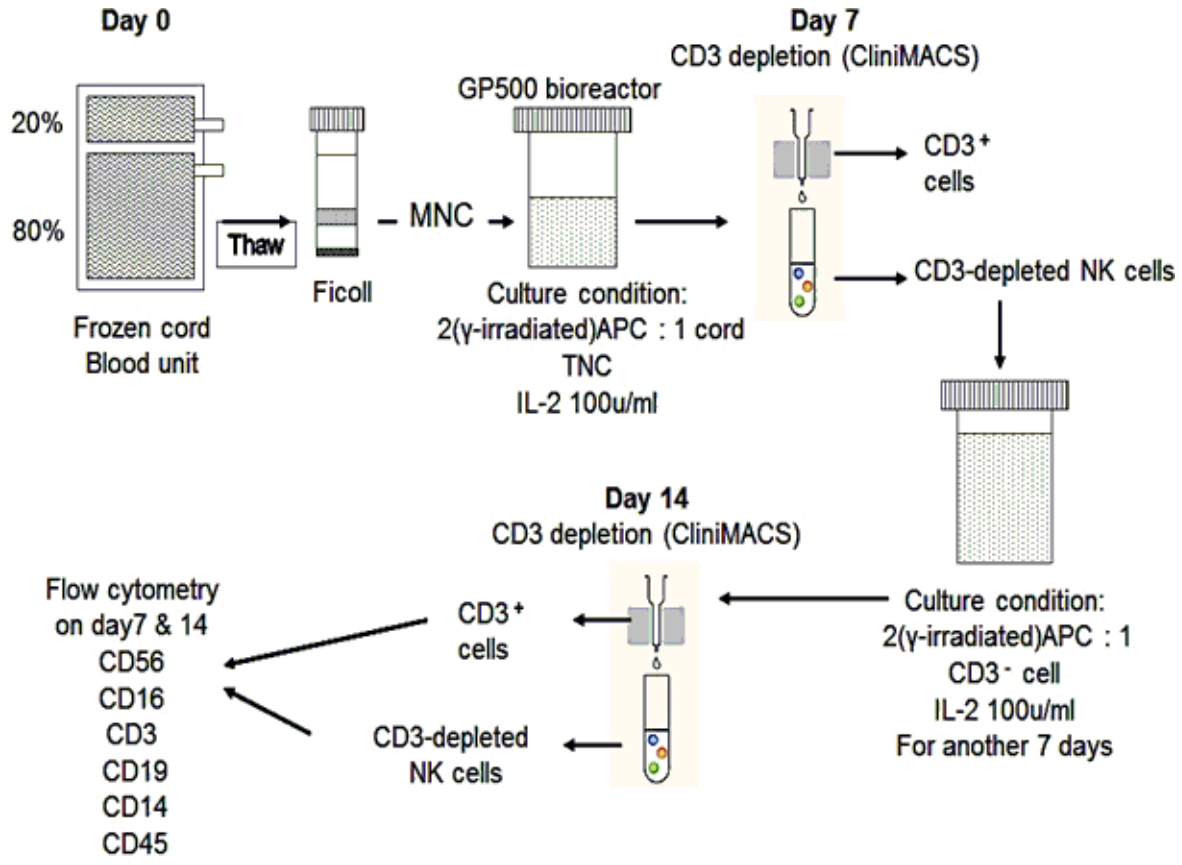

Fig. 1. GMP-compliant method of expansion of CB NK cells.

Using this technology, our colleague Nina Shah conducted the first study of CB-NK cells for patients with myeloma receiving high-dose melphalan and autologous HSCT (MDACC 2011-0379).[14] In that trial CB-NK cells in doses up to 1e8 cells/kg could be reliably produced for clinical use and were well tolerated in the setting of high dose-melphalan and ASCT for myeloma. In that trial lenalidomide at 10 mg PO daily was used as immunomodulatory agent, with good tolerance. The early results suggest high activity from this treatment in the population of patients with myeloma enrolled in that trial.

Preclinical data indicate that ex vivo activated and expanded CB-NK cells can mediate dose-dependent cytotoxicity against different B lymphoma cell lines, which is enhanced

in the presence of lenalidomide.[15] Those preclinical results and our clinical experience in myeloma have prompted us to further study of this novel cellular therapy in patients with B-cell lymphoma receiving an ASCT.

3.0 Patient Eligibility

Inclusion criteria:

1. Age 15-70
2. Patients with B-cell lymphoma who are candidates to autologous stem-cell transplantation:
   - 2.1. Primary refractory or relapsed diffuse large B-cell lymphoma in response to salvage treatment.
   - 2.2. Primary refractory or relapsed follicular lymphoma or other indolent B-cell histology in response to salvage treatment.
   - 2.3. Chemosensitive mantle-cell lymphoma in first or later line of treatment.
3. Adequate renal function, as defined by estimated serum creatinine clearance >/= 60 ml/min and a normal serum creatinine for age.
4. Adequate hepatic function (SGOT and/or SGPT </= 3 x ULN; total bilirubin </= 2 x ULN or </= 3 x ULN for Gilbert's disease.
5. Adequate pulmonary function with FEV1, FVC and DLCO (corrected for Hgb) >/= 50% of the predicted value.
6. Adequate cardiac function with left ventricular ejection fraction >/= 40%. No uncontrolled arrhythmias or symptomatic cardiac disease.
7. Performance status <2 (ECOG).
8. Negative Beta HCG in woman with child-bearing potential.

Exclusion criteria:

1. Primary CNS lymphoma.
2. Grade >/= 3 non-hematologic toxicity from prior therapy that has not resolved to </= G1.
3. Prior whole brain irradiation.
4. Active hepatitis B, either active carrier (HBsAg +) or viremic (HBV DNA >/= 10,000 copies/mL, or >/= 2,000 IU/mL).
5. Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients with chronic hepatitis C or positive hepatitis C serology.
6. Active infection requiring parenteral antibiotics.
7. HIV infection.
8. Radiation therapy in the month prior to enroll.
9. Breastfeeding females.

4.0 Pretreatment Evaluation

4.1. Anytime before enrollment (as early as possible):
HLA typing (A, B, C, and DRB1).

4.2. The studies listed below will be done within 30 days prior to starting treatment, only if not already done within this time period:

Lab work:
CBC with differential, SGPT, SGOT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, PT and PTT, complete urinalysis, blood typing and infectious disease panel (CMV Ab, HBsAg, HBcAb, HCVAb, HIV 1/2 Ab, HTLV I/II Ab, and Syphilis RPR).
Chest X ray.
Pulmonary function tests with
DLCO. EKG.
Echocardiogram or MUGA.

4.3. The following will be performed before admission if clinically indicated: Brain MRI.
Bone marrow biopsy and aspirate with cytogenetic studies.
PET/CT

4.4. Prior to start Preparative Regimen:
Women of childbearing age must have a pregnancy test within 10-14 days and again 24 hours before prescribing lenalidomide, then 28 days (+/-2 days) after therapy discontinued.

5.0 Study Registration

Each patient will be evaluated and approved for enrollment by the primary attending physician and the Study Chairman (or his designee). The study research coordinator will register each patient on protocol. All protocol participants will be registered in the institutional CORe system.

6.0 Treatment Plan

The investigational component of the proposed treatment plan is the infusion of ex-vivo expanded CB NK cells in the setting of autologous stem cell transplantation.

Apheresis of autologous peripheral blood progenitor cells (target 6 million CD34+/Kg, minimum 2 million CD34+/Kg) will be completed prior to beginning NK cell production.

The transplant day is referred as day zero (D0), treatment plan activities prior or after D0 are denominated as day minus (D-) or day plus (D+).

The production of the NK cells will be carried out by the Good Manufacturing Process (GMP) Laboratory at M.D. Anderson Cancer Center. This process will start no less than 14 days (D-19) prior to their infusion on D-5.

Chemotherapy agents doses and administration

Day	
No later than -19	Begin NK cell production
-13	Outpatient rituximab 375 mg/m2 IV* Admission
-12	Carmustine 300 mg/m2 IV
-11	Etoposide 200 mg/m2 IV BID Cytarabine 200 mg/m2 IV BID
-10	Etoposide 200 mg/m2 IV BID Cytarabine 200 mg/m2 IV BID
-9	Etoposide 200 mg/m2 IV BID Cytarabine 200 mg/m2 IV BID
-8	Etoposide 200 mg/m2 IV BID Cytarabine 200 mg/m2 IV BID
-7	Melphalan 140 mg/m2 Lenalidomide, 10 mg PO Rituximab 375 mg/m2 IV*
-6	Lenalidomide, 10 mg PO
-5	CB NK Infusion (up to 1 x 10^8/kg) Lenalidomide, 10 mg PO
-4	Lenalidomide, 10 mg PO
-3	Lenalidomide, 10 mg PO
-2	Lenalidomide, 10 mg PO
-1	Rest
0	Autologous PBPC infusion

* Rituximab: CD20+ patients only

All drugs are commercially available, and patients will receive the commercial supply.

On D-13, patient will receive rituximab at 375 mg/m2 as an outpatient. This will be followed by admission to start hydration.

On D-12, carmustine will be administered at a dose of 300 mg/m^2 IV over 2 hours.

On D-11 to D-8, etoposide will be administered at a dose of 200 mg/m^2 IV BID over 3 hours, and cytarabine will be administered at a dose of 200 mg/m^2 IV BID over 1 hour.

On D-7, melphalan will be administered at a dose of 140 mg/m^2 IV over 30 minutes, lenalidomide at a dose of 10 mg PO, and rituximab at a dose of 375 mg/m^2 IV.

On D-6 to D-2, lenalidomide will be administered at a dose of 10 mg PO.

On D-5, the NK cell infusion will be administered intravenously. Premedication will

include Benadryl 25 mg IV and Tylenol 650 mg po. **The use of steroids is contraindicated from d-8 until d+3.**

Obtention of NK cells:
Frozen cord blood units will be thawed and mononuclear cells will be isolated by Ficoll density gradient centrifugation. NK cells will be generated over 14 days in liquid cultures using APC feeder cells as described in detail in the Chemistry, Manufacturing and Controls (CMC).

NK Product Release Criteria
The following minimum criteria will be required for release of the expanded NK cells for reinfusion:

Test	Specifications
Gram Stain	No Organisms Seen
Visual Inspection	No Evidence of Contamination
Endotoxin	< 5 EU/kg
CD3+ Cells	< 2 x 105/kg CD3+ cells
Immunophenotyping	> 80% $CD16^{+}$ $CD56^{+}$ Undetectable $CD32^{+}$ $CD19^{+}$ $CD56^{-}$ of viable cells
Viability (7AAD) (Final Product)	≥ 70%
NK Cell Dose (CD16+CD56+)	≤ 1 x 10^{8} NK Cells/kg

If more than 2e5 CD3+ cells/kg are present, a second cycle of CD3 depletion may be performed. The cell dose for infusion may be reduced so that the infused CD3+ cells are 2e5/ kg or less.

On D0, autologous stem cell infusion minimum cell dose of 2e6 cells/kg. This infusion can be administrated as in-patient or out-patient following standard SCT/CT department procedures. Steroids will NOT be used.

G-CSF (filgrastim-sndz, Zarxio) at a dose of 5 mcg/kg/day (round up to the nearest vial) subcutaneously beginning on D+5, and continuing until evidence of an absolute neutrophil count (ANC) of 0.5 x 10^{9}/L per 3 consecutive days.

Optional Procedure: With the patient's consent, if NK cell doses higher than 1 x 10^{8} are

generated, or if the patient cannot receive the NK cells, the cells may be cryopreserved in the Stem Cell Laboratory. The cells may be used for research or discarded. If the patient refuses, the cells will be destroyed.

Administration of Lenalidomide:
From D-7 to D-2, lenalidomide will be administered at a dose of 10 mg PO daily.

Lenalidomide will be provided in accordance with the Revlimid REMS™ program. Per standard Revlimid REMS™ program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS™ program.

Females of childbearing potential must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10-14 days prior to and again 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days).

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Reduced Dose BEAM: In patients who are >65 or with substantial comorbidities, a reduced dose of BEAM (with each dose of cytarabine and etoposide decreased to 100 mg/m2) can be used, at the discretion of the patient's transplant physician. (See Appendices E. and F.)

In patients whose lymphomas are CD20-negative, the use of rituximab will be omitted.

Supportive treatment
All patients will receive supportive care as clinically indicated following standard practice, except that **steroids will be contraindicated from d-8 until d+3.**

7.0 Evaluation During Study

1. Peripheral blood for NK chimerism studies:
The first 12 patients enrolled will have chimerism analysis up to twice a week (as permitted by laboratory availability) from D-4 to D+7, then only if positive for donor NK cells, weekly up to around D+30 (+/- 3 days). After D+30 and until D+100 is not mandatory, only if positive for donor NK cells and if the patient comes for routine follow up.

2. GvHD assessment:
After the NK infusion (D-5) at each visit or as clinically indicated. When symptoms of GvHD are suspected a biopsy must be done prior to initiating treatment.

3. Disease assessments around D+30, D+100, and D+180:
These evaluations follow our standard practice. If clinically indicated these studies may be done at other time points which can replace the nearest planned timepoint.

- History and physical exam.
- Lab work: CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, urinalysis.
- PET study if it was positive pretransplant. If it was negative, CT scans of the neck, chest abdomen and pelvis.
- Bone marrow aspirate and biopsy if positive pretransplant.

4. The following lab tests are to be performed as frequently as clinically indicated: CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, urinalysis.

5. Antitumor responses will be evaluated according to the Lugano Revised Criteria for Response Assessment (see Appendix G.).[16]

6. Pregnancy Testing:
Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

For FCBP, pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to prescribing lenalidomide. (prescriptions must be filled within 7 days) and at Day +28 (+/- 2 days) post the last dose (D-2) of lenalidomide.

7. Correlative Studies (Optional):
To determine persistence of donor-derived CB-NK cells in the recipient we will collect serial PB samples at D-4, D0 (before infusion of PBPC), D+7 and weekly thereafter, until negative results are obtained.

We will employ our institution's standard DNA microsatellite chimerism assay to detect donor CB-NK cells.[17] Briefly, PCR-based microsatellite polymorphism analysis will be performed using capillary electrophoresis (CE-PCR) on DNA from the pre-transplant, CB donor and post-transplant PB samples. DNA from sorted T-lymphocytes (T-cells), myeloid cell (M-cells) and/or NK-cells will also be used in addition to the total DNA, as applicable. A total of 8 microsatellite regions (D6S264, D3S1282, D18S62, D3S1300, DM1, AR, D11S987 and D9S171) will be assessed in each specimen to identify the most distinct or discriminating (informative) marker/s between CB donor versus recipient DNA. The area under the curve for the informative marker will be used to calculate the

percent engraftment using the formula: % engraftment = 100 x [Donor/(Donor+Recipient)] DNA in post-transplant sample. The lower limit of detection for this assay has been established to be at 1%.

In parallel, we will perform multiparameter flow cytometry to analyze the source (patient or CB) and the phenotype of circulating NK cells. PB MNCs will be subjected to ficoll-separation. Thereafter, cells will be stained for the following: CD56, CD3, CD16, PAN KIR, NKG2D, NKG2A, NKp30, NK p44, NKp46, NKG2C. When possible, chimerism will be determined by flow cytometry using fluorochrome-conjugated antibodies against HLA groups Bw4 or Bw6.

8.0 Reporting Requirements

The Principal Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Adverse events and protocol specific data will be entered into REDCap/CORe. REDCap/CORe will be used as the electronic case report form for this protocol. Concomitant medications will captured in participants' medical records.

Severity of the adverse events (AEs)
The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.03 (CTCAE) from Day -5 (the start of NK cell infusion) up to D+30 (+3 days if necessary). Events not included in the CTCAE chart will be scored as follows:

General grading:
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death

Causality Assessment
The investigational component of the treatment plan of this study is the infusion of ex-vivo expanded CB NK cells when administrated with lenalidomide, high-dose chemotherapy with BEAM and autologous stem cell transplantation.

Therefore, events known to be caused by the NK cell infusion and its direct consequences will be assessed as definitely related when assessing the causality. When the relationship of the adverse event cannot be rule out between the NK cell infusion and the treatment plan, the event will be scored as probably or possible related.

Events known to be related to drugs used as part of the treatment plan as well as to

drugs used as supportive treatment will be scored as unrelated to the NK cells infusion.

Causality will be determined as per the guidelines above and based on the expected toxicities listed below.

The Principal Investigator or physician designee will be the final arbiter in determining the causality assessment.

AEs related to the NK cells infusion:

1. These expected events will be monitored during the first 24 hours post infusion:

- Fever,
- Chills,
- Decrease in blood pressure,
- Rash,
- Shortness of breath.

2. Unexpected and related events:

- Grade 4 NK infusion related toxicity,
- Failure to engraft by D+28 or delayed engraftment,
- Grades 3-5 allergic reactions related to study cell infusion,
- Grade 3-5 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy or due to preparative chemotherapy and occurring within 30 days (+3 days if necessary) post-transplant,
- Grades 3-4 acute GVHD occurring within 45 days post-transplant,[10]
- Treatment-related death within 8 weeks of the study cell infusion.[32]

Expected AEs related to high dose chemotherapy followed by autologous stem cell infusion include the following:

- Related to myelosuppression: thrombocytopenia, bleeding, platelets and RBCs transfusions.
- Fever: Non Neutropenic or Neutropenic without infection.
- Infections in the presence or absence of neutropenia.
- Readmissions (lasting <10 days).
- Cytopenias post transplant including secondary graft failure.
- Low blood pressure due to dehydration requiring fluid replacement.
- Fluid overload leading to cardiac dysfunction.
- GI related: nausea, vomiting, diarrhea, mucositis.
- Organ dysfunction: cardiac, pulmonary, hepatic, CNS and/ or renal.
- Stem Cell Transplant Syndromes: Cytokine Storm, TTP, hemorrhagic cystitis, interstitial pneumonitis (including pulmonary hemorrhage).

Adverse events data collection

REDCap/CORe will be used as the electronic case report form (eCRF) for this protocol.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug.

Adverse events will be entered into the eCRF from day -5 to day +30. The collection of adverse events will reflect the onset and resolution date and maximum grade. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Intermittent events should be labeled as such and followed until resolution. Subjects who are removed from study due to an adverse event will continue to be followed until resolution of the event, evidence emerges that the event is stable and will not progress, or until death.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy and otherwise meet the criteria for a reportable adverse event as defined above. They are to be captured under the signs, symptoms or diagnoses associated with them.

Those adverse events that are suspected unexpected severe adverse reactions (SUSARs) should be reported to FDA in an expedited fashion as detailed in 21CFR312.32. Adverse events will be reported in aggregate as part of the IND's annual report.

The Principal Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Adverse events will be documented based on all available evidence, including the flowsheet in the electronic patient medical record.

Concurrent medication

As stated in the treatment plan, patients treated on this protocol will require supportive care treatment (concurrent medication). These medications are considered standard of care and have no scientific contributions to the protocol, therefore no data will be captured on the various medications needed or their sides effects.

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- Patients who withdraw consent due to toxicities will be evaluable and considered treatment failures.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional

Review Board policy.

A sterility and mycoplasma sample is removed from final fresh CB-NK product, as additional testing. Because of the nature of the final product to be infused, these results won't be available at time of release; therefore this testing is not considered part of the release criteria. As a rapid microbial test, we perform a gram stain and endotoxin test as release criteria of the final fresh CB-NK product.

The expected acceptable results for the Mycoplasma and Sterility are the following:

Additional Monitoring Tests:

Test	Specifications
Sterility	No Growth at 14 days
Mycoplasma (PCR)	Negative

In the event the 14-day sterility or mycoplasma PCR results on the final cultured product return positive after the product has been infused, the Laboratory Director, Laboratory Medical Director, Laboratory Quality Assurance Unit, Principle Investigator, and the Investigational New Drug (IND) Office Sponsor will be notified. The Quality Assurance Unit will conduct an investigation to determine if any corrective and/or preventative actions are required. The investigation and proposed corrections for a failure of lot release sterility testing will include: identification of the microorganism(s) and anti-microbial agent sensitivity testing; evaluation of the current procedure for collecting and processing the product to determine the step at which contamination could be introduced; development of changes in procedures that will assist in preventing sterility lapses in the future; and implementation of appropriate testing to ensure that such changes to procedures produce a sterile product.

The Principal Investigator will be responsible for notifying the appropriate regulatory agencies (FDA, IRB) of deviations and adverse events. Additionally, we will report the sterility failure, results of investigation of the cause and any corrective actions, in an information amendment submitted to the IND in a timely manner, within 30 calendar days after initial receipt of the positive culture test result.

9.0 Criteria for Removal from the Study

The study duration will be the time from study registration until death, patient request, disease progression, or day +180 after transplantation, whichever occurs first.

10.0 Statistical Considerations

This is a phase II trial of high dose chemotherapy (Rituximab +BEAM + Lenalidomide) as a preparative regimen + umbilical cord blood derived NK cells + autologous stem cell transplant (autosct) for treatment of lymphoma that requires a stem cell transplant. A maximum of 40 patients will be treated, with an expected accrual rate of 2 patients per month. The primary outcome for safety monitoring is transplant related mortality within 30 days, TRM30. A TRM30 probability of .10 will be considered unacceptably high. The method of Thall and Sung will be used for safety monitoring [18]. Assuming that pE = Pr(TRM30 with the experimental regimen) follows a non-informative beta (.10, .90) prior, and assuming standard probability pS ~ beta(100,900), the trial will be stopped early if Pr(pS < pE | data) > .50. Applying this rule continuously, the trial will be stopped early if [# TRM30] / [# patients evaluated] is greater than or equal to 1/7, 2/17, 3/27, 4/37 or 5/39.

Pr(TRM30) will be estimated using a 95% credible interval assuming a beta(.50, .50) prior.

This rule has the following operating characteristics.

True Pr(TRM30)	Pr(Stop Early)	Sample Size Quartiles
.20	.98	2 4 7
.15	.92	2 5 14
.10	.74	3 7 40
.09	.69	4 10 40
.08	.62	4 15 40
.07	.55	4 23 40
.06	.48	5 40 40
.05	.39	6 40 40
.04	.32	7 40 40
.03	.24	40 40 40
.02	.16	40 40 40
.01	.07	40 40 40

The stopping rule and operating characteristics were calculated using multc99.

Secondary Outcomes. Relapse-free survival (RFS) time, overall survival (OS) time, NK cell persistence, with NK cells measured weekly for 14 weeks will be recorded. RFS will be defined as the time from transplant to either progression/relapse or death, whichever occurs first, or last contact. OS will be defined as the time from transplant to death or last contact.

Data Analyses. Unadjusted RFS and OS will be estimated by the method of Kaplan and Meier [19]. A Bayesian hierarchical regression model [20] will be fit to the longitudinal NK cell data to assess its patterns over time and association with patient

covariates, including type of lymphoma, age, and disease severity.

It is extremely unlikely that any patient in this trial would withdraw. In the case of this unlikely event, all withdrawals because of toxicity will be considered treatment failures in all analyses. In the case that a subject withdraws from the study for a reason other than toxicity, analyses both including a non-toxicity related withdrawal scored as a treatment failure and excluding a non-toxicity related withdrawal will be performed to assess sensitivity of final inferences.

A Safety Summary will be submitted to the IND Office Medical Monitor after the first 7 patients complete their 30 days of study treatment and every 10 evaluable patients thereafter, in cumulative method. Evaluability implies having completed 30 days on study and being assessed for the primary endpoint, i.e., TRM within 30 days.

11.0 Background Drug Information

11.1 Rituximab

Rituximab is associated with hypersensitivity reactions that may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with Rituximab infusion as part of an infusion-related symptom complex. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Patients who develop clinically significant arrhythmias as a result of Rituximab therapy should undergo cardiac monitoring during and after subsequent infusions of Rituximab. Patients with pre-existing cardiac conditions, including arrhythmias and angina, have experienced recurrences during Rituximab therapy and should be monitored during and immediately after the infusion.

Rituximab rapidly decreases levels of benign and malignant CD20+ cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hr after the first Rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (ie, bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed up closely and appropriate laboratory monitoring performed.

After treatment for and resolution of tumor lysis syndrome, subsequent Rituximab therapy has been administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

Warnings and precautions:

Bowel obstruction/perforation: Abdominal pain, bowel obstruction, and perforation have been reported (rarely fatal), with an average onset of symptoms of ~6 days (range: 1-77 days); complaints of abdominal pain or repeated vomiting should be evaluated,

especially if early in the treatment course.

• Hepatitis B virus reactivation: [U.S. Boxed Warning]: Hepatitis B virus (HBV) reactivation may occur with use and may result in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) prior to therapy initiation; monitor patients for clinical and laboratory signs of hepatitis or HBV during and for several months after treatment. Discontinue rituximab (and concomitant medications) if viral hepatitis develops and initiate appropriate antiviral therapy. Reactivation has occurred in patients who are HBsAg positive as well as in those who are HBsAg negative but are anti-HBc positive; HBV reactivation has also been observed in patients who had previously resolved HBV infection. HBV reactivation has been reported up to 24 months after therapy discontinuation. Use cautiously in patients who show evidence of prior HBV infection (eg, HBsAg positive [regardless of antibody status] or HBsAG negative but anti-HBc positive); consult with appropriate clinicians regarding monitoring and consideration of antiviral therapy before and/or during rituximab treatment. The safety of resuming rituximab treatment following HBV reactivation is not known; discuss reinitiation of therapy in patients with resolved HBV reactivation with physicians experienced in HBV management.

• Infections: Use is not recommended if severe active infection is present; serious and potentially fatal bacterial, fungal, and either new or reactivated viral infections may occur during treatment and after completing rituximab. Infections have been observed in patients with prolonged hypogammaglobulinemia, defined as hypogammaglobulinemia >11 months after rituximab exposure; monitor immunoglobulin levels as necessary. Associated new or reactivated viral infections have included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue rituximab (and concomitant chemotherapy) in patients who develop viral hepatitis and initiate antiviral therapy. Discontinue rituximab in patients who develop other serious infections and initiate appropriate anti-infective treatment.

• Infusion reactions: [U.S. Boxed Warning]: Severe (occasionally fatal) infusion-related reactions have been reported, usually with the first infusion; fatalities have been reported within 24 hours of infusion; monitor closely during infusion; discontinue for severe reactions and provide medical intervention for grades 3 or 4 infusion reactions. Reactions usually occur within 30-120 minutes and may include hypotension, angioedema, bronchospasm, hypoxia, urticaria, and in more severe cases pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylaxis. Risk factors associated with fatal outcomes include chronic lymphocytic leukemia, female gender, mantle cell lymphoma, or pulmonary infiltrates. Closely monitor patients with a history of prior cardiopulmonary reactions or with pre-existing cardiac or pulmonary conditions and patients with high numbers of circulating malignant cells (>25,000/mm3). Prior to infusion, premedicate patients with acetaminophen and an antihistamine (and methylprednisolone for patients with RA). Discontinue infusion for severe reactions and serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after the infusion in patients

who develop clinically significant arrhythmias or who have a history of arrhythmia or angina. Medications for the treatment of hypersensitivity reactions (eg, bronchodilators, epinephrine, antihistamines, corticosteroids) should be available for immediate use; treatment is symptomatic. Mild-to-moderate infusion-related reactions (eg, chills, fever, rigors) occur frequently and are typically managed through slowing or interrupting the infusion. Infusion may be resumed at a 50% infusion rate reduction upon resolution of symptoms. Due to the potential for hypotension, consider withholding antihypertensives 12 hours prior to treatment.

• Mucocutaneous reactions: [U.S. Boxed Warning]: Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis) have been reported; onset has been variable but has occurred as early as the first day of exposure. Discontinue in patients experiencing severe mucocutaneous skin reactions; the safety of re-exposure following mucocutaneous reactions has not been evaluated.

• Progressive multifocal leukoencephalopathy: [U.S. Boxed Warning]: Progressive multifocal leukoencephalopathy (PML) due to JC virus infection has been reported with rituximab use; may be fatal. Cases were reported in patients with hematologic malignancies receiving rituximab either with combination chemotherapy, or with hematopoietic stem cell transplant. Cases were also reported in patients receiving rituximab for autoimmune diseases who had received concurrent or prior immunosuppressant therapy. Onset may be delayed, although most cases were diagnosed within 12 months of the last rituximab dose. A retrospective analysis of patients (n=57) diagnosed with PML following rituximab therapy, found a median of 16 months (following rituximab initiation), 5.5 months (following last rituximab dose), and 6 rituximab doses preceded PML diagnosis. Clinical findings included confusion/disorientation, motor weakness/hemiparesis, altered vision/speech, and poor motor coordination with symptoms progressing over weeks to months (Carson, 2009). Promptly evaluate any patient presenting with neurological changes; consider neurology consultation, brain MRI and lumbar puncture for suspected PML. Discontinue rituximab in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants.

11.2 Etoposide

Etoposide (VP-16) is a semisynthetic podophyllotoxin derivative with antineoplastic activity.

Pharmaceutical data: VP-16 is supplied as 100 mg/5cc ampules.

Solution preparation: The contents of the vial are diluted with 0.9% sodium chloride for injection, USP. The final concentration of the admixture must be 0.2 mg/mL - 0.4 mg/mL. Solutions prepared above 0.4 mg/mL may contain precipitate.

Route of administration: Slow IV infusion.

Known side-effects: Myelosuppression, primarily granulocytopenia is the dose-limiting toxicity. Other side effects include gastrointestinal toxicity comprising of nausea, emesis and mucositis. At high doses reversible hepatotoxicy is seen. Acute side effects include occasional bronchospasm and hypotension. These can be avoided by slow intravenous administration.

Hypersensitivity reaction: May cause anaphylactic-like reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. In addition, facial/tongue swelling, coughing, chest tightness, cyanosis, laryngospasm, diaphoresis, hypertension, back pain, loss of consciousness, and flushing have also been reported less commonly. Incidence is primarily associated with intravenous administration (up to 2%) compared to oral administration (<1%). Infusion should be interrupted and medications for the treatment of anaphylaxis should be available for immediate use. High drug concentration and rate of infusion, as well as presence of polysorbate 80 and benzyl alcohol in the etoposide intravenous formulation, have been suggested as contributing factors to the development of hypersensitivity reactions. Etoposide intravenous formulations may contain polysorbate 80 and/or benzyl alcohol, while etoposide phosphate (the water soluble prodrug of etoposide) intravenous formulation does not contain either vehicle. Case reports have suggested that etoposide phosphate has been used successfully in patients with previous hypersensitivity reactions to etoposide.

• Secondary malignancies: Secondary acute leukemias have been reported with etoposide, either as monotherapy or in combination with other chemotherapy agents.

Pharmacokinetics: The main site of metabolism is in the liver. Major metabolites of etoposide are hydroxy acids and cistactone which appear in the plasma and urine. The half-life of the drug is 4 to 11 hours.

Mechanism of action: Two different dose dependent responses are seen. At high concentrations (10 ug/ml) lysis of cells entering mitosis is seen. At low concentrations (0.3 to 10 ug/ml) cells are inhibited from entering prophase. The predominant macromolecular affect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or by the formation of free radicals.

11.3. Cytarabine

Cytarabine is a synthetic antimetabolite antineoplastic agent.

Dosing information: Usual induction dose for ANLL (acute non-lymphocytic leukemia) has been 100 to 200 mg/m2 daily for 5 to 7 days (in combination with other cytoxic agents).
Pharmacokinetics: Following IV administration, cytarabine is widely distributed to areas including the CNS and tears; the drug is orally active. Cytarabine is metabolized in the liver to an inactive metaolite; both cytarabine and its metabolite are excreted in the urine. The elimination half-life is between 1 and 3hours.

Side Effects: The major toxic effect of cytarabine is myelosuppression resulting in megaloblastic changes in erythropoiesis and reticulocytopenia. Other adverse effects include neuropathies, GI distress, hepatic toxicity, and hypersensitivity.

Clinical Applications: Cytarabine is useful in various neoplastic disorders including myelocyticleukemia, lymphoblastic leukemia, and non lymphocytic.

11.4. Melphalan

Melphalan is an alkylating agent with cell cycle nonspecific cytotoxic effects on tumor cells.

Dosing Information: The usual dose for conditioning in stem cell transplantation is 100-200 mg/m^2intravenously.

Pharmacokinetics: Orally administered melphalan demonstrates considerable variation in bio availability, does not undergo active metabolism, and is primarily eliminated in the feces. However, compromised renal function may significantly impact melphalan excretion.

Side Effects:

(>10%) Gastrointestinal: Nausea and vomiting, diarrhea, oral mucosa ulcer
Hematologic & oncologic: Anemia, bone marrow depression, leukopenia (nadir: 14 to 21 days; recovery: 28 to 35 days), metastases (·20%; cumulative dose and duration dependent; includes acute myeloid leukemia, myeloproliferative syndrome, carcinoma), thrombocytopenia (nadir: 14 to 21 days; recovery: 28 to 35 days)
(1% to 10%) Hypersensitivity: Hypersensitivity reaction (IV: 2%; includes bronchospasm, dyspnea, edema, hypotension, pruritus, skin rash, tachycardia, urticaria)
Frequency not defined:
Cardiovascular: Cardiotoxicity (angina pectoris, cardiac arrhythmia, hypertension, myocardial infarction; with high-dose therapy), hepatic veno-occlusive disease (hepatic sinusoidal obstruction syndrome; SOS; high-dose IV melphalan), vasculitis
Central nervous system: Brain disease, flushing sensation, seizure (with high-dose therapy), tingling sensation
Dermatologic: Allergic skin reaction, alopecia, maculopapular rash, pruritus
Endocrine & metabolic: Amenorrhea, SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Gastrointestinal: Mucositis (with high-dose therapy), paralytic ileus (with high-dose therapy), stomatitis
Genitourinary: Hemorrhagic cystitis, inhibition of testicular function, nephrotoxicity (with high-dose therapy), ovarian function suppression, sterility
Hematologic & oncologic: Agranulocytosis, bone marrow failure (irreversible), hemolytic anemia, hemorrhage (with high-dose therapy)
Hepatic: Hepatitis, increased serum transaminases, jaundice
Hypersensitivity: Anaphylaxis (rare), hypersensitivity reaction

Infection: Infection, sepsis
Local: Injection site reaction (injection site necrosis, ulceration)
Neuromuscular & skeletal: Myelopathy (radiation)
Renal: Increased blood urea nitrogen
Respiratory: Interstitial pneumonitis, pulmonary fibrosis

Clinical Applications: Melphalan has a broad spectrum of antitumor activity, but its main use in the palliative treatment of multiple myeloma and non-resectable.

11.5. Carmustine

Carmustine is a nitrosourea derivative alkylating agent.

Dosing Information: As a single agent 150 to 200 mg/m2 IV.

Pharmacokinetics: Carmustine is highly lipid soluble and readily crosses into the CSF. The drug is rapidly metabolized with no intact drug detectable in the plasma after 15 minutes; some metabolites are known to be active. About 60 to 70% of a dose is eliminated in the urine.

Side Effects*:* Delayed and cumulative myelosuppression is the most frequent and profound toxicity of Carmustine. Thrombocytopenia is usually more serious than leukopenia; however, both may be dose-limiting. Other adverse effects include pulmonary fibrosis, nausea and vomiting, hepatotoxicity, and nephrotoxicity.

Clinical Applications: Carmustine is used alone or in combination with other appropriate therapeutic measures in the treatment of various neoplastic conditions such as Hodgkin's disease, brain tumors, multiple myeloma, and non-Hodgkin's lymphoma.

11.6. Lenalidomide

Common trade named: Revlimid®

Class
Angiogenesis inhibitor
immunomodulating agents (IMiDs).
Antineoplastic agent
Tumor Necrosis factor (TNF) blocking agent

Administration
Lenalidomide capsule are administrated orally with water. Patients should not break, chew or open the capsules

Monitoring
Platelet count, hemoglobin, WBC, and differential at start of therapy and prior to each subsequent course of therapy; serum creatinine, liver function tests, thyroid function tests; monitor for signs and symptoms of thromboembolism.

Women of childbearing age must have a pregnancy test within 10-14 days and 24 hours before lenalidomide, then 28 days (+/- 2 days) after therapy discontinued.

Pregnancy Testing
Females must follow pregnancy testing requirements as outlined in the Revlimid REMS® program.

Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

For FCBP, pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to prescribing lenalidomide. (prescriptions must be filled within 7 days) and at Day +28 (+/- 2 days) post the last dose (D-2) of lenalidomide.

Contraindications
- Hypersensitivity of lenalidomide products
- Previous resistance to the drug
- Pregnancy

Precautions
- No formal studies have been conducted in patients with renal impairment. this drug is known to be excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.
- Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients with hepatic impairment have not been studied.
- Age: lenalidomide has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.
- Check pregnancy test before administering lenalidomide
- Check CBC before administering lenalidomide
- Hypersensitivity reaction; do not re challenge
- Impairment of fertility
- Mutagenic, potentially
- Severe bone marrow depression
- Women of childbearing age should avoid becoming pregnant
- monitor for signs and symptoms of thromboembolism: prophylaxis

Adverse effects
>10%:
- Cardiovascular: Peripheral edema (8% to 21%) - Central nervous system: Fatigue (31% to 38%), pyrexia (21% to 23%), dizziness (20% to 21%), headache (20%)
- Dermatologic: Pruritus (42%), rash (16% to 36%), dry skin (14%)
- Endocrine & metabolic: Hyperglycemia (15%), hypokalemia (11%)
- Gastrointestinal: Diarrhea (29% to 49%), constipation (24% to 39%), nausea (22% to 24%), weight loss (18%), dyspepsia (14%), anorexia (10% to 14%), taste perversion (6% to 13%), abdominal pain (8% to 12%)
- Genitourinary: Urinary tract infection (11%)
- Hematologic: Thrombocytopenia (17% to 62%; grades 3/4:10% to 50%), neutropenia (28% to 59%; grades 3/4: 21% to 53%), anemia (12% to 24%: grades 3/4: 6% to 9%); myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction

- Neuromuscular & skeletal: Muscle cramp (18% to 30%), arthralgia (10% to 22%), back pain (15% to 21%), tremor (20%), weakness (15%), paresthesia (12%), limb pain (11%)
- Ocular: Blurred vision (15%)
- Respiratory: Nasopharyngitis (23%), cough (20%), dyspnea (7% to 20%), pharyngitis (16%), epistaxis (15%), upper respiratory infection (14% to 15%), pneumonia (11% to 12%)

Pregnancy category - X
- Breast feeding: Infant risk cannot be ruled out

- How supplied: 5 mg, 10 mg, 15 mg and 25 mg capsules.

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