TITLE: A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy

PROTOCOL NO.: KIT-302-03-02

INVESTIGATIONAL DRUGS: Amlodipine besylate and celecoxib

DOSAGE FORM: Capsule [over-encapsulated (OE) tablet and capsule, respectively]

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DATE OF VERSION: December 16, 2016

VERSION: 4

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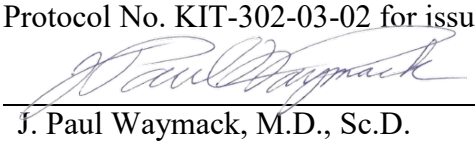
PROTOCOL SIGNATURE SHEET

The undersigned has reviewed the format and content of this protocol and has approved Protocol No. KIT-302-03-02 for issuance.



16 Dec 2016

J. Paul Waymack, M.D., Sc.D.
Chief Medical Officer
Kitov Pharmaceuticals, Ltd.

Date

INVESTIGATOR SIGNATURE SHEET

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

I will provide copies of the protocol and of the preclinical and clinical information on the test articles, 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 articles 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 October 2013 revision.

Investigator's Signature: _____ Date: _____

Investigator's Printed Name: _____

Investigational Site Name: _____

LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitor
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
bd	twice a day
BE	bioequivalence
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
COX-2	cyclooxygenase-2
CRF	case report form
CRO	contract research organization
CYP2C9	cytochrome P450 2C9
DBP	diastolic blood pressure
DBP_{24h}	average 24-hour ambulatory diastolic blood pressure
DBP_{day}	average daytime (9:00 to 21:00) diastolic blood pressure
DBP_{night}	average night-time (01:00 to 06:00) diastolic blood pressure
ECG	electrocardiogram
FCDP	fixed combination drug product
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
LC-MS/MS	liquid chromatography tandem mass spectroscopy
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimetres of mercury
MMRM	mixed model for repeated measures
NSAID	non-steroidal anti-inflammatory drug
OBP	office blood pressure
OE	over-encapsulated

OTC	over-the-counter
PHI	Protected Health Information
PK	pharmacokinetic
PP	per-protocol
PTAE	pretreatment adverse event
qd	once a day
SAE	serious adverse event
SBP	systolic blood pressure
SBP_{24h}	average 24-hour ambulatory systolic blood pressure
SBP_{day}	average daytime (9:00 to 21:00) ambulatory systolic blood pressure
SBP_{night}	average night-time (01:00 to 06:00) ambulatory systolic blood pressure
TBD	to be determined
TEAE	treatment emergent adverse event
US	United States
WCBP	women of childbearing potential
WHO	World Health Organization

PROTOCOL SYNOPSIS

Name of Sponsor/ Company:	Kitov Pharmaceuticals, Ltd.
Name of Finished Products:	Norvasc® (amlodipine besylate) tablets (10 mg amlodipine besylate base) Celebrex® (celecoxib) capsules (200 mg celecoxib) Each of the formulations will be individually over-encapsulated (OE) and matched placebos will be used to allow for blinding.
Name of Active Ingredients:	Amlodipine besylate and celecoxib
Title of Study:	A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy
Protocol No.:	KIT-302-03-02
Investigators/Study Centers/Locations:	TBD/TBD/TBD
Phase of Development:	Phase 3
Study Period:	Up to 6 weeks per subject (initial Screening visit to Final visit); approximately 8 months for the entire trial (first subject enrolled to last subject completed)
Primary Objective:	To demonstrate that the mean reduction in average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBP_{day}) after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together once a day (qd) for 14 days in adult subjects with existing hypertension is no less than half the mean reduction in SBP_{day} after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.
Secondary Objectives:	To evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension on secondary efficacy endpoints using a serial gatekeeping strategy. If and only if the primary efficacy endpoint is statistically achieved, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses. 1. Difference in mean change in body weight from baseline to end of treatment between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together, amlodipine tablets (10 mg) given alone (with matched celecoxib placebo), and placebo]; 2. Difference in the mean reduction in average 24-hour ambulatory systolic blood pressure (SBP_{24h}) from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms; 3. Difference in the mean reduction in average 24-hour ambulatory diastolic blood pressure (DBP_{24h}) from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms; 4. Difference in the mean change in creatinine clearance from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms.

	To evaluate the safety of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension. To evaluate the effect of celecoxib on the mean plasma concentrations of amlodipine in adult subjects with existing hypertension after 14 days of treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together compared to amlodipine tablets (10 mg) given alone (with matched celecoxib placebo).
Methodology:	This is a multi-center, randomized, double blind, placebo controlled trial to evaluate the effect of celecoxib on the efficacy, safety, and pharmacokinetics of amlodipine in subjects with existing hypertension requiring antihypertensive therapy. Approximately 105 adult subjects with existing hypertension who require and are currently using pharmacological therapy with a single agent that is not a calcium channel blocker to control their hypertension will be randomized 3:3:1 to one of three treatment arms: 1. OE Norvasc® tablet (10 mg amlodipine besylate) + OE Celebrex® capsule (200 mg celecoxib); 2. OE Norvasc® tablet (10 mg amlodipine besylate) + matched placebo for OE Celebrex® capsule; 3. Matched placebo for OE Norvasc® tablet + matched placebo for OE Celebrex® capsule. All drugs will be administered orally qd for 14 days (Days 0-13) for a total of 14 doses. The total number of subjects planned (105) is an approximation. Once the 105th subject is randomized to treatment (Day 0), any subject that is currently participating in the washout period will be allowed to complete the washout period and if found eligible will be enrolled into the trial. These subjects will continue to be randomized 3:3:1 as noted above. No further subjects will be brought in for the Initial Screening Visit once the 105th subject is randomized. **Initial Screening Visit (Day -14 to -10):** Each subject will be provided with oral and written information (ICF) describing the study and will have any questions answered. Subjects that consent in writing to participate in the study will undergo eligibility assessments, including complete medical history, comprehensive physical examination, height, body weight in underwear and a light gown, body mass index (BMI), vital signs (BP, pulse rate, respiration rate, and oral body temperature), 12-lead electrocardiogram (ECG), hematology, serum chemistry, urinalysis, serum pregnancy test for women of childbearing potential (WCBP), urine drug screen, and record medications taken within 30 days prior to initial screening visit. Subjects who meet eligibility criteria based on the above initial screening visit procedures will be instructed to cease taking their current BP medication. Monitoring for pretreatment adverse events (PTAEs) will begin upon completion of the initial screening visit procedures and will continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Any untoward medical occurrence that initiates or worsens after completion of the initial screening visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE. Subjects will be instructed to return to the clinic in 9 to 13 days. **Final Screening Visit (Day -1)** Subjects will return to the clinic after 9 to 13 days of washout for their final screening visit (Day -1). They will undergo the following procedures: solicit for history of PTAEs since the previous visit and record medications taken since prior visit. Those who continue to meet eligibility criteria will be given an ambulatory blood pressure monitor (ABPM), instructed in its use, and have the positioning of their ABPM checked. They will be instructed to wear it at all times for the next 25 hours and to return to the clinic the following day.

	Study Day 0: When the subjects return to clinic the following day, the ABPM will be collected and the data contained therein downloaded and analysed. If subjects are found to be hypertensive, based upon their ABPM measurement, they will undergo additional baseline procedures as described below. If the subject's BP is too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), the subject will not be enrolled and they will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. If the subject is found to be normotensive ($SBP_{day} \leq 135$ mmHg), the subject will not be enrolled. The subject's primary care doctor will be informed that he/she has been found not to be hypertensive. No subject will be randomized until these baseline ABPM data have been reviewed and it has been documented that the subject meets entry BP criteria. Subjects who meet the BP criteria ($SBP_{day} > 135$ and ≤ 169 mmHg and $DBP_{day} \leq 110$ mmHg) following completion of the 10- to 14-day washout period will undergo the following additional baseline procedures: solicit for history of PTAEs since the previous visit, targeted physical examination, body weight in underwear and a light gown, vital signs, orthostatic hypotension evaluation, serum chemistry, and record medications taken since last visit. Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized 3:3:1 to one of three treatment arms. The subjects will then be administered their first dose of study drugs in the clinic. Monitoring for treatment emergent adverse events (TEAEs) will begin immediately following administration of the first dose of study drugs and will continue throughout the study. Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE. Subjects will remain in the clinic under observation for one hour following their first dose and will be solicited for TEAE history prior to leaving the clinic. Subjects will be provided with sufficient study drugs for the remainder of the 2-week treatment period, and instructed to take the study drugs qd in the morning. Subjects will be provided with a diary and instructed to record any concomitant medications taken and details of study drug administration. Subjects will be instructed to return to clinic the morning of Day 6. **Study Day 6:** Subjects will return to clinic on the morning of Day 6 and will be solicited for history of TEAEs since the previous visit. The study drug containers will be collected and unused study drug counted and recorded. The diary will be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. Subjects will be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects will then be administered their Day 6 dose of study drugs, and instructed to wear the ABPM at all times for the next 25 hours. Subjects will be given back their remaining study drug supply and diary, instructed to record any concomitant medications taken and details of study drug administration, and instructed to return to clinic the following day. **Study Day 7:** The Day 7 study drugs will be self-administered at home within 24 hours ± 1 hour from the Day 6 dose. Subjects will return to clinic on the morning of Day 7 (after the home administration of study drugs). The diary will be reviewed for any concomitant medications taken and for details of study drug administration since the previous visit. The study drug containers will be collected and unused study drug counted and recorded. Subjects will be solicited for history of TEAEs since the previous visit. A targeted physical examination will be performed and body weight in underwear and light gown and vital signs will be measured. An orthostatic hypotension test will be performed. Subjects will have BP as measured by the ABPM recorded and the ABPM collected. Subjects will have blood collected for measurement of creatinine (and calculation of creatinine clearance) and electrolytes. If the Investigator determines that it is safe for the subject to continue in the study, the subject will have their remaining study drug supply returned to them, and instructed to take the study drugs at home on Days 8-12, between 0700 and 1000 hours, and preferably at

	approximately the same time each day. Subjects will be given back their diary and instructed to record any concomitant medications taken and details of study drug administration, and instructed to return to the clinic in 6 days (on the morning of Day 13). If the subject's BP is too elevated for them to continue safely in the study (i.e., SBP_{24h} > 169 mmHg or DBP_{24h} > 110 mmHg), blood will be drawn for renal profile testing. The subject will be instructed to cease taking study drugs, instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 7 days (Day 14). **Study Day 13:** Subjects will return to clinic on the morning of Day 13 (except for those discontinued from study drug due to excessive hypertension or other safety reasons) and will be solicited for history of TEAEs since the previous visit. The diary will be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. The study drug containers will be collected and any unused study drug counted and recorded. Subjects will be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects will then be administered their Day 13 dose of study drugs (final dose), and instructed to wear the ABPM at all times for the next 25 hours. Subjects will be given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to clinic the following day. **Study Day 14:** Subjects will return to clinic on the morning of Day 14. The diary will be reviewed for any concomitant medications taken since the previous visit. Subjects will be solicited for history of TEAEs since the previous visit. A comprehensive physical examination will be performed and body weight in underwear and a light gown and vital signs will be measured. BP as measured by the ABPM will be recorded and the ABPM collected, and an orthostatic hypotension evaluation will be performed. The following additional evaluations will be performed: 12-lead ECG, hematology, serum chemistry, urinalysis, and urine pregnancy test for WCBP. In addition, subjects will have a blood sample collected 24 hours ± 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the pharmacokinetic (PK) blood collections. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine. Following the Day 14 evaluations, the subjects will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 14 days (Day 28). **Study Day 28:** Subjects will return to clinic on Day 28 for their final study visit (follow-up visit). The diary will be reviewed for any concomitant medications taken since the prior visit. Subjects will be solicited for history of TEAEs since the previous visit. A targeted physical examination will be performed and vital signs will be measured. For subjects whose study drugs are discontinued at Day 7, this follow-up visit will still occur on Day 28 (i.e., these subjects will return to the clinic for both the Day 14 and Day 28 visits).
Number of Subjects (planned):	Approximately 105 randomized subjects. Once the 105th subject is randomized to treatment (Day 0), any subject that is currently participating in the washout period will be allowed to complete the washout period and if found eligible will be randomized.
Diagnosis and Main Criteria for Inclusion:	**Inclusion Criteria** 1. Adult 40 to 75 years of age; 2. Existing hypertension that is being treated using pharmacological therapy with a single agent that is not a calcium channel blocker;

	3. SBP_{day} > 135 and ≤ 169 mmHg and DBP_{day} ≤ 110 mmHg at Day 0 (i.e., after the 10- to 14-day washout from prior BP medication); 4. Body Mass Index (BMI) of 18.5 to 34.9 kg/m^2; 5. Healthy (other than hypertension) as determined by the Investigator based on medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests; 6. A negative pregnancy test at initial screening visit; 7. If WCBP, agree to use a highly effective form of birth control while on study (from Screening through final study visit); Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Forms of birth control include intrauterine device (IUD), birth control patch or vaginal ring, oral, or injectable or implanted contraceptives, or a vasectomized partner, or abstinence from sexual intercourse. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. A woman that is postmenopausal (≥2 years since last menstrual period) or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) is not considered a WCBP. 8. Able to comprehend and sign an ICF. **Exclusion Criteria** 1. Resting systolic BP > 169 mmHg or a resting diastolic BP > 110 mmHg at initial screening visit while on their standard antihypertensive therapy (where resting is defined as supine for at least 10 minutes with minimal interaction); 2. Weight < 55 kg; 3. Fragile health; 4. Evidence of clinically significant findings on screening evaluations (clinical, laboratory, and ECG) which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of safety data; 5. Current or recent history (within four weeks prior to initial screening visit) of a clinically significant bacterial, fungal, or mycobacterial infection; 6. Current clinically significant viral infection; 7. History of malignancy, with the exception of cured basal cell or squamous cell carcinoma of the skin; 8. Major surgery within four weeks prior to initial screening visit; 9. Presence of a malabsorption syndrome possibly affecting drug absorption (e.g., Crohn's disease or chronic pancreatitis); 10. Active peptic ulceration or history of gastrointestinal bleeding; 11. History of myocardial infarction, congestive heart failure, or stroke; 12. Any current cardiovascular disease (other than hypertension); 13. History of psychotic disorder; 14. History of alcoholism or drug addiction or current alcohol or drug use that, in the opinion of the Investigator, will interfere with the subject's ability to comply with the dosing schedule and study evaluations; 15. History of any illicit drug use within one year prior to initial screening visit; 16. Positive drug screen at initial screening visit. A positive drug screen for opiates only (with all other drug tests negative) will not be a basis for exclusion if the subject took over-the-counter narcotics as indicated on the product label within 24 hours prior to the drug screen; 17. Current treatment or treatment within 30 days prior to first dose of study drugs with another investigational drug or current enrollment in another clinical trial;

	18. Known history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; 19. Known hypersensitivity to amlodipine or celecoxib; 20. Known hypersensitivity to the inactive ingredients in the OE study drugs; 21. Asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic type reactions after taking acetylsalicylic acid or NSAIDs including cyclooxygenase-2 (COX-2) inhibitors; 22. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule and study evaluations; 23. Pregnant or lactating; 24. Unable to correctly use ABPM after instruction on its use; 25. Subjects with Child-Pugh Class B or C cirrhosis; 26. Subjects currently taking a calcium channel blocker or any NSAID for any reason will be excluded. Subjects will not be withdrawn from these drugs to be enrolled in the trial; 27. Subjects that took a calcium channel blocker in the past for any indication; 28. Creatinine clearance < 50 ml/min as estimated by the Cockroft-Gault equation; 29. Known cytochrome P450 2C9 (CYP2C9) poor metabolizer; 30. Subjects with allergy or hypersensitivity to sulfonamides.
Test Product, Dose and Mode of Administration:	**Active Pharmaceutical Ingredients** Amlodipine is a calcium (Ca) channel blocker. The chemical name of amlodipine is 3-ethyl-5-methyl (±) 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)- 1,4-dihydro-6 methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Amlodipine besylate has a molecular weight of 567.06 and a molecular formula of $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$. Celecoxib is a sulfa NSAID and selective COX-2 inhibitor. The chemical name of celecoxib is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. Celecoxib has a molecular weight of 381.38 and a molecular formula of $C_{17}H_{14}F_3N_3O_2S$. **Drug Products** Two commercial formulations will be used for this trial. This study is a double blind, placebo controlled study. Therefore, the commercial formulations will be OE and matched placebos will be used to allow for blinding. The two commercial formulations are as follows: 1. Norvasc® (amlodipine besylate) tablets (10 mg amlodipine besylate, Pfizer): Each tablet contains 10 mg amlodipine besylate (base equivalent) and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate. 2. Celebrex® (celecoxib) capsules (200 mg celecoxib, GD Searle): Each capsule contains 200 mg celecoxib and the following inactive ingredients: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, and sodium lauryl sulfate. **Dose and Mode of Administration** All subjects will take study drugs by mouth qd for 14 days (Days 0-13) for a total of 14 doses. With the exception of Days 6 and 13, when study drug intake is at the time of fitting the ABPM and of Day 7, when study drug intake is 24 hours ± 1 hour later, the subjects should be instructed to take their study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day. Subjects will be randomized 3:3:1 to one of three treatment arms: 1. OE Norvasc® tablet (10 mg amlodipine besylate) + OE Celebrex® capsule (200 mg celecoxib);

	2. OE Norvasc® tablet (10 mg amlodipine besylate) + matched placebo for OE Celebrex® capsule; 3. Matched placebo for OE Norvasc® tablet + matched placebo for OE Celebrex® capsule.
Duration of Treatment:	14 days (qd on Days 0-13)
Criteria for Evaluation:	**Primary Endpoint** The primary efficacy endpoint for this trial will be the difference in the mean change in SBP_{day} from baseline (Day -1 to Day 0) to end of treatment (Day 13 to Day 14) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) (arm 2). **Secondary Endpoints** The effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on secondary efficacy endpoints will be evaluated using a serial gatekeeping strategy. If and only if the primary blood pressure efficacy endpoint is statistically achieved, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses. 1. Difference in mean change in body weight from baseline (Day 0) to end of treatment (Day 14) between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1), amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2), and placebo (arm 3)]; 2. Difference in the mean reduction in SBP_{24h} from baseline (Day -1 to Day 0) to end of treatment (Day 13 to Day 14) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2); 3. Difference in the mean reduction in DBP_{24h} from baseline (Day -1 to Day 0) to end of treatment (Day 13 to Day 14) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2); 4. Difference in the mean change in creatinine clearance from baseline (Day 0) to end of treatment (Day 14) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2). The safety of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension (arm 1) is a secondary endpoint of this trial. Safety will be assessed primarily based on reported TEAEs. The severity of both PTAEs and TEAEs will be graded according to World Health Organization (WHO) Toxicity Criteria. Secondary safety assessments will include physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis. The effect of celecoxib on plasma levels of amlodipine in adult subjects with existing hypertension is a secondary endpoint of this trial. Mean plasma concentrations of amlodipine after 14 days of treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) will be compared to evaluate for a PK drug-drug interaction.

Statistical Methods for Primary Efficacy Analysis:	The primary efficacy endpoint for this trial will be the difference in the mean reduction in SBP_{day} from Day 0 to Day 14 between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2), and specifically that the lower limit of the 95% confidence interval for the arm 1 subjects is at least 50% of the mean reduction in the arm 2 subjects. A two-sample t-test will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) is non-inferior to the control treatment with amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2). H_0: $\Delta SBP_{day,1} - 0.5(\Delta SBP_{day,2}) \geq 0$ H_1: $\Delta SBP_{day,1} - 0.5(\Delta SBP_{day,2} < 0$ Where $\Delta SBP_{day,1}$ is the reduction in SBP_{day} for subjects in arm 1. $\Delta SBP_{day,2}$ is the reduction in SBP_{day} for subjects in arm 2. For the primary analysis, an intent-to-treat (ITT) data set will be used comprising of randomized subjects with a valid ABPM measurement from Day –1 to Day 0 and also either a valid ABPM measurement from Day 13 to Day 14, where a subject completes the 14-day treatment plan, or a valid ABPM measurement from Day 6 to Day 7, where a subject is withdrawn from treatment at Day 7 because of an $SBP_{24h} > 169$ mmHg and/or a $DBP_{24h} > 110$ mmHg.
Statistical Methods for Secondary Efficacy Analysis:	A serial gatekeeping strategy will be used to evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on secondary efficacy endpoints. If and only if the primary blood pressure efficacy endpoint is statistically achieved, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses. 1. Difference in mean change in body weight from baseline (Day 0) to Day 14 (or Day 7 for subjects withdrawn from treatment at Day 7) between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1), amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2), and placebo (arm 3)]; 2. Difference in the mean reduction in SBP_{24h} from the baseline (Day –1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or to the Day 6 to Day 7 ABPM measurement for subjects withdrawn from treatment at Day 7) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2); 3. Difference in the mean reduction in DBP_{24h} from the baseline (Day –1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or to the Day 6 to Day 7 ABPM measurement for subjects withdrawn from treatment at Day 7) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2); 4. Difference in the mean change in creatinine clearance from baseline (Day 0) to Day 14 (or Day 7 for subjects withdrawn from treatment at Day 7) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2). Analysis of variance (ANOVA) will be utilized to compare body weight changes among the three treatment arms. Change in body weight will be the response with treatment arm

	as the predictive factor. There will be no covariate adjustments. Post-hoc comparisons for individual differences will use the Bonferroni Method. H_0: $\Delta BW_1 = \Delta BW_2 = \Delta BW_3$ H_1: At least one difference. Where ΔBW_1 is the reduction in body weight for subjects in arm 1 ΔBW_2 is the reduction in body weight for subjects in arm 2 ΔBW_3 is the reduction in body weight for subjects in arm 3 A two-sample t-test for superiority will be used for the secondary blood pressure efficacy analyses to test the one-sided hypotheses that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) lowers SBP_{24h} to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2). H_0: $\Delta SBP_{24h,1} - \Delta SBP_{24h,2} = 0$ H_1: $\Delta SBP_{24h,1} - \Delta SBP_{24h,2} > 0$ Where $\Delta SBP_{24h,1}$ is the reduction in SBP_{24h} for subjects in arm 1 $\Delta SBP_{24h,2}$ is the reduction in SBP_{24h} for subjects in arm 2 For the next endpoint, SBP_{24h} will be replaced with DBP_{24h}. For the creatinine clearance endpoint, a two-sample t-test for superiority will be used for the analysis to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) improves creatinine clearance to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).
Statistical Methods for PK Drug-Drug Interaction Analysis:	Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collections. Blood samples will be collected on Day 14, approximately 24 hours after receiving the final dose of study drugs. The plasma concentration of amlodipine will be determined by a validated liquid chromatography tandem mass spectroscopy (LC-MS/MS) method. A t-test will compare the plasma concentration of amlodipine in those subjects who receive amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) with those who receive amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1).
Statistical Methods for Safety Analysis:	Data from all subjects who receive at least one dose of study drug will be incorporated into the final safety analysis. Safety will be assessed primarily based on reported TEAEs. Clinically significant laboratory abnormalities will be reported as adverse events (AEs) [i.e., either as PTAEs or TEAEs, depending on when they initiate or worsen]. The incidence of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and will be further categorized by treatment arm, severity, and assigned relationship to study drug. The incidence of PTAEs will be tabulated by MedDRA system organ class and preferred term, and will be further categorized by severity. The incidence for each PTAE and TEAE will be provided as the total number of subjects that experienced the PTAE or TEAE, as well as the percentage of the population that this represents. If a PTAE or TEAE is reported more than once for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables. Chi-square analysis or an exact binomial test will be used to compare TEAE rates between treatment arms.

	PTAEs and TEAEs will be separately listed for individual subjects, along with information regarding onset and end dates, onset time where available, severity, seriousness, relationship to study drug (only in the case of TEAEs), action taken, and outcome. Separate listings and tabular summaries of PTAEs and TEAEs that lead to withdrawal from the study will be generated. Separate listings and tabular summaries of serious PTAEs and TEAEs will also be generated. Secondary safety assessments, including physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). The clinical laboratory results will also be summarized with respect to laboratory normal ranges and absolute changes from baseline. Comparisons among treatment arms will be performed using chi-square, binomial, and logistic analyses for dichotomous variables (e.g. normal/abnormal) and analysis of covariance (ANCOVA) for continuous variables.

1. BACKGROUND

KIT-302 is an oral fixed combination drug product (FCDP) consisting of the calcium (Ca) channel blocker antihypertensive drug amlodipine besylate and the non-steroidal anti-inflammatory drug (NSAID) celecoxib. Amlodipine besylate and celecoxib are marketed in the United States (US) and worldwide as individual branded and generic prescription drug products, and as combination drug products with other prescription drugs, in the case of amlodipine. Kitov Pharmaceuticals, Ltd. (Kitov) is developing KIT-302 as a "convenience reformulation" FCDP intended to facilitate and improve patient compliance with the once a day (qd) administration of its individual components, amlodipine besylate and celecoxib, when used together for the intended patient population.

Long-term treatment with celecoxib is most commonly used in treating patients with osteoarthritis. This population is generally more aged than an average cross-section of people. It is therefore to be expected that a significant percentage of these patients will also have hypertension. Thus, it can be anticipated that a significant number of patients requiring chronic celecoxib therapy will also require chronic antihypertensive therapy. KIT-302 is intended to treat these patients.

The proposed indications for KIT-302 are a subset of those for the combined labeling of the individual marketed prescription drug products (i.e., amlodipine besylate tablets and celecoxib capsules), and in particular, a subset of those for which qd administration is an option. Thus, the proposed indications in the usage section of the KIT-302 product labeling are anticipated to read as follows: "KIT-302 is indicated for the treatment of hypertension, to lower blood pressure, in patients who also require the use of a NSAID for relief of the signs and symptoms of osteoarthritis. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions."

The formulation of KIT-302 consists of amlodipine besylate and celecoxib co-formulated in a single immediate release tablet. The dosage form was developed so that it will show bioequivalence (BE) to the individually marketed prescription amlodipine besylate tablets and celecoxib capsules given together. The strengths of the KIT-302 tablets reflect the three different possible combinations of the strengths of individual marketed prescription drug products for the proposed indications.

The previous human experience with the KIT-302 formulation (i.e., the FCDP) is limited to bioavailability studies in healthy volunteers under fasted (Study No. DXE-P6-039) and fed states (Study No. DXE-P6-127 and Study No. TRC 009/10219). However, an efficacy study (Study No. KIT-302-03-01) was conducted using the individual components, amlodipine besylate and celecoxib, and the latter have been approved and marketed in the US and worldwide for many years (amlodipine besylate tablets were first approved in 1992 and celecoxib capsules were first approved in 1998), and have well-established clinical safety profiles.

Amlodipine besylate tablets are recognized as being generally safe for patients. Post-marketing surveillance has confirmed the safety of amlodipine besylate tablets. While generally regarded as safe, celecoxib and other NSAIDs can cause gastrointestinal ulcerations and cardiovascular problems. Copies of the prescribing information for prescription amlodipine besylate [Norvasc® (amlodipine besylate) tablets] and prescription celecoxib [Celebrex® (celecoxib) capsules] are

included in Appendices F and G, respectively. These product labelings list the adverse events (AEs) that can be expected from the drug substances.

The concomitant oral administration of labeled doses of amlodipine besylate and celecoxib does not appear to present any new safety issues in terms of potential additive or synergistic pharmacodynamic, pharmacokinetic (PK), or toxicological interactions. The FCDP is not anticipated to produce systemic exposures to either drug greater than those associated with current clinical use of either drug administered alone or in combination.

Study No. DXE-P6-039 and Study No. DXE-P6-127 demonstrated that a single oral dose of the highest strength KIT-302 dosage form (10 mg amlodipine besylate/200 mg celecoxib) is BE to the individual commercially available products given together (10 mg amlodipine besylate tablet + 200 mg celecoxib capsule) in healthy volunteers under fasted and fed conditions, respectively. The combination was well tolerated, and no new AE findings occurred relative to the individual prescribing information for amlodipine besylate tablets and celecoxib capsules.

The findings of Study No. DXE-P6-127 were consistent with the earlier pilot BE study in healthy males under fed conditions (Study No. TRC 009/10219). In the latter study, two prototype formulations of KIT-302 were evaluated, and prototype formulation 1 was shown to be BE to the individual commercial drugs given together. Prototype formulation 1 was pursued for the manufacture of registration stability lots of KIT-302 FCDP and one of the resulting lots was used for the full BE studies (Study Nos. DXE-P6-039 and DXE-P6-127). As with the full BE studies, the pilot BE study showed the formulation to be well tolerated, with no new AE findings.

In November 2015, Kitov completed a phase 3 pivotal study (KIT-302-03-01) comparing amlodipine monotherapy at a dose of 10 mg/day, with the combination of the components of KIT-302 at a dose of 10 mg amlodipine plus 200 mg celecoxib/day. The study also included a double placebo arm and a celecoxib monotherapy arm (200 mg/day). For the combination arm, two separate capsules were used, one containing the commercial amlodipine tablet and one containing the commercial celecoxib capsule. Each of the commercial formulations were individually OE, as were the matched placebo tablets and capsules to allow for blinding.

One hundred fifty-two (152) adult subjects with newly diagnosed hypertension who required pharmacological therapy to control their hypertension were randomized 1.5:1.5:1:1 to one of the four treatment arms (amlodipine/celecoxib: 10/200 mg, 10/0 mg, 0/200 mg, and 0/0 mg) and were administered study drug once a day for 14 days. Subjects underwent 24-hour ambulatory blood pressure monitoring at baseline, during the initial 24 hours of therapy, after one week of therapy, and after two weeks of therapy.

The mean changes in average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBP_{day}), average daytime (9:00 to 21:00) diastolic blood pressure (DBP_{day}), average night-time (01:00 to 06:00) ambulatory systolic blood pressure (SBP_{night}), and average night-time (01:00 to 06:00) diastolic blood pressure (DBP_{night}) from baseline to end of therapy are listed below. Subjects in the amlodipine monotherapy arm had a mean reduction in SBP_{day} of 8.8 ± 8.1 mm Hg after 14 days of treatment, whereas subjects in the amlodipine + celecoxib arm had a mean reduction of 10.6 ± 9.2 mm Hg. The combination was shown to be statistically non-inferior to amlodipine alone ($p < 0.001$), and the primary efficacy endpoint of the study was successfully achieved. Further, the

change in SBP_{day} showed a synergistic effect with the combination over amlodipine monotherapy. The change in DBP_{day} showed a similar synergistic effect with the combination over amlodipine monotherapy and this synergy was even greater with respect to the SBP_{night} and DBP_{night} changes. Celecoxib monotherapy did tend to raise blood pressure (BP), not lower it, as expected, although statistical significance was not achieved.

Changes in Blood Pressure from Baseline to End of Therapy (Mean ± Standard Deviation mm Hg)

	SBP_{day}	DBP_{day}	SBP_{night}	DBP_{night}
Placebo	-2.1 ± 8.2	-0.3 ± 5.4	-1.4 ± 9.2	0.0 ± 6.2
Celecoxib	-0.5 ± 8.8	-1.5 ± 5.1	-1.7 ± 12.3	0.3 ± 7.1
Amlodipine	-8.8 ± 8.1	-5.5 ± 5.1	-6.4 ± 11.4	-3.2 ± 7.8
Amlodipine + Celecoxib	-10.6 ± 9.2	-7.5 ± 6.4	-10.5 ± 10.6	-7.0 ± 8.6

Consistent with the known potential of celecoxib to alter renal physiology, the celecoxib monotherapy arm showed a trend towards worsened function as measured by the change in serum creatinine from baseline to end of therapy relative to the placebo arm. In contrast, the amlodipine monotherapy showed a trend towards improved renal function compared to placebo. Further, the combination of the two (amlodipine + celecoxib) showed a trend towards improved renal function that was greater than that noted for amlodipine alone.

The oral administration of 10 mg amlodipine besylate and 200 mg celecoxib, either individually (i.e., with a matched placebo) or in combination once daily for 14 days in adult subjects with newly diagnosed hypertension who required pharmacological therapy was well tolerated. No deaths or serious adverse events (SAEs) were reported in Study No. KIT-302-03-01. Of the AEs that were considered to be related to the study drugs (i.e., assigned as either a suspected adverse reaction or adverse reaction by the Investigator), all were mild in severity, except for a single incidence of headache that was moderate in severity. Further, all of these AEs fully resolved.

Study No. KIT-302-03-01 also included the collection of PK blood samples at the end of the study (i.e., steady state; Day 14) in a subset of the trial population to evaluate for drug-drug interactions. The analyses showed that amlodipine had no statistically significant effect on the plasma levels of celecoxib. However, celecoxib reduced the plasma levels of amlodipine by approximately a third ($p < 0.001$). The mechanism for the enhancement in efficacy (lowering of BP) and trend towards improved renal function despite the reduction in the plasma concentration of amlodipine is currently unknown. Kitov hypothesizes that celecoxib prevents the fluid retention amlodipine causes (it acts in a manner similar to a diuretic) as evidenced by the reduced rate of oedema reported in patients receiving the combination therapy in the trial (8.2%) as opposed to those receiving amlodipine monotherapy (15.6%). Such a diuretic type effect would be expected to lower BP.

For further details regarding Study No. KIT-302-03-01 and the bioavailability studies, please refer to the most current version of the Investigator's Brochure (IB) for KIT-302.

This study will be performed in compliance with the current ICH guidelines for GCP and all applicable regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary efficacy objective of this study is to demonstrate that the mean reduction in SBP_{day} after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension is no less than half the mean reduction in SBP_{day} after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

1. To evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension on secondary efficacy endpoints using a serial gatekeeping strategy. If and only if the primary efficacy endpoint is statistically achieved, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses.
    a. Difference in mean change in body weight from baseline to end of treatment between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together, amlodipine tablets (10 mg) given alone (with matched celecoxib placebo), and placebo];
    b. Difference in the mean reduction in average 24-hour ambulatory systolic blood pressure (SBP_{24h}) from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms;
    c. Difference in the mean reduction in average 24-hour ambulatory diastolic blood pressure (DBP_{24h}) from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms;
    d. Difference in the mean change in creatinine clearance from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms.
2. To evaluate the safety of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension.
3. To evaluate the effect of celecoxib on the mean plasma concentrations of amlodipine in adult subjects with existing hypertension after 14 days of treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together compared to amlodipine tablets (10 mg) given alone (with matched celecoxib placebo).

3. STUDY DESIGN

This is a multi-center, randomized, double blind, placebo controlled trial to evaluate the effect of celecoxib on the efficacy, safety, and pharmacokinetics of amlodipine in subjects with existing hypertension requiring antihypertensive therapy.

Approximately 105 adult subjects who require and are currently using pharmacological therapy with a single agent that is not a calcium channel blocker to control their hypertension will be randomized 3:3:1 to one of three treatment arms:

1. OE Norvasc® tablet (10 mg amlodipine besylate) + OE Celebrex® capsule (200 mg celecoxib);

2. OE Norvasc® tablet (10 mg amlodipine besylate) + matched placebo for OE Celebrex® capsule;

3. Matched placebo for OE Norvasc® tablet + matched placebo for OE Celebrex® capsule.

All drugs will be administered orally qd for 14 days (Days 0-13) for a total of 14 doses. The total number of subjects planned (105) is an approximation. Once the 105th subject is randomized to treatment (Day 0), any subject that is currently participating in the washout period will be allowed to complete the washout period and if found eligible will be enrolled into the trial. These subjects will continue to be randomized 3:3:1 as noted above. No further subjects will be brought in for the Initial Screening Visit once the 105th subject is randomized.

Initial Screening Visit (Day -14 to -10): Each subject will be provided with oral and written information (ICF) describing the study and will have any questions answered. Subjects that consent in writing to participate in the study will undergo eligibility assessments, including complete medical history, comprehensive physical examination, height, body weight in underwear and a light gown, body mass index (BMI), vital signs (BP, pulse rate, respiration rate, and oral body temperature), 12-lead electrocardiogram (ECG), hematology, serum chemistry, urinalysis, serum pregnancy test for women of childbearing potential (WCBP), urine drug screen, and record medications taken within 30 days prior to initial screening visit.

Subjects who meet eligibility criteria based on the above initial screening visit procedures will be instructed to cease taking their current BP medication. Monitoring for pretreatment adverse events (PTAEs) will begin upon completion of the initial screening visit procedures and will continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Any untoward medical occurrence that initiates or worsens after completion of the initial screening visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE. Subjects will be instructed to return to the clinic in 9 to 13 days.

Final Screening Visit (Day -1) Subjects will return to the clinic after 9 to 13 days of washout for their final screening visit (Day -1). They will undergo the following procedures: solicit for history of PTAEs since the previous visit and record medications taken since prior visit. Those who continue to meet eligibility criteria will be given an ambulatory blood pressure monitor (ABPM),

instructed in its use, and have the positioning of their ABPM checked. They will be instructed to wear it at all times for the next 25 hours and to return to the clinic the following day.

Study Day 0: When the subjects return to clinic the following day, the ABPM will be collected and the data contained therein downloaded and analysed. If subjects are found to be hypertensive, based upon their ABPM measurement, they will undergo additional baseline procedures as described below. If the subject's BP is too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), the subject will not be enrolled and they will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. If the subject is found to be normotensive ($SBP_{day} \leq 135$ mmHg), the subject will not be enrolled. The subject's primary care doctor will be informed that he/she has been found not to be hypertensive. No subject will be randomized until these baseline ABPM data have been reviewed and it has been documented that the subject meets entry BP criteria.

Subjects who meet the BP criteria ($SBP_{day} > 135$ and ≤ 169 mmHg and $DBP_{day} \leq 110$ mmHg) following completion of the 10- to 14-day washout period will undergo the following additional baseline procedures: solicit for history of PTAEs since the previous visit, targeted physical examination, body weight in underwear and a light gown, vital signs, orthostatic hypotension evaluation, serum chemistry, and record medications taken since last visit. Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized 3:3:1 to one of three treatment arms. The subjects will then be administered their first dose of study drugs in the clinic.

Monitoring for treatment emergent adverse events (TEAEs) will begin immediately following administration of the first dose of study drugs and will continue throughout the study. Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE. Subjects will remain in the clinic under observation for one hour following their first dose and will be solicited for TEAE history prior to leaving the clinic. Subjects will be provided with sufficient study drugs for the remainder of the 2-week treatment period, and instructed to take the study drugs qd in the morning. Subjects will be provided with a diary and instructed to record any concomitant medications taken and details of study drug administration. Subjects will be instructed to return to clinic the morning of Day 6.

Study Day 6: Subjects will return to clinic on the morning of Day 6 and will be solicited for history of TEAEs since the previous visit. The study drug containers will be collected and unused study drug counted and recorded. The diary will be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. Subjects will be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects will then be administered their Day 6 dose of study drugs, and instructed to wear the ABPM at all times for the next 25 hours. Subjects will be given back their remaining study drug supply and diary, instructed to record any concomitant medications taken and details of study drug administration, and to return to clinic the following day.

Study Day 7: The Day 7 study drugs will be self-administered at home within 24 hours ± 1 hour from the Day 6 dose. Subjects will return to clinic on the morning of Day 7 (after the home administration of study drugs). The diary will be reviewed for any concomitant medications taken

and for details of study drug administration since the previous visit. The study drug containers will be collected and unused study drug counted and recorded. Subjects will be solicited for history of TEAEs since the previous visit. A targeted physical examination will be performed and body weight in underwear and light gown, and vital signs will be measured. An orthostatic hypotension test will be performed. Subjects will have BP as measured by the ABPM recorded and the ABPM collected. Subjects will have blood collected for measurement of creatinine (and calculation of creatinine clearance) and electrolytes.

If the Investigator determines that it is safe for the subject to continue in the study, the subject will have their remaining study drug supply returned to them, and instructed to take the study drugs at home on Days 8-12, between 0700 and 1000 hours, and preferably at approximately the same time each day. Subjects will be given back their diary and instructed to record any concomitant medications taken and details of study drug administration, and instructed to return to the clinic in 6 days (on the morning of Day 13).

If the subject's BP is too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), blood will be drawn for renal profile testing. The subject will be instructed to cease taking study drugs, instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 7 days (Day 14).

Study Day 13: Subjects will return to clinic on the morning of Day 13 (except for those discontinued from study drug due to excessive hypertension or other safety reasons) and will be solicited for history of TEAEs since the previous visit. The diary will be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. The study drug containers will be collected and any unused study drug counted and recorded. Subjects will be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects will then be administered their Day 13 dose of study drugs (final dose), and instructed to wear the ABPM at all times for the next 25 hours. Subjects will be given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to clinic the following day.

Study Day 14: Subjects will return to clinic on the morning of Day 14. The diary will be reviewed for any concomitant medications taken since the previous visit. Subjects will be solicited for history of TEAEs since the previous visit. A comprehensive physical examination will be performed and body weight in underwear and a light gown and vital signs will be measured. BP as measured by the ABPM will be recorded and the ABPM collected. An orthostatic hypotension evaluation will be performed. The following additional evaluations will be performed: 12-lead ECG, hematology, serum chemistry, urinalysis, and urine pregnancy test for WCBP.

In addition, subjects will have a blood sample collected 24 hours ± 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collections. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine.

Following the Day 14 evaluations, the subjects will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 14 days (Day 28).

Study Day 28: Subjects will return to clinic on Day 28 for their final study visit (follow-up visit). The diary will be reviewed for any concomitant medications taken since the prior visit. Subjects will be solicited for history of TEAEs since the previous visit. A targeted physical examination will be performed and vital signs will be measured. For subjects whose study drugs are discontinued at Day 7, this follow-up visit will still occur on Day 28 (i.e., these subjects will return to the clinic for both the Day 14 and Day 28 visits).

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

A subject may be included in this study if he or she meets all of the following criteria:

1. Adult 40 to 75 years of age;

2. Existing hypertension that is being treated using pharmacological therapy with a single agent that is not a calcium channel blocker;

3. $SBP_{day} > 135$ and ≤ 169 mmHg and $DBP_{day} \leq 110$ mmHg at Day 0 (i.e., after the 10- to 14-day washout from prior BP medication);

4. Body Mass Index (BMI) of 18.5 to 34.9 kg/m^2;

5. Healthy (other than hypertension) as determined by the Investigator based on medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests;

6. A negative pregnancy test at initial screening visit;

7. If WCBP, agree to use a highly effective form of birth control while on study (from Screening through final study visit);

   Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Forms of birth control include intrauterine device (IUD), birth control patch or vaginal ring, oral, or injectable or implanted contraceptives, or a vasectomized partner, or abstinence from sexual intercourse. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

   A woman that is postmenopausal (≥2 years since last menstrual period) or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) is not considered a WCBP.

8. Able to comprehend and sign an ICF.

4.2 Exclusion Criteria

A subject will be excluded from this study if he or she meets any of the following criteria:

1. Resting systolic BP > 169 mmHg or a resting diastolic BP > 110 mmHg at initial screening visit while on their standard antihypertensive therapy (where resting is defined as supine for at least 10 minutes with minimal interaction);

2. Weight < 55 kg;

3. Fragile health;

4. Evidence of clinically significant findings on screening evaluations (clinical, laboratory, and ECG) which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of safety data;

5. Current or recent history (within four weeks prior to initial screening visit) of a clinically significant bacterial, fungal, or mycobacterial infection;

6. Current clinically significant viral infection;

7. History of malignancy, with the exception of cured basal cell or squamous cell carcinoma of the skin;

8. Major surgery within four weeks prior to initial screening visit;

9. Presence of a malabsorption syndrome possibly affecting drug absorption (e.g., Crohn's disease or chronic pancreatitis);

10. Active peptic ulceration or history of gastrointestinal bleeding;

11. History of myocardial infarction, congestive heart failure, or stroke;

12. Any current cardiovascular disease (other than hypertension);

13. History of psychotic disorder;

14. History of alcoholism or drug addiction or current alcohol or drug use that, in the opinion of the Investigator, will interfere with the subject's ability to comply with the dosing schedule and study evaluations;

15. History of any illicit drug use within one year prior to initial screening visit;

16. Positive drug screen at initial screening visit. A positive drug screen for opiates only (with all other drug tests negative) will not be a basis for exclusion if the subject took over-the-counter narcotics as indicated on the product label within 24 hours prior to the drug screen;

17. Current treatment or treatment within 30 days prior to first dose of study drugs with another investigational drug or current enrollment in another clinical trial;

18. Known history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C;

19. Known hypersensitivity to amlodipine or celecoxib;

20. Known hypersensitivity to the inactive ingredients in the OE study drugs;

21. Asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic type reactions after taking acetylsalicylic acid or NSAIDs including cyclooxygenase-2 (COX-2) inhibitors;

22. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule and study evaluations;

23. Pregnant or lactating;

24. Unable to correctly use ABPM after instruction on its use;

25. Subjects with Child-Pugh Class B or C cirrhosis;

26. Subjects currently taking a calcium channel blocker or any NSAID for any reason will be excluded. Subjects will not be withdrawn from these drugs to be enrolled in the trial;

27. Subjects that took a calcium channel blocker in the past for any indication;

28. Creatinine clearance < 50 ml/min as estimated by the Cockroft-Gault equation*;

    **Cockroft-Gault equation:*

    estimated creatinine clearance = (140 – age) X body weight (kg)/72 X P_{Cr} (mg/dL)

    multiply by 0.85 for women

29. Known cytochrome P450 2C9 (CYP2C9) poor metabolizer;

30. Subjects with allergy or hypersensitivity to sulfonamides.

4.3 Withdrawal of Subjects

A subject may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

Subjects will be withdrawn from this study if one or more of the following events occur:

1. Subject requests to be withdrawn from study;

2. Allergic reaction or hypersensitivity reaction to the study drugs;

3. The subject's BP is too elevated for them to continue safely in the study (i.e., SBP_{24h} > 169 mmHg or DBP_{24h} > 110 mmHg);

4. AE (PTAE or TEAE) that in the judgment of the Investigator poses unacceptable risk to the subject;

5. Intercurrent illness that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of

the Investigator poses a significant risk to the subject for continued participation in the study;

6. Pregnant or suspected of being pregnant;

7. Use of prohibited medication (listed in Section 5.6) that in the judgment of the Investigator and Sponsor's Medical Monitor poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of this study;

8. Significant protocol violation or noncompliance on the part of the subject or the Investigator including inability to correctly use the ABPM;

9. Sponsor terminates the study or the Investigational Site terminates the study at their site;

10. Any other reason that in the judgment of Investigator poses unacceptable risk to the subject.

If a subject is withdrawn from the study, the date and reason will be recorded in the source documents and the case report form (CRF), and the Day 14 and Day 28 study evaluations will be performed if feasible. Any subject withdrawn due to a study drug-related TEAE (adverse reaction or suspected adverse reaction per the definitions in Section 8.1.3) will be followed until resolution or stabilization of the event.

If subject becomes pregnant or is suspected of being pregnant, study drugs will be discontinued immediately, and the subject will be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The subject will be followed until delivery or other termination of pregnancy for outcome.

Subjects may choose to withdraw authorization to use and disclose their Protected Health Information (PHI) as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 or foreign equivalent where appropriate. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator or Sponsor prior to the date of such withdrawal will continue to be used and disclosed.

4.4 Termination of Trial

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator must notify the IRB/IEC in writing of a premature termination of a study or closure of Investigational Site, and must send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drugs.

5. STUDY DRUGS

5.1 Description of Investigational Drugs

5.1.1 Active Pharmaceutical Ingredients

Amlodipine besylate is a Ca channel blocker. The chemical name of amlodipine is 3-ethyl-5-methyl (±) 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)- 1,4-dihydro-6 methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Amlodipine besylate has a molecular weight of 567.06 and a molecular formula of $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$.

Celecoxib is a sulfa NSAID and selective COX-2 inhibitor. The chemical name of celecoxib is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. Celecoxib has a molecular weight of 381.38 and a molecular formula of $C_{17}H_{14}F_3N_3O_2S$.

5.1.2 Drug Products

Two commercial formulations will be used for this trial. The two formulations are as follows:

1. Norvasc® (amlodipine besylate) tablets (10 mg amlodipine besylate, Pfizer): Each tablet contains 10 mg amlodipine besylate (base equivalents) and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

2. Celebrex® (celecoxib) capsules (200 mg celecoxib, GD Searle): Each tablet contains 200 mg celecoxib and the following inactive ingredients: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, and sodium lauryl sulfate.

This study is a double blind, placebo controlled study. Therefore, the commercial formulations will be OE and matched placebos will be used to allow for blinding. The capsules used for OE will be back-filled with microcrystalline cellulose. So as to aid in identifying the study drugs, opaque, white DB, AA hard gelatin capsules will be used to over-encapsulate the celecoxib capsules and the matched placebo. Opaque, Swedish Orange DB, AAA hard gelatin capsules will be used to over-encapsulate the amlodipine tablets and the matched placebo.

Subjects will be required to take two capsules on a qd basis. One will be an OE Norvasc® tablet or matched placebo for the OE Norvasc® tablet. The second will be an OE Celebrex® capsule or matched placebo for the OE Celebrex® capsule. Each of the OE drug products will be supplied in a separate container. Subjects will therefore be instructed to take one capsule from each of the two containers on a qd basis.

5.1.3 Packaging and Labeling

The Sponsor will supply all study drugs for this trial. The Investigational Site personnel and the subjects will be blinded to the treatment.

The study drugs will be supplied in 15-count high-density polyethylene bottles with child resistant closures.

The double-blind labeling kit (carton) will contain one 15-count bottle of OE Norvasc® tablet or matched placebo for the OE Norvasc® tablet and one 15-count bottle of OE Celebrex® capsule or matched placebo for the Celebrex® capsule.

Medications will be labeled according to the requirements of local law and legislation. Each patient kit, and the two bottles of study drug within the kit, will be labeled with a randomization number. Label text will be approved according to agreed Kitov procedures, and a copy of the labels will be made available to the study site upon request. Copies of the labels will be available in the study files.

Copies of the product labeling for the two commercial formulations (amlodipine tablets and celecoxib capsules) are included in Appendices F and G, respectively.

5.1.4 Storage and Handling

At the Investigational Site, all study drugs will be stored in a locked, secure area to prevent unauthorized access. The study drugs should be stored in compliance with the label requirements. The study drugs will be stored in the original packaging at controlled room temperature (15-30°C or 59-86°F) protected from light. The subjects will be instructed to store the study drug provided in the take home kits in the original packaging at controlled room temperature protected from light.

5.2 Randomization

This is a randomized, double blind, placebo controlled study. Subjects will be randomized 3:3:1 to one of three treatment arms:

1. OE Norvasc® tablet (10 mg amlodipine besylate) + OE Celebrex® capsule (200 mg celecoxib);

2. OE Norvasc® tablet (10 mg amlodipine besylate) + matched placebo for OE Celebrex® capsule;

3. Matched placebo for OE Norvasc® tablet + matched placebo for OE Celebrex® capsule.

Randomization will take place on Day 0 when the subject returns to clinic and is found to have hypertension based upon the ABPM recordings and continues to meet eligibility criteria following baseline procedures.

A computer-generated randomization schedule will be used for assigning the sequence in which subjects are assigned to treatment arms. The randomization code will be prepared in blocks of 7. Initial shipments to individual Investigational sites will include 5 patient kits with sequential randomization numbers. As subjects are enrolled, the Investigator will take the next sequential kit number in the block provided and assign it to the subject. The Investigational sites will be re-supplied in the same fashion (i.e., 5 patient kits).

Approximately 105 subjects are to be randomized. Therefore, a sufficient number of subjects will be screened so as to achieve approximately 105 subjects entering the randomization phase (starting at Day 0). Once the 105th subject is randomized to treatment (Day 0), any subject that is currently participating in the washout period will be allowed to complete the washout period and if found eligible will be enrolled into the trial. These subjects will continue to be randomized 3:3:1 as noted above. No further subjects will be brought in for the Initial Screening Visit once the 105th subject is randomized.

In the event of a medical emergency or a serious TEAE that is unexpected (as defined in Section 8.1.4) and possibly related to the study drug(s) (i.e., an adverse reaction or suspected adverse reaction as defined in Section 8.1.3), the blind will be broken for the subject that experiences the event. An emergency code break envelope for each subject will be provided to each Investigational Site and also to the Pharmacovigilance Officer at PM Clinical LTD. In the event that the Investigational Site personnel need to unblind the study treatment and cannot access the relevant code break envelope at the site, they can contact the Pharmacovigilance Officer at any time at:

Pharmacovigilance Officer: Dr. Stefania De Santis

Telephone: +39 0692919456

Mobile: +39 3894547423

5.3 Study Drug Administration

All subjects will take study drugs by mouth qd for 14 days (Days 0-13) for a total of 14 doses. With the exception of Days 6 and 13, when study drug intake is at the time of fitting the ABPM and of Day 7, when study drug intake is 24 hours ± 1 hour later, the subjects shall be instructed to take the study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day. At each dose, subjects will take one capsule from each of the two containers (i.e., an OE Norvasc® tablet or matched placebo for the OE Norvasc® tablet and an OE Celebrex® capsule or matched placebo for the OE Celebrex® capsule).

The first dose of study drugs (morning dose on Day 0) will be taken in the clinic. Study Day 6 and Study Day 13 doses will also be taken in clinic. All remaining doses will be self-administered at home. Subjects will be provided with a diary to record the details of study drug administration including the time each dose is taken.

Study drugs will only be dispensed to subjects randomized to treatment under this protocol, and only as directed by this protocol. Administration of study drugs will be accurately recorded in each subject's source documents and CRF.

5.4 Measuring Subject Compliance

A total of 14 doses of study drugs will be administered. The first dose will be administered in the clinic on Study Day 0, as will Study Day 6 and Day 13 doses. The remainder of the doses will be self-administered at home. Subjects will be provided with a diary to record details of study drug administration for each dose (date, time, number of capsules), and will be instructed to return the completed diary at the Day 6, Day 7, and Day 13 clinic visits.

Subjects will also be instructed to bring both of their study drug containers back to the clinic at Day 6, Day 7, and Day 13. The Investigational Site personnel will collect the study drug containers, and will count and record unused study drug.

5.5 Drug Accountability

In accordance with current GCP, the Investigational Site will account for all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the Investigational Site. Copies of the study drug accountability record will be provided to the Sponsor.

Investigational supplies will be retained at the clinical site pending instructions for disposition by the Sponsor at the end of the study.

5.6 Concomitant Medications

All medications (or treatments) other than study drugs taken or received by the subject at any time during the study from the first dose of study drugs through the final study visit assessment will be considered concomitant medications. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the CRF.

Subjects are not to consume any NSAIDs (other than study drug) from the initial screening visit to the final study visit (Day 28). Subjects will be instructed to take acetaminophen for any pain that develops from the time of enrollment until completion of the study or for the treatment of any fever that occurs and is deemed to require pharmacological therapy during the course of this study.

Subjects are not to consume any calcium channel blocker (other than study drug) from the initial screening visit to Day 14. Further, a subject will not be eligible to participate in this trial if they have ever taken calcium channel blockers for any indication.

Subjects are not to consume their current BP medication from the initial screening visit to Day 14. Following the Day 14 evaluations, subjects will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. If subjects are found to be too hypertensive to continue safely in the study after 7 days of study drug administration, they will be removed from the study and instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner.

Subjects are not to take any other investigational drugs beginning 30 days prior to the first dose of study drugs and continuing until the final study visit (Day 28).

Information about the known drug interactions with amlodipine and celecoxib can be found in the product labelings for prescription amlodipine tablets and celecoxib capsules which are included in Appendices F and G, respectively.

Subjects are to avoid consumption of grapefruit juice for the duration of the study.

6. SCHEDULE OF EVENTS

The schedule of events is provided in tabular format in Appendix A, and is summarized below by study visit.

6.1 Screening Visits

6.1.1 Initial Screening Visit (Day -14 to -10)

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents.

Each subject will be provided with oral and written information (ICF) describing the study and will have any questions answered. Written informed consent must be obtained prior to performing any screening evaluations.

The initial screening visit will occur on Day -14 to -10. Subjects will undergo the following screening procedures:

1. Record demographic data (date of birth/age at Screening, gender, and race);
2. Complete medical history, including baseline concurrent illness assessment;
3. Review and record medications taken within 30 days prior to initial screening visit;
4. Height, body weight while only wearing underwear and a light gown, and BMI as determined by Weight (kg)/Height $(m)^2$;
5. Comprehensive physical examination (see Section 8.2);
6. Vital signs (BP, pulse rate, respiration rate, and oral body temperature);
7. 12-lead ECG;
8. Blood sampling for hematology and serum chemistry (see Appendix B for list of tests);
9. Serum pregnancy test for WCBP only;
10. Collection of urine for urinalysis (see Appendix B for list of tests);
11. Urine drug screen (see Appendix B for list of tests);
12. Assessment of inclusion and exclusion criteria.

Subjects who meet eligibility criteria based on the above initial screening assessments will be instructed as follows:

1. Cease taking current BP medication;

2. Do not take any NSAIDs (other than the study drug) for the duration of the study (through Day 28);

3. Use acetaminophen for the treatment of any pain or fever that develops while on study and that is deemed to require pharmacological therapy;

4. Do not take any calcium channel blocker (other than study drug) through the Day 14 evaluations;

5. Do not take any other investigational drugs for the duration of the study (through Day 28);

6. For WCBP: Use adequate contraceptive methods for the duration of the study (through Day 28). For this study, a woman who has been surgically sterilized or who has been in a state of amenorrhea for more than two years will be deemed not to be of child bearing potential;

7. Return to the clinic in 9 to 13 days (on the morning of Day -1);

8. Do not consume any grapefruit juice for the remainder of the study.

Monitoring for PTAEs will begin upon completion of the initial screening visit procedures and will continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Any untoward medical occurrence that initiates or worsens after completion of the initial screening visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE.

6.1.2 Final Screening Visit (Day -1)

Subjects will return to clinic after 9 to 13 days of washout for their final screening visit (Day -1). They will undergo the following procedures:

1. Solicit history of PTAEs since prior visit;

2. Review and record medications taken since prior visit.

Those subjects who continue to meet eligibility criteria will be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. They will be instructed to wear it at all times for the next 25 hours and to return to the clinic the following day (Day 0).

6.2 Study Day 0

Subjects will return to clinic the morning of Day 0. The ABPM will be collected and the data contained therein will be downloaded and analyzed. A determination will be made based upon these ABPM data as to whether or not the subject meets the BP criteria for enrollment. No subject will be randomized until these baseline ABPM data have been reviewed and it has been documented that the subject meets entry BP criteria.

If the SBP_{day} is less than or equal to 135 mmHg, the subject will be deemed to be normotensive, from a clinical trial standpoint. The subject will not be enrolled in the study. The subject's primary care doctor will be informed that he/she has been found not to be hypertensive.

If the SBP_{day} is greater than 135 mmHg and ≤ 169 mmHg and the DBP_{day} ≤ 110 mmHg, the subject will be deemed to be hypertensive and to meet the BP criteria for this trial. These subjects will undergo additional baseline procedures as described below.

If the subject's BP is too elevated for them to continue safely in the study (i.e., SBP_{24h} > 169 mmHg and/or DBP_{24h} > 110 mmHg), the subject will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. The subject will not be enrolled in the study.

Subjects who meet the BP criteria for the trial following completion of the 10- to 14-day washout period will undergo the following additional baseline procedures:

1. Solicit history of PTAEs since prior visit;
2. Review and record medications taken since last visit;
3. Targeted physical examination (see Section 8.2);
4. Body weight while only wearing underwear and a light gown;
5. Vital signs (BP, pulse rate, respiration rate, and oral body temperature);
6. Orthostatic hypotension evaluation (see Section 8.4);
7. Blood sampling for serum chemistry (see Appendix B for list of tests);
8. Review of inclusion/exclusion criteria.

Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized 3:3:1 to one of three treatment arms. The subjects will then be administered their first dose of study drugs in the clinic.

TEAE monitoring will begin immediately following administration of the first dose of study drugs and will continue throughout the study. Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE. Subjects will remain in the clinic under observation for one hour following their first dose and will be solicited for TEAE history prior to leaving the clinic. Prior to leaving the clinic, the following procedures will be performed:

1. Instruct subjects to continue to not take their prescribed BP medication;
2. Instruct subjects to continue to not take any NSAIDs, calcium channel blockers, or investigational drugs (other than the study drugs);
3. For WCBP: Instruct subjects to continue to use adequate contraceptive methods;

4. Provide subjects with sufficient study drugs for the remainder of the 2-week treatment period and instruct subjects to take the study drugs qd in the morning at home, except for the mornings of Days 6 and 13 when the drug will be taken in the clinic. The subjects will be instructed to take the Day 1-5 study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day;

5. Provide subjects with a diary and instruct subjects to record any concomitant medications taken and details of study drug administration;

6. Instruct subjects to return to the clinic in 6 days (the morning of Day 6), and to bring the completed diary and study drug containers with any unused study drug.

6.3 Study Day 6

Subjects will return to clinic on the morning of Day 6 and will undergo the following procedures:

1. Solicit history of TEAEs since the previous visit;

2. Collect study drug containers and count and record unused study drug;

3. Review diary for details of study drug administration and any concomitant medications taken since the previous visit;

4. Provide subjects with ABPM, instruct in its use, and check the positioning of the ABPM.

Following the placement of the ABPM, the subjects will be administered their Day 6 dose of study drugs in the clinic. Prior to leaving the clinic, the following procedures will be performed:

1. Instruct subjects to wear the APBM at all times for the next 25 hours;

2. Subjects will be given back their remaining study drug supply and instructed to take the Day 7 study drugs at home 24 hours ± 1 hour after the Day 6 study drugs;

3. Subjects will be given back their diary and instructed to record any concomitant medications taken and details of study drug administration;

4. Instruct subjects to return to the clinic the following day (on the morning of Day 7), and to bring the completed diary and study drug containers with any unused study drug.

6.4 Study Day 7

The Day 7 study drugs will be self-administered at home within 24 hours ± 1 hour from the Day 6 dose. Subjects will return to clinic on the morning of Day 7 (after the home administration of study drugs). The following evaluations will be performed:

1. Solicit history of TEAEs since the previous visit;

2. Review diary for details of study drug administration and concomitant medications since the previous visit;

3. Collect study drug containers, and count and record unused study drug;

4. Targeted physical examination (see Section 8.2);

5. Body weight while only wearing underwear and a light gown;

6. Vital signs (BP, pulse rate, respiration rate, and oral body temperature);

7. Orthostatic hypotension evaluation (see Section 8.4);

8. Collect the ABPM and download the systolic and diastolic BP values obtained by the ABPM and incorporate into the subject's medical record and CRF;

9. Blood sampling for measurement of creatinine (and calculation of creatinine clearance) and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium).

If, after completing the Day 7 evaluations, the Investigator determines that it is safe for the subject to continue in the study, the following procedures will be performed:

1. Instruct subjects to continue to not take their prescribed BP medication;

2. Instruct subjects to continue to not take any NSAIDs, calcium channel blockers, or investigational drugs (other than the study drugs);

3. For WCBP: Instruct subjects to continue to use adequate contraceptive methods;

4. Subjects will be provided back their remaining study drug supply and instructed to take qd in the morning at home starting with the morning dose on Day 8, except for the study drugs on Day 13 which are to be taken in clinic. The subjects will be instructed to take the Day 8-12 study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day;

5. Subjects will be provided back their diary and instructed to record any concomitant medications taken and details of study drug administration;

6. Instruct subjects to return to the clinic in 6 days (on the morning of Day 13), and to bring the completed diary and study drug containers with any unused study drug.

If during the Day 7 visit, the subject's BP is too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg and/or $DBP_{24h} > 110$ mmHg), blood will be drawn for renal profile testing (see Section 8.5). The subject will be instructed to cease taking study drugs, instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 7 days (Day 14).

6.5 Study Day 13

Subjects will return to clinic on the morning of Day 13 (except for those discontinued from study drug due to excessive hypertension or other safety reasons at Day 7) and will undergo the following procedures:

1. Solicit history of TEAEs since the previous visit;
2. Review diary for details of study drug administration and concomitant medications since the previous visit;
3. Collect study drug containers and count and record any unused study drug;
4. Provide subjects with an ABPM, instruct in its use, and check the positioning of the ABPM.

Following the placement of the ABPM, the subjects will be administered their Day 13 dose of study drugs (final dose) in the clinic. Prior to leaving the clinic, the following procedures will be performed:

1. Instruct subjects to wear the APBM at all times for the next 25 hours;
2. Subjects will be given back their diary and instructed to record any concomitant medications taken between visits;
3. Instruct subjects to return to clinic the following day (on the morning of Day 14), and to bring the completed diary to the clinic.

6.6 Study Day 14

Subjects will return to clinic on the morning of Day 14. The following evaluations will be performed:

1. Solicit history of TEAEs since the previous visit;
2. Review diary for details of concomitant medications since the previous visit;
3. Comprehensive physical examination (see Section 8.2);
4. Body weight while only wearing underwear and a light gown;
5. Vital signs (BP, pulse rate, respiration rate, and oral body temperature);
6. Collect the ABPM and download the systolic and diastolic BP values obtained by the ABPM and incorporate into the subject's medical record and CRF;
7. Orthostatic hypotension evaluation (see Section 8.4);
8. 12-lead ECG;

9. Blood sampling for hematology and serum chemistry (see Appendix B for list of tests);

10. Collection of urine for urinalysis (see Appendix B for list of tests);

11. Urine pregnancy test for WCBP only;

12. Blood sample will be collected at 24 hours ± 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collections. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine.

Following the Day 14 evaluations, the following procedures will be performed:

1. Instruct subjects to resume taking their prescribed BP medication as directed by the study doctor or general practitioner;

2. Instruct subjects to continue to not take any NSAIDs or investigational drugs for the remainder of the study (through Day 28);

3. For WCBP: Instruct subjects to continue to use adequate contraceptive methods for the remainder of the study (through Day 28);

4. Subjects will be provided back their diary and instructed to record any concomitant medications taken between visits;

5. Subjects will be instructed to return to the clinic in 14 days (Day 28) for final study visit (follow-up visit), and to bring the completed diary to the visit.

6.7 Study Day 28

Subjects will return to clinic on Day 28 for their final study visit (follow-up visit). The following evaluations will be performed:

1. Solicit history of TEAEs since last visit;

2. Review diary for details of concomitant medications taken since last visit;

3. Targeted physical examination (see Section 8.2);

4. Vital signs (BP, pulse rate, respiration rate, and oral body temperature).

For subjects whose study drug is discontinued at Day 7, this follow up-visit will still occur on Day 28 (i.e., these subjects will return to the clinic for both the Day 14 and Day 28 visits).

6.8 Duration of Participation

The total duration of participation for subjects in this study will be up to 6 weeks (initial screening visit through follow-up visit).

7. ASSESSMENT OF EFFICACY

7.1 Continuous Recording of Blood Pressure

BP will be recorded, using ABPM, on three 25-hour periods during the trial: Day -1 to Day 0, Day 6 to Day 7, and Day 13 to Day 14. Subjects deemed to be too hypertensive to continue in the study after 7 days of study drug administration, will only have one 25-hour ABPM measurement following randomization: Day 6 to Day 7. Those treated with study drugs for 14 days, will have two 25-hour ABPM measurements following randomization: Day 6 to Day 7 and Day 13 to Day 14.

Subjects will have the ABPM fitted to their upper extremity with the greater BP (See Section 8.3). They will be instructed not to remove the monitor and will be shown how to refit it, in case it becomes dislodged.

ABPM measurements will be recorded as described in Appendix D. The subject's baseline systolic and diastolic BP values will be the SBP_{day}, SBP_{night}, SBP_{24h}, DBP_{day}, DBP_{night}, and DBP_{24h} obtained during the Day -1 to Day 0 ABPM measurement.

Although BP will be manually taken during clinic visits as part of the safety assessments (Section 8.3), it is the values obtained from the ABPM that will constitute the official BP values for all efficacy determinations and calculations for this study.

7.2 Body Weight

Body weight will be measured at Screening, Day 0, Day 7, and at Day 14. The weight measurements will be made using a calibrated scale with the subject wearing only underwear and a light gown.

The body weight measurements will serve a dual function as both a secondary efficacy endpoint and a secondary assessment for safety. Further, the measurement of the change in body weight from baseline to the end of treatment will serve as an indirect measure of renal function.

7.3 Renal Function

Renal function as measured by estimated creatinine clearance is a secondary efficacy assessment of this trial. Creatinine clearance will be estimated at the initial screening visit, Day 0, Day 7, and Day 14. Creatinine clearance will be estimated by the Cockroft-Gault equation as follows:

estimated creatinine clearance = (140 – age) X body weight (kg)/72 X P_{Cr} (mg/dL)

multiply by 0.85 for women

8. ASSESSMENT OF SAFETY

Safety will be assessed primarily based on reported TEAEs. Secondary safety assessments will include the following: physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis. Refer to Appendix A (Schedule of Events) for the timing of these safety assessments.

8.1 Adverse Events

8.1.1 Definitions

8.1.1.1 Adverse Event

An AE is defined in the Guideline for Good Clinical Practice E6(R1) (ICH Harmonised Tripartite Guideline, dated June 10, 1996) as follows:

> Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any untoward medical occurrence that initiates or worsens after completion of the initial screening visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE.

Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE.

8.1.1.2 Serious Adverse Event

An SAE is defined in the Guideline for Good Clinical Practice E6(R1) (ICH Harmonised Tripartite Guideline, dated June 10, 1996) as follows:

> Any untoward medical occurrence that at any dose:
>
> - results in death,
> - is life-threatening,
> - requires inpatient hospitalization or prolongation of existing hospitalization,
> - results in persistent or significant disability/incapacity, or
> - is a congenital anomaly/birth defect.

PTAEs meeting the above definition for SAE (disregarding the "at any dose" part of the definition) will be considered serious PTAEs.

TEAEs meeting the above definition for SAE will be considered serious TEAEs

8.1.2 Severity of Adverse Events

The severity of PTAEs and TEAEs will be graded according to WHO Toxicity Criteria (Appendix C).

The severity of PTAEs and TEAEs not classified by the above referenced toxicity grading scale will be categorized using the following definitions:

Mild: discomfort noted, but no disruption of normal daily activity

Moderate: discomfort noted of sufficient severity to reduce or adversely affect normal activity

Severe: incapacitating, with inability to work or perform normal daily activity

8.1.3 Relationship of Treatment Emergent Adverse Events to the Study Drug

The Investigator should assess the relationship of TEAEs to the study drug and classify as one of the following:

1. **Adverse reaction**: AE that is caused by the study drug.

2. **Suspected adverse reaction**: AEs for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction. Examples of the types of evidence that would suggest reasonable possibility of a causal relationship between the drug and the AE are as follows:

    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

    - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

3. **Unrelated**: AE for which there is evidence that the AE definitely has an etiology other than the study drug.

8.1.4 Expectedness of Adverse Events

An unexpected AE is one for which the nature or severity of the event is not consistent with the applicable study drug information (i.e., the most current version of the IB, the current product labeling for amlodipine tablets, and the current product labeling for celecoxib capsules) or listed in this protocol.

This study will enroll older subjects with existing hypertension. To that end, PTAEs and TEAEs can be expected due to the subjects' age and underlying conditions. These include: hypertension, hypertensive crisis, myocardial infarction, congestive heart failure, stroke both hemorrhagic and ischemic, any adult forms of cancer, and gastrointestinal ulcerations with complications including hemorrhage and perforation.

By definition, PTAEs initiate prior to administration of the first dose of study drugs, and thus a comparison against study drug specific risk information is inappropriate for determining expectedness of PTAEs. Thus, only AEs that can be expected due to subject age and underlying conditions are relevant for the expectedness determination for PTAEs.

8.1.5 Monitoring of Adverse Events

Monitoring for PTAEs will begin upon completion of the initial screening visit procedures and will continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Any untoward medical occurrence that initiates or worsens after completion of the initial screening visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE.

Monitoring for TEAEs will begin immediately following administration of the first dose of study drugs and will continue throughout the study. Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE.

Subjects will be instructed to report all PTAEs and TEAEs experienced during the study, and subjects will be assessed for the occurrence of PTAEs and TEAEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All study drug-related TEAEs (adverse reaction or suspected adverse reaction per the definitions in Section 8.1.3) will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

8.1.6 Routine Reporting of Adverse Events

PTAEs and TEAEs, whether or not associated with study drug administration, will be recorded on the AE form of the CRF and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);

2. Date of onset of any new AE or the worsening of a previously observed AE. For the days when the subject is in the clinic, the time (based on a 24-hour clock) of onset should be recorded if available;

3. Date of resolution of the event (or confirmation ongoing). For the days when the subject is in the clinic, the time (based on a 24-hour clock) of resolution should be recorded if available;

4. Whether the event is serious (per definition in Section 8.1.1.2), and if so, the reason it is considered serious;

5. Severity of AE (per definitions in Section 8.1.2);

6. Assessment of the relationship of the AE to the study drug (per definitions in Section 8.1.3). Relationship assessments will only be made for TEAEs;

7. Whether the event is expected (per definition in Section 8.1.4);

8. Action taken in treating the AE (including concomitant medications or therapies administered) and/or change in study drug administration or dose (including whether the Study Drug was temporarily interrupted or discontinued);

9. Outcome of AE (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown). Fatal should only be used when death is possibly related to the AE. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed until an outcome is known or followed up to the final study visit. Any subject with a possible study drug-related TEAE at the final study visit will be followed until resolution or stabilization of the event. Further, any serious TEAE, whether or not related to study drugs that occurs within 14 days following the last dose of study drugs will be followed until resolution or stabilization of the event.

8.1.7 Reporting of Serious Adverse Events, Including Death

Serious PTAEs or serious TEAEs, including death due to any cause, which occur during this study or within 14 days following the last dose of the study drugs, whether or not related to the administration of study drugs, must be reported by the Investigator or other Investigational Site personnel directly to the Pharmacovigilance Officer at PM Clinical LTD by fax **within 24 hours of learning of the event**. The Pharmacovigilance Officer will forward this information to the Medical Monitor for review. The contact information for the Pharmacovigilance Officer is provided below.

Pharmacovigilance Officer: Dr. Stefania De Santis

Telephone: +39 0692919456

Mobile: +39 3894547423

Fax: +39 0656561998

SAE Forms will be provided by the Sponsor or Sponsor designated CRO. If all information is not known at the time of initial reporting, an initial report should still be made. In the event there is a question as to whether the experience is serious, the information should be forwarded to the Pharmacovigilance Officer, who will then forward the information on to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Pharmacovigilance Officer. In the case of fatality, autopsy reports will be furnished to the Pharmacovigilance Officer as soon as available.

In the event of a medical emergency or a serious TEAE that is unexpected (as defined in Section 8.1.4) and possibly related to the study drug(s) (i.e., an adverse reaction or suspected adverse reaction as defined in Section 8.1.3), the blind will be broken for the subject that experiences the event. An emergency code break envelope for each subject will be provided to each Investigational Site and also to the Pharmacovigilance Officer. In the event that the Investigational Site personnel need to unblind the study treatment and cannot access the relevant code break envelope at the site, they can contact the Pharmacovigilance Officer at any time.

The following information about the subject and the reported SAE will be collected on the SAE Form:

1. Subject identification including subject number, initials, and date of birth;

2. Randomization number (only for serious TEAE);

3. Date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose (only for serious TEAEs). If the serious TEAE does not require breaking of the blind, certain study drug specific details will not be available to enter in the initial SAE Form, but will be reported in the SAE Form updates;

4. Date of last dose of study drugs (i.e., prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose (only for serious TEAEs). If the serious TEAE does not require breaking of the blind, certain study drug specific details will not be available to enter in the initial SAE Form, but will be reported in the SAE Form updates;

5. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);

6. Date of onset of the event. For the days when the subject is in the clinic, the time (based on a 24-hour clock) of onset should be recorded if available;

7. Date of resolution of the event (or confirmation ongoing). For the days when the subject is in the clinic, the time (based on a 24-hour clock) of resolution should be recorded if available;

8. Severity of the event (see Section 8.1.2);

9. Assessment of the attributability of the event to the study drug (see Section 8.1.3) (only for serious TEAE);

10. Why event is considered serious (per definition in Section 8.1.1.2);

11. Whether the event is expected (see Section 8.1.4);

12. Action taken in treating the event and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, whether the study drug was temporarily interrupted or discontinued, and whether the subject was discontinued from the study);

13. Outcome of AE (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown). Fatal should only be used when death is possibly related to the AE. If an outcome is not available at the time of the initial report, follow-up will proceed until resolution or stabilization of the event and an updated SAE Form will be issued.

14. All concomitant medications (including doses, routes, regimens, and indications) taken within 30 days prior to the initial screening visit through the point of onset of the event;

15. Pertinent laboratory data;

16. Medical history.

The Investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drug and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol;

2. Discontinuation or suspension of the study;

3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings;

4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study medication-related.

Any SAE that is determined by the Sponsor to be reportable to the Food and Drug Administration (FDA) as an Investigational New Drug application (IND) Safety Report [as defined in 21 Code of Federal Regulations (CFR) 312.32] will be reported to FDA by the Sponsor within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his or her IRB/IEC. Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor designated CRO within the specified time frames, and will be provided to the Investigator for submission to his or her IRB/IEC.

8.2 Physical Examination

A comprehensive physical examination will be performed at the initial screening visit and on Day 14. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological exam.

A targeted physical examination will be performed at baseline (Day 0) and at the Day 7 and Day 28 visit. This examination will specifically target the cardiovascular system and will include vital signs, plus an examination of the extremities to check for the presence of edema, as well as an examination to document any other evidence of a cardiovascular problem. Any areas of concern from the medical history or noted on the prior physical examination or indicated by subject symptoms or other findings as determined by the Investigator or designee may also be examined.

8.3 Vital Signs

Vital sign measurements (BP, pulse rate, respiration rate, and oral body temperature) will be collected on the days and times noted in the Schedule of Events (Appendix A). Vital signs will be taken with the subject in the sitting position after 5 minutes of rest, except for at the initial screening visit, where vital signs will be taken with the subject in the supine position after at least 10 minutes of rest with minimal interaction.

Measurements of BP made when subjects are at the Investigational Site as part of their clinic visits will be made using the standard American Heart Association criteria (Chobanian, 2003). This will require the following technique be utilized:

1. Clinic visit BP measurements will be taken at the initial screening visit, in the morning on Days 0, 7, and 14, and at the follow-up visit (Day 28). On Day 0, the BP measurements will be taken in the morning prior to the first dose of study drugs. On Day 7, the subject will self-administer their study drugs at home prior to coming to the clinic, and therefore, the BP measurements will be taken after the subject has taken their daily dose of study drugs;

2. A determination will be made as to which upper extremity has the greater BP;

3. Prior to taking the subject's BP, the subject will rest in the sitting position for a period of 5 minutes, except for at the initial Screening visit, where BP measurements will be taken with the subject in the supine position after at least 10 minutes of rest with minimal interaction;

4. At the completion of the rest period, three readings will be taken. There will be a one minute interval between each measurement;

5. The subject's recorded BP will be an average of the three recordings taken over approximately three minutes.

6. At the initial screening visit (Day –10 to -14), three readings will be taken on each arm, as described. The averages for each arm will be calculated. The arm with the higher average systolic BP will be used for all further BP measurements including ABPM measurements.

The continuous recording of BP by ABPM (Section 7.1) at Day -1 to Day 0, Day 6 to Day 7, and Day 13 to Day 14, will serve a dual function as both the official BP values for all efficacy determinations and calculations and an additional BP assessment for safety.

8.4 Orthostatic Hypotension Evaluations

Orthostatic hypotension will be evaluated at baseline (Day 0), Day 7, and Day 14.

For this determination, the subject will be placed supine for 5 minutes. At the end of that time a manual BP will be assayed three times. The average of these three will be used as the baseline value. The subject will then be asked to stand vertically and two manual BPs will be obtained: the first will be one minute after standing and the second will be three minutes after standing. Orthostatic hypotension will be defined as a decrease in systolic BP of > 25 mmHg from baseline in either of the readings, or a decrease in diastolic BP of > 15 mmHg in either of the readings compared to the baseline average.

In addition to these quantitative measurements, specific comparisons in reported AE rates for terms associated with hypotension will be made. These events will include dizziness, falls, light-headedness, and vertigo.

8.5 ECG

A 12-lead ECG will be obtained at the initial screening visit and at the Day 14 visit. The 12-lead ECGs will be performed with the subject in the recumbent position after 5 minutes of rest.

8.6 Hematology, Serum Chemistry, and Urinalysis

Blood and urine for clinical safety laboratory assessments will be collected at the initial screening visit, Day 0 (serum chemistry only), and on Day 14. The samples will be prepared using standard procedures. A detailed listing of the hematology, serum chemistry, and urinalysis tests that will be

performed is provided in Appendix B. A regional laboratory will perform the clinical laboratory tests.

In addition, at Day 7, blood will be collected for a subset of serum chemistry tests. Specifically, the testing will be limited to creatinine (and calculation of creatinine clearance) and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium).

Also, if the subject's BP at Day 7 is too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg and/or $DBP_{24h} > 110$ mmHg), blood will be drawn for renal profile testing (non-fasting). The renal profile testing will include the following tests: creatinine, calcium, chloride, carbon dioxide, albumin, blood urea nitrogen (BUN), protein, phosphorus, glucose, and potassium.

9. ASSESSMENT OF PHARMACOKINETICS

9.1 Blood Collection

Subjects will have a venous blood sample collected at 24 hours ± 1 hour post-dose on Day 14 to measure plasma concentrations of amlodipine. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collection. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine.

See PK procedures manual for specific information regarding the procedures for PK blood sample collection, processing, and shipment to bioanalytical laboratory.

9.2 Bioanalytical Method

Plasma samples will be assayed for amlodipine by a Sponsor designated laboratory using a validated LC-MS/MS method.

9.3 Pharmacokinetic Analysis

As blood will only be collected at a single time point in this trial, plasma concentration-time curves and noncompartmental analyses are not planned. See Section 10 for planned statistical analysis of plasma concentration data.

10. STATISTICS

10.1 Data Sets

10.1.1 Intent-to-Treat (ITT)

The ITT data set will be comprised of randomized subjects with at least a valid baseline (Day –1 to Day 0) ABPM measurement and either

a) A valid final (Day 13 to Day 14) ABPM measurement, where a subject completes the treatment program.

or

b) A valid Day 6 to Day 7 ABPM measurement, where a subject is withdrawn from the treatment program at that point because of an $SBP_{24h} > 169$ mmHg and/or a $DBP_{24h} > 110$ mmHg, or if they are withdrawn for any other reason.

As noted in Section 6.4, if at the time of the Day 7 clinic visit subjects have too elevated a BP to be able to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), the study drug will be discontinued and the subjects will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. In this case, both mixed model for repeated measures (MMRM) and last observation carried forward (LOCF) techniques will be used with comparative sensitivity analysis.

Subjects that do not have the two paired valid ABPM measurements, as required (baseline and final, for those who complete the treatment program, or baseline and Day 6 to Day 7, for those withdrawn from the study), will not be included.

10.1.2 Per-protocol (PP)

The PP data set will be comprised of randomized subjects with at least a valid baseline (Day –1 to Day 0) ABPM measurement and also a valid final (Day 13 to Day 14) ABPM measurement.

Dropouts and subjects who had major violations of the protocol will be excluded. Major protocol violations will include missing more than 25% of scheduled doses of study drugs, and taking prohibited medications including any NSAIDs or calcium channel blockers (other than the study drugs).

All randomized subjects should receive their initial dose of study drugs in the clinic immediately following randomization.

10.2 Statistical Analysis of Efficacy Data

10.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this trial will be the difference in the mean reduction in SBP_{day} from the baseline (Day –1 to Day 0) ABPM measurement to the final (Day 13 to Day 14) ABPM

measurement, where a subject completes the 14-day treatment plan, or to the Day 6 to Day 7 ABPM measurement, where a subject is withdrawn from treatment at Day 7, between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) (arm 2).

The primary efficacy endpoint will be that the lower limits of the 95% confidence interval for SBP_{day} reduction in treatment arm 1 will be at least 50% of the mean reduction in treatment arm 2.

10.2.2 BP Change Comparisons

Statistics are based on the reduction in BP from the baseline ABPM measurement (Day –1 to Day 0) to the post-dose ABPM measurement (Day 13 to Day 14 or if a LOCF is required Day 6 to Day 7), as this represents the efficacy of the treatment. Reductions will be, therefore, represented by positive numbers and increases by negative numbers. For this reason, the change in BP from baseline to final ABPM measurement will be a paired subtraction of the final ABPM measurement from the baseline ABPM measurement. Sensitivity analysis will compare these results with those of the PP dataset and an MMRM analysis.

10.2.3 Primary Efficacy Endpoint Analysis

A two-sample t-test will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) is non-inferior to half of the effect achieved with the control treatment with amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

$$H_0: \Delta SBP_{day,1} - 0.5(\Delta SBP_{day,2}) \geq 0 \text{ mmHg}$$

$$H_1: \Delta SBP_{day,1} - 0.5(\Delta SBP_{day,2}) < 0 \text{ mmHg}$$

Where $\Delta SBP_{day,1}$ is the change, for subjects in arm 1, in the SBP_{day} from the baseline ABPM measurement ($SBP_{day,1,0}$) to the final ABPM measurement ($SBP_{day,1,14}$).

$$\Delta SBP_{day,1} = SBP_{day,1,0} - SBP_{day,1,14}.$$

$\Delta SBP_{day,2}$ is the change, for subjects in arm 2, in SBP_{day} from the baseline ABPM measurement ($SBP_{day,2,0}$) to the final ABPM measurement ($SBP_{day,2,14}$).

$$\Delta SBP_{day,2} = SBP_{day,2,0} - SBP_{day,2,14}.$$

Refer to Appendix H for further details regarding the efficacy analysis, and in particular the non-inferiority margin.

10.2.4 Secondary Efficacy Endpoints

Recall that subjects will be randomized 3:3:1 to one of three treatment arms:

1. OE Norvasc® tablet (10 mg amlodipine besylate) + OE Celebrex® capsule (200 mg celecoxib);

2. OE Norvasc® tablet (10 mg amlodipine besylate) + matched placebo for OE Celebrex® capsule;

3. Matched placebo for OE Norvasc® tablet + matched placebo for OE Celebrex® capsule.

A serial gatekeeping strategy will be used to evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on secondary efficacy endpoints. If and only if the statistical significance is achieved for the primary efficacy endpoint, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses.

1. Difference in mean change in body weight from baseline (Day 0) to Day 14 measurement (or if a LOCF is required, the Day 7 measurement) between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1), amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2), and placebo (arm 3)];

2. Difference in the mean reduction in SBP_{24h} from the baseline (Day -1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or if a LOCF is required, the Day 6 to Day 7 ABPM measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2);

3. Difference in the mean reductions in DBP_{24h} from the baseline (Day –1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or if a LOCF is required, the Day 6 to Day 7 ABPM measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2);

4. Difference in the mean change in creatinine clearance from baseline (Day 0) to the Day 14 measurement (or if a LOCF is required, the Day 7 measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

10.2.5 Secondary Efficacy Endpoints Analysis

If the primary efficacy endpoint analysis fails to demonstrate statistical success, no further efficacy analyses will be performed. However, if it is successful, the following secondary hierarchical analysis to evaluate for the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on secondary efficacy endpoints will be performed in the order listed. The analysis will only proceed to the next endpoint in the list if the alpha is met for the prior analyses.

1. Analysis of Variance (ANOVA) will be used to compare the changes in body weight among the three treatment arms. The omni-bus test will conclude if any differences exist with post-hoc comparisons identifying specific differences between treatment arms. Any statistically significant differences will be sufficient to pass this gate in the study-wide gate keeping strategy.

H_0: $\Delta BW_1 = \Delta BW_2 = \Delta BW_3$

H_1: At least one difference, $\Delta BW_i - \Delta BW_j \neq 0$

Where ΔBW_1 is the change, for subjects in arm 1, in body weight from the baseline measurement to the post-treatment measurement.

ΔBW_2 is the change, for subjects in arm 2, in body weight from the baseline measurement to the post-treatment measurement.

ΔBW_3 is the change, for subjects in arm 3, in body weight from the baseline measurement to the post-treatment measurement.

2. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) lowers SBP_{24h} to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

H_0: $\Delta SBP_{24h,1} - \Delta SBP_{24h,2} = 0$

H_1: $\Delta SBP_{24h,1} - \Delta SBP_{24h,2} > 0$

Where $\Delta SBP_{24h,1}$ is the change, for subjects in arm 1, in SBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

$\Delta SBP_{24h,2}$ is the change, for subjects in arm 2, in SBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

3. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) lowers DBP_{24h} to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

H_0: $\Delta DBP_{24h,1} - \Delta DBP_{24h,2} = 0$

H_1: $\Delta DBP_{24h,1} - \Delta DBP_{24h,2} > 0$

Where $\Delta DBP_{24h,1}$ is the change, for subjects in arm 1, in DBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

$\Delta DBP_{24h,2}$ is the change, for subjects in arm 2, in DBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

4. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) improves creatinine clearance to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

H_0: $\Delta CC_1 - \Delta CC_2 = 0$

H_1: $\Delta CC_1 - \Delta CC_2 > 0$

Where ΔCC_1 is the change, for subjects in arm 1, in creatinine clearance from the baseline creatinine clearance to the post-treatment creatinine clearance.

ΔCC_2 is the change, for subjects in arm 2, in creatinine clearance from the baseline creatinine clearance to the post-treatment creatinine clearance.

10.3 Statistical Analysis of Pharmacokinetic Data

Subjects will have a blood sample drawn on Day 14, approximately 24 hours after receiving the final dose of study drugs, for the measurement of amlodipine concentration. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collection. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine.

The plasma concentration of amlodipine will be determined by validated LC-MS/MS method. All plasma concentration values below the lower limit of quantification (LLOQ) will be reported as zero. Individual amlodipine plasma concentration data will be listed.

A t-test will compare the plasma concentration of amlodipine in those subjects who receive amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) with those who receive amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1).

10.4 Statistical Analysis of Safety Data

Data from all subjects who receive at least one dose of study drug will be incorporated into the final safety analysis.

Safety will be assessed primarily based on reported TEAEs. Clinically significant clinical laboratory abnormalities will be reported as AEs (i.e., either as PTAEs or TEAEs, depending on when they initiate or worsen). The incidence of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and will be further categorized by treatment arm, severity, and assigned relationship to study drug. The incidence of PTAEs will be tabulated by MedDRA system organ class and preferred term, and will be further categorized by severity.

The incidence for each PTAE and TEAE will be provided as the total number of subjects that experienced the PTAE or TEAE, as well as the percentage of the population that this represents. If a PTAE or TEAE is reported more than once for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

TEAE rates across treatment arms will be analyzed using the chi square test or an exact binomial test (e.g., Suissa and Shuster, 1985).

PTAEs and TEAEs will be separately listed for individual subjects, along with information regarding onset and end dates, onset time where available, severity, seriousness, relationship to

study drug (only in the case of TEAEs), action taken, and outcome. Separate listings and tabular summaries of PTAEs and TEAEs that lead to withdrawal from the study will be generated. Separate listings and tabular summaries of serious PTAEs and serious TEAEs will also be generated.

Secondary safety assessments, including physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). The clinical laboratory results will also be summarized with respect to laboratory normal ranges and absolute changes from baseline. Comparisons among treatment arms will be performed using chi-square, binomial, and logistic analyses for dichotomous variables (e.g. normal/abnormal) and analysis of covariance (ANCOVA) for continuous variables.

10.5 ABPM Measurement Weighting

1) Each measurement shall be weighted according to half the duration to the preceding measurement and half the duration to the succeeding measurement up to maxima of half the expected intervals as follows:

Time of Day (in minutes)	Max Preceding Weight	Max Succeeding Weight
09:00 to 09:20 (540 to 560)	15 min	10 min
09:21 to 21:39 (550 to 1299)	10 min	10 min
21:40 to 21:59 (1300 to 1319)	10 min	15 min
22:00 to 08:59 (0 to 539 and 1320 to 1439)	15 min	15 min

2) All statistics shall be based on weighted measurements. For daytime and night-time statistics, weights for the first measurements within the respective periods shall be truncated at the start of the period and weights for the last measurements within the respective periods shall be truncated at the end of the period.

3) Hourly mean pressures shall be based on the weights of measurements occurring within the hour. Each hour shall be defined by "m \ 60", where m is the number of minutes from midnight on the day the monitor is fitted and \ represents the quotient of the Euclidian division. ($m \equiv (m \setminus 60) \times 60 + m \bmod 60$)

10.6 ABPM Study Measurements

1) A measurement shall be regarded as valid if it contains values for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and

   a. SBP is between 50 mmHg and 300 mmHg.

   b. DBP is between 40 mmHg and 150 mmHg.

   c. Pulse pressure is between 10 mmHg and 150 mmHg.

d. HR is between 40 bpm and 150 bpm.

2) The first study measurement shall be

a. The nearest valid measurement to the drug intake time on the day the monitor is fitted that is both a) between 07:00 and 10:00 and b) within 15 minutes of the drug intake time.

b. If there is no valid measurement within this period, a 1-hour grace period is permitted. It is, therefore, the nearest valid measurement to the drug intake time on the day the monitor is fitted that is both a) between 06:00 and 11:00 and b) within 75 minutes of the drug intake time.

c. If there is no valid measurement within this period, or if no drug intake time is recorded (e.g., Day-1), the first valid measurement recorded between 07:00 and 10:00.

d. If there is no valid measurement within this period, the first valid measurement recorded between 06:00 and 11:00.

e. If there is no valid measurement within this period, the nearest valid measurement to the drug intake time on the day the monitor is fitted, if that is recorded, or first valid measurement otherwise.

3) Measurements recorded during the first hour, from the first study measurement, shall be regarded as white-coat window measurements. The period covered by these measurements defines the white-coat window.

4) The last study measurements shall be

a. The earliest valid measurement that is a) at least 25 h after the first study measurement b) at least 25 h after the drug intake time on the day the monitor is fitted and c) less than 25 h after the end of the white-coat window

b. If there is no valid measurement within this period, a 1-hour grace period is permitted. It is, therefore, the earliest valid measurement that is a) at least 24 h after the first study measurement b) at least 24 h after the drug intake time on the day the monitor is fitted and c) less than 26 h after the end of the white-coat window

c. If there is no valid measurement within this period, the latest measurement that is less than 26 h after the end of the white-coat window.

5) Measurements before the first study measurement and measurements after the last study measurement shall be disregarded.

6) Invalid measurements and measurements that result in an error shall not be regarded as study measurements.

7) Measurements recorded during the white-coat window are not included in daytime, night-time and 24 h statistics.

10.7 ABPM Validity

1) An ABPM measurement shall be defined as valid if the data comply with the following criteria:

    a. The time of the first study measurement is between 07:00 and 10:00.

    b. The duration, from the first study measurement to the last study measurement, is at least 25 h (1500 min).

    c. There are at least 21 study measurements recorded during the standard daytime period (09:00 to 21:00)

    d. There are at least 8 study measurements recorded during the standard night-time period (01:00 to 06:00)

    e. There are at least 35 study measurements recorded after the white-coat window

    f. There are no more than 3 hours with a total measurement weight of less than 20 min and no more than 2 consecutive hours with total measurement weights each of less than 20 min.

2) An ABPM measurement shall be defined as valid within tolerance if the data comply with the following criteria:

    a. The time, of the first study measurement is between 06:00 and 11:00.

    b. The duration, from the first study measurement to the last study measurement, is at least 24 h (1440 min).

    c. There are at least 20 study measurements recorded during the standard daytime period (09:00 to 21:00)

    d. There are at least 7 study measurements recorded during the standard night-time period (01:00 to 06:00)

    e. There are at least 34 study measurements recorded after the white-coat window

    f. There are no more than 3 hours with a total measurement weight of less than 20 min and no more than 2 consecutive hours with total measurement weights each of less than 20 min.

3) An ABPM measurement shall be defined as invalid if it is not valid within tolerance.

10.8 ABPM Statistics

1) Average 24-hour, daytime and night-time pressures are calculated as

$$\overline{v_{p,r}} = \frac{\sum_{i=FSM}^{LSM} v_{r,i} w_{p,i}}{\sum_{i=FSM}^{LSM} w_{p,i}}$$

where r is SBP or DBP

p is 24-hour, daytime or night-time

$v_{r,i}$ is the SBP or DBP for measurement i

$w_{p,i}$ is the weight of the measurement for period p, zero if the measurement does not belong to that period

FSM is the first study measurement

LSM is the last study measurement

2) The standard deviations are calculated as

$$s_{p,r} = \sqrt{\frac{\sum_{i=FSM}^{LSM} v_{r,i}^2 w_{p,i} - \overline{v_{p,r}}^2 \sum_{i=FSM}^{LSM} w_{p,i}}{\frac{M_p - 1}{M_p} \sum_{i=FSM}^{LSM} w_{p,i}}}$$

where M_p is the number of non-zero weighted measurements in period p

10.9 Sample Size

1) The sample size is to be based on the hypothesis that the mean reduction in SBP_{day} from Day 0 to Day 14 of subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) minus half the mean reduction in SBP_{day} from Day 0 to Day 14 of subjects treated with amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) is at least 0.

2) Formula

Sample size is based on the formula

$$n = \left\lceil 2\left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{d}\right)^2 s^2 \right\rceil$$

where

s is the standard deviation (8.7)

d is the anticipated mean difference (6.2)

α is the one-sided level of significance (0.05)

1-β is the power, one-sided (80%)

$\lceil \rceil$ is the ceiling function

3) Margin

The margin is based on a mean reduction of 8.8 mmHg in SBP_{day} for the Amlodipine+Placebo group and a mean reduction of 10.6 mmHg for the Amlodipine+Celecoxib group as seen in the previous study, KIT-302-03-01. To ensure that at least half the effect is maintained, a value of 10.6 – 0.5(8.8) = 6.2 mmHg should be set for *d*.

4) Standard Deviation

The standard deviation is based on an 8.1 mmHg standard deviation for the Amlodipine+Placebo group and a 9.2 mmHg standard deviation for the Amlodipine+Celecoxib group in the previous study (KIT-302-03-01). The pooled standard deviation for the power and sample size justification is 8.7 mmHg.

5) Loss to Follow-up Adjustment

The final sample size is rounded up to allow for a loss to follow-up. The study selected a round number at least 10% larger than the number necessary to protect against potential subjects not fully participating in the entire trial.

Refer to Appendix H for further details regarding the determination of sample size.

11. ACCESS TO SOURCE DOCUMENTS

The Investigator will make the source documents for this trial available for monitoring by the Sponsor or its representatives, or by regulatory authorities or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study drug and therefore may be disclosed by the Sponsor as required for

disclosure as a public company to other clinical investigators, to other pharmaceutical companies, to the FDA and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Data Collection

All data required by the study protocol will be entered onto CRFs and must be verifiable against source documents. CRFs will be completed for every subject who signs an informed consent and has screening procedures performed.

Only authorized Investigational Site personnel will enter data on the CRFs. Any corrections to data entered into the CRF will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The CRFs will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date each subject's CRF, verifying that the information is true and correct.

12.2 Study Monitoring

The study will be monitored to evaluate the progress of the study, to verify the accuracy and completeness of the CRFs, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the study monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study.

The study monitor will compare the CRF data against source documentation in order to verify its accuracy and completeness. The Investigator and research staff will collaborate with the study monitor to resolve any identified data discrepancies in a timely manner.

The study monitor will record any protocol deviations identified, including, but not limited to, subjects that were enrolled even though they did not meet all eligibility criteria, subjects who took concomitant medications specifically prohibited by the protocol, subjects who received the wrong study drug or incorrect dose, and subjects who failed to comply with the protocol-defined dietary restrictions. The Investigator and research staff will collaborate with the study monitor to identify the reason for each protocol deviation.

The study monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and research staff will collaborate with the study monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

12.3 Data Management

After the CRFs have been reviewed by the study monitor and all identified discrepancies have been identified, the Investigator signed copy of the CRF will be forwarded to Data Management. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

All CRF data will be entered into a validated database and an electronic audit trial of edits maintained. Laboratory data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

12.4 Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff will cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

12.5 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision, as described in Appendix E.

13.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

13.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, Investigator's Brochure, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to initiation of the study.

Amendments to the protocol will be subject to the same requirements as the original protocol. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the Investigator's Brochure provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC and to the Sponsor. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

13.4 Informed Consent

No study related procedures, including screening evaluations, will be performed until the subject has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. Further, the ICF will identify the Sponsor, the Principal Investigators and institutional affiliations, potential conflicts of interest, provisions for treating

subjects who are harmed as a consequence of participation in the study, and provisions for post-trial access.

The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study 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 ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the subject to use and/or disclose PHI in compliance with HIPAA or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

13.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor's Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was effected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

14. PUBLICATION POLICY

All information and data obtained in the course of the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical trial agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

This trial will be registered in a publicly accessible database (clinicaltrials.gov) not later than 21 days after enrollment of the first subject. Results of this trial, including negative and inconclusive, as well as positive results, will be made publicly available.

15. PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the subjects. The Sponsor is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to subjects.

16. REFERENCES

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT JR, Roccella EJ. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. 2003. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 42:1206-1252.

Suissa S, Shuster JJ. 1985. Exact unconditional sample sizes for the 2 x 2 binomial trial. Journal of the Royal Statistical Society, Series A. 148:317-327.

Wu MC, Bailey KR. 1989. Estimation and comparison of changes in the presence of informative censoring: conditional linear models. Biometrics. 45:939-955.

APPENDIX A: SCHEDULE OF EVENTS

Event	Screening		Baseline/ 1st Dose	Remainder of Treatment Period			Follow-up	
	Initial Screening Visit	Final Screening Visit	Day 0	Day 6	Day 7	Day 13	Day 14 [a]	Day 28 [a]
	Day –14 to -10	Day -1						
Informed consent [b]	X							
Record demographic data	X							
Complete medical history	X							
Monitor for pretreatment adverse events (PTAEs) [k]	X	X	X					
Record prior medications	X	X	X					
Record concomitant medications (CM)			X	X	X	X	X	X
Height and BMI	X							
Body weight while only wearing underwear and a light gown	X		X		X		X	
Comprehensive physical examination [c]	X						X	
Targeted physical examination [d]			X		X			X
Vital Signs [e]	X [e]		X		X		X	X
Provide ABPM and instruct on use		X		X		X		
25-hour monitoring of BP via ABPM [f]		X		X		X		
Orthostatic hypotension evaluation			X		X		X	
12-lead ECG	X						X	
Hematology [g]	X						X	
Serum chemistry [g]	X		X		X [g]		X	
Serum pregnancy test [h]	X							
Urine pregnancy test [h]							X	
Urinalysis [g]	X						X	

Event	Screening		Baseline/ 1st Dose	Remainder of Treatment Period			Follow-up	
	Initial Screening Visit	Final Screening Visit	Day 0	Day 6	Day 7	Day 13	Day 14 [a]	Day 28 [a]
	Day –14 to -10	Day -1						
Urine drug screen [g]	X							
Review inclusion/exclusion criteria	X	X	X					
Randomization [i]			X					
Administer study drug in clinic [j]			X	X		X		
Provide diary to record CMs and study drug details			X					
Review diary				X	X	X	X	X
Collect study drug containers/capsule count				X	X	X		
Monitor for treatment emergent adverse events (TEAEs) [k]			X	X	X	X	X	X
Blood collection for PK [l]							X	

a. If a subject is discontinued from study drug early, all study evaluations described for Day 14 and Day 28 will be performed if feasible. Study drug-related AEs (adverse reaction or suspected adverse reaction per the definitions in Section 8.1.3) will be followed until resolution or stabilization.
b. ICF must be signed prior to performing any other screening evaluations
c. Comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological exam
d. Targeted physical examination will specifically target the cardiovascular system and will include vital signs, plus an examination of the extremities to check for the presence of edema, as well as an examination to document any other evidence of a cardiovascular problem. Any areas of concern from the medical history or noted on the prior physical examination or indicated by subject symptoms or other findings as determined by the Investigator or designee may also be examined.
e. BP, pulse rate, respiration rate, and oral body temperature. At the Initial Screening Visit, the arm with the higher average clinical visit systolic BP will be determined and used for all further BP measurements including ABPM measurements (see Section 8.3).
f. BP will be continually recorded with an ABPM on one to three 25-hour periods during the trial: Day -1 to Day 0, Day 6 to Day 7, and Day 13 to Day 14 (see Section 7.1 for further detail)
g. See Appendix B for a list of the specific hematology, serum chemistry, urinalysis, and drug tests. The serum chemistry tests at Day 7 will be limited to creatinine (and calculation of creatinine clearance) and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium), rather than the full panel listed in Appendix B.
h. Only for WCBP
i. Only after all other baseline procedures have been completed and the subject's eligibility is confirmed. Subjects will be randomized 3:3:1 to one of three treatment arms (see Section 5.2)

j. Subjects will take study drug by mouth qd for 14 days (Days 0-13) for a total of 14 doses. With the exception of Days 0, 6 and 13, when study drug intake is at the time of clinic visit, the subjects shall be instructed to take the study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day. At each dose, subjects will take one capsule from each of the two containers (OE Norvasc® tablet or matched placebo for the OE Norvasc® tablet and OE Celebrex® capsule or matched placebo for OE Celebrex® capsule). The first dose of study drug (morning dose on Day 0) and the Day 6 and Day 13 doses will be taken in the clinic, and all remaining doses will be self-administered at home. Subjects will be provided with a diary to record the details of study drug administration.

k. Monitoring for PTAEs will begin upon completion of the initial screening visit procedures and will continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Monitoring for TEAEs will begin immediately following administration of the first dose of study drugs and will continue throughout the study. Subjects will be solicited for PTAE history at Day -1 and Day 0 (pre-dose). Subjects will be solicited for TEAE history prior to leaving the clinic on Day 0 and on Days 6, 7, 13, 14, and 28. In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

l. For PK analysis, blood samples will be obtained at 24 hours ± 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that have UV-shielded lights will participate in the PK blood collection. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample will be collected and analyzed for all participating subjects, regardless of whether they are in a treatment arm that receives amlodipine.

APPENDIX B: CLINICAL LABORATORY TESTS

Hematology

Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin conc.
Mean corpuscular volume
Mean platelet volume
Platelet count
Red blood cell distribution width
Red blood cell count
White blood cell count
White blood cell differential
(% & absolute):
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils

Serum Chemistry[1]

Albumin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine[2]
Gamma glutamyl transferase
Glucose
Iron
Lactate dehydrogenase

Serum Chemistry (cont.)

Phosphorus
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Uric acid

Urinalysis

Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen

Urine Drug Screen:

Amphetamines
Barbiturates
Benzodiazepines
Cannabis and metabolites
Cocaine and metabolites
Methadone
Methamphetamine
Methylenedioxymethamphetamine
Opiates
Phencyclidine

WCBP Only

Serum pregnancy test (Screening)
Urine pregnancy test (Day 14)

[1] The serum chemistry tests at Day 7 will be limited to creatinine and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium).
[2] Including calculation of creatinine clearance.

APPENDIX C: WORLD HEALTH ORGANIZATION TOXICITY CRITERIA

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology	WBC (x103/l)	4	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
	Platelets (x103/l)	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
	Hemoglobin (g/dL)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
	Granulocytes/Bands (x103/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Lymphocytes (x103/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Hemorrhage	None	Mild, no	Gross, 1 - 2 units transfusion per episode	Gross, 3 - 4 units transfusion per episode	Massive, > 4 units transfusion per episode
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
	Prothrombin time (Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic	Hyperglycemia (mg/dL)	< 116	116 - 160	161 – 250	251 - 500	> 500 or ketoacidosis
	Hypoglycemia (mg/dL)	> 64	55 – 64	40 – 54	30 - 39	< 30
	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
	Hypercalcemia (mg/dL)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	13.5
	Hypocalcemias (mg/dL)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6
	Hypomagnesemia (mg/dL)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	—
	Vomiting	None	1 episode in 24 hr	2 - 5 episodes in 24 hr	6 - 10 episodes in 24 hr	> 10 episodes in 24 hr or requiring parenteral support
	Diarrhea	None	Increase of 2 - 3 stools / day over pre-Rx	Increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	Increase of 7 - 9 stools/day, or incontinence, or severe cramping	Increase of > 10 stools/day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers but can eat solids	Painful erythema, edema, or ulcers and cannot eat solids	Requires parenteral or enteral support for alimentation
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
	ALK or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
	Liver- clinical	No change from baseline	-----	-----	Precoma	Hepatic coma
Kidney, bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
	Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	Nephrotic syndrome
	Hematuria	Negative	Microscopic only	Gross, no clots no Rx needed	Gross and clots bladder irrigation	Requires trans- fusion or cystectomy
	Weight gain/loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	20.00%	-----
Pulmonary	Pulmonary	None or no change	Asymptomatic, with abnormality in PFTs	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac	Cardiac arrhythmias	None	Asymptomatic, transient, requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring; or hypo- tension, or ventricular tachycardia or fibrillation
	Cardiac function	None	Asymptomatic, decline of resting ejection fraction by less than 20 % of baseline value	Asymptomatic, decline of resting ejection fraction by more than 20 % of baseline value	Mild CHF, responsive to therapy	Severe of refractory CHF
	Cardiac ischaemia	None	Non-specific T-wave flattening	Asymptomatic, ST and T wave changes suggesting ischaemia	Angina without evidence of infraction	Acute myocardial infarction
	Cardiac- pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion; drainage required	Tamponade; drainage urgently required
	Hypertension	None or no change	Asymptomatic, transient increase by greater than 20 mmHg (D) or to > 150/100 if previously WNL. No treatment required.	Recurrent or persistent increase by greater than 20 mmHg (D) or to > 150/100 if previously WNL. No treatment required.	Requires therapy	Hypertensive crisis
	Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypo-tension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization; resolves within 48 hours of stopping the agent	Requires therapy and hospitalization for > 48 hr after stopping the agent

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neurologic	Neuro: sensory	None or no change	Mild paraesthesias; loss of deep tendon reflexes	Mild or moderate objective sensory loss moderate paraesthesias	Severe objective sensory loss or paraesthesias that interfere with function	-----
	Neuro: motor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
	Neuro: cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, (>50% waking hr), agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic psychosis
	Neuro: cerebellar	None	Slight incoordination, dysdiadochokinesia	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
	Neuro: mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
	Neuro: headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-----
	Neuro: constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hr
	Neuro: hearing	None or no change	Asymptomatic, hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
	Neuro: vision	None or no change	-----	-----	Symptomatic subtotal loss of vision	Blindness

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Pain	None	Mild	Moderate	Severe	Reg. narcotics
Skin	Skin	None or no change	Scattered macular ot papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Alopecia	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	-----	-----
Allergy	Allergy	None	Transient rash, drug fever < 38oC (100.4oF)	Urticaria, drug fever 38oC (100.4oF), mild bronchospasm	Serum sickness, bronchospasm requiring parenteral medication	Anaphylaxis
Local	Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	plastic surgery indicated
Fever of unknown origin	Fever of unknown origin	None	37.1 - 38.0ºC 98.7º - 100.4ºF	38.1º - 40.0ºC 100.5º - 104ºF	> 40.0ºC > 104.0ºF for less than 24 hr	> 40.0ºC (>104ºF) for more than 24 hr or accompanied by hypotension
Infection	Infection	None	Mild	Moderate	Severe	Life-threatening
Additional events	Asthenia	Analogous to Karnofsky index (WHO grading)				
	Chills	Analogous to fever				
	Peripheral edema	Analogous to weight gain				
	Anorexia	Analogous to weight loss				

APPENDIX D: ABPM PROCEDURE

D.1 ABPM Fitting Procedure

D.1.1 The ABPM measurements will be collected with the Spacelabs 90207 monitor (Spacelabs Healthcare, Issaqua, WA, USA). The blood pressure monitoring equipment, both hardware and software, will be consistent across all subjects.

D.1.2 The ABPM device shall be programmed to record measurements every 20 min between 09:00 and 21:59 and every 30 min between 22:00 and 08:59.

D.1.3 The investigator shall ensure that a valid measurement is recorded manually upon fitting the monitor. This manual measurement shall take place between 07:00 and 10:00 on Day -1, Day 6, and Day 13. The date and time shall be noted in the subject diary.

D.1.4 With the exception of Day 0, when study drug intake is in the clinic after determination of eligibility (and at least 25 hours after the Day-1 ABPM was initiated), Days 6 and 13, when study drug intake is at the time of fitting the ABPM device (following fitting) and Day 7, when study drug intake is 24 h ± 1 h after the Day 6 dose, the subject shall be instructed to take the study drugs between 07:00 and 10:00, and preferably at approximately the same time each day.

D.1.5 The subject shall be instructed to record bed time, rising time and drug-intake times in the subject diary.

D.1.6 The ABPM shall be worn for a minimum of 25 h. This is the optimal duration, as it provides for a full 24 h after the white-coat window.

D.2 ABPM Removal Procedure

D.2.1 The ABPM may be removed from the subject once 25 hours have elapsed since the recorded time of the first study measurement.

D.2.2 The ABPM measurements shall be uploaded.

APPENDIX E: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (OCTOBER 2013)

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX F: PACKAGE INSERT FOR NORVASC® (AMLODIPINE BESYLATE) TABLETS (MARCH 2015)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NORVASC safely and effectively. See full prescribing information for NORVASC.

NORVASC® (amlodipine besylate) tablets, for oral administration
Initial U.S. Approval: 1987

----------INDICATIONS AND USAGE----------

NORVASC is a calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:

- Hypertension (1.1)
  - NORVASC is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Coronary Artery Disease (1.2)
  - Chronic Stable Angina
  - Vasospastic Angina (Prinzmetal's or Variant Angina)
  - Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%

----------DOSAGE AND ADMINISTRATION----------

- Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. (2.1)
  - Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily. (2.1)
- Pediatric starting dose: 2.5 mg to 5 mg once daily. (2.2)

Important Limitation: Doses in excess of 5 mg daily have not been studied in pediatric patients. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 2.5 mg, 5 mg, and 10 mg (3)

----------CONTRAINDICATIONS----------

- Known sensitivity to amlodipine (4)

----------WARNINGS AND PRECAUTIONS----------

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely. (5.1)
- Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of NORVASC, particularly in patients with severe obstructive coronary artery disease. (5.2)
- Titrate slowly in patients with severe hepatic impairment. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reaction to amlodipine is edema which occurred in a dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are fatigue, nausea, abdominal pain, and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or *www.pfizer.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Do not exceed doses greater than 20 mg daily of simvastatin. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use only if the potential benefit justifies the risk. (8.1)
- Nursing: Discontinue when administering NORVASC. (8.3)
- Pediatric: Effect on patients less than 6 years old is not known. (8.4)
- Geriatric: Start dosing at the low end of the dose range. (8.5)

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypertension

NORVASC® is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including NORVASC.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

NORVASC may be used alone or in combination with other antihypertensive agents.

1.2 Coronary Artery Disease (CAD)

Chronic Stable Angina

NORVASC is indicated for the symptomatic treatment of chronic stable angina. NORVASC may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

NORVASC is indicated for the treatment of confirmed or suspected vasospastic angina. NORVASC may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD

In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, NORVASC is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily, and the maximum dose is 10 mg once daily.

Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORVASC to other antihypertensive therapy.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary artery disease: The recommended dose range for patients with coronary artery disease is 5–10 mg once daily. In clinical studies, the majority of patients required 10 mg *[see Clinical Studies (14.4)]*.

2.2 Children

The effective antihypertensive oral dose in pediatric patients ages 6–17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients *[see Clinical Pharmacology (12.4), Clinical Studies (14.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 2.5 mg white, diamond, flat-faced, beveled edged, with "NORVASC" on one side and "2.5" on the other
Tablets: 5 mg white, elongated octagon, flat-faced, beveled edged, with "NORVASC" on one side and "5" on the other
Tablets: 10 mg white, round, flat-faced, beveled edge, with "NORVASC" on one side and "10" on the other

4 CONTRAINDICATIONS

NORVASC is contraindicated in patients with known sensitivity to amlodipine.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.2 Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of NORVASC, particularly in patients with severe obstructive coronary artery disease.

5.3 Patients with Hepatic Failure

Because NORVASC is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, titrate slowly when administering NORVASC to patients with severe hepatic impairment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) at doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are reflected in the table below. The incidence (%) of side effects that occurred in a dose related manner are as follows:

	Amlodipine			Placebo
	2.5 mg N=275	5 mg N=296	10 mg N=268	N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse reactions that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

	NORVASC (%) (N=1730)	Placebo (%) (N=1250)
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	NORVASC		Placebo	
	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,[1] back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,[1] myalgia.

Psychiatric: sexual dysfunction (male[1] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,[1] epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,[1] rash,[1] rash erythematous, rash maculopapular.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

[1] These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

In the CAMELOT and PREVENT studies *[see Clinical Studies (14.4)]*, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

7 DRUG INTERACTIONS

7.1 Impact of Other Drugs on Amlodipine

CYP3A Inhibitors
Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment *[see Clinical Pharmacology (12.3)]*.

CYP3A Inducers
No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Sildenafil
Monitor for hypotension when sildenafil is co-administered with amlodipine *[see Clinical Pharmacology (12.2)]*.

7.2 Impact of Amlodipine on Other Drugs

Simvastatin
Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily *[see Clinical Pharmacology (12.3)]*.

Immunosuppressants
Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively, 8 times[2] and 23 times[2] the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

[2] Based on patient weight of 50 kg.

8.3 Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

8.4 Pediatric Use

NORVASC (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years *[see Clinical Studies (14.1)]*. Effect of NORVASC on blood pressure in patients less than 6 years of age is not known.

8.5 Geriatric Use

Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited.

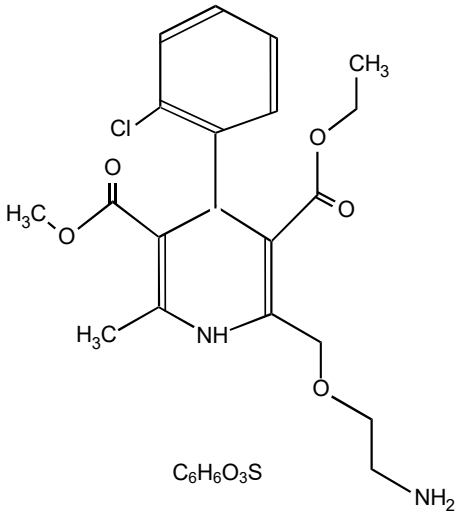
Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

11 DESCRIPTION

NORVASC is the besylate salt of amlodipine, a long-acting calcium channel blocker.

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. NORVASC (amlodipine besylate) Tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, NORVASC reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: NORVASC has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of NORVASC in vasospastic (Prinzmetal's or variant) angina.

12.2 Pharmacodynamics

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, NORVASC produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies

of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with NORVASC is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of NORVASC resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with NORVASC have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, NORVASC has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: NORVASC does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving NORVASC and concomitant beta-blockers. In clinical studies in which NORVASC was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, NORVASC therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Drug interactions

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect *[see Drug Interactions (7.1)]*.

12.3 Pharmacokinetics

After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of NORVASC is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Drug interactions

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of other drugs on amlodipine

Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see Drug Interactions (7.1)]*.

Impact of amlodipine on other drugs

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone *[see Drug Interactions (7.2)]*.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7.2)]*.

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7.2)]*.

12.4 Pediatric Patients

Sixty-two hypertensive patients aged 6 to 17 years received doses of NORVASC between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.[3] For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose.[3]

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose[3] of 10 mg/day on a mg/m^2 basis).

[3] Based on patient weight of 50 kg

14 CLINICAL STUDIES

14.1 Effects in Hypertension

Adult Patients

The antihypertensive efficacy of NORVASC has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on NORVASC and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to NORVASC 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

14.2 Effects in Chronic Stable Angina

The effectiveness of 5–10 mg/day of NORVASC in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 NORVASC, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for NORVASC 10 mg, and averaged 7.9% (38 sec) for NORVASC 5 mg. NORVASC 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of NORVASC in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

14.3 Effects in Vasospastic Angina

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, NORVASC therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 NORVASC and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

14.4 Effects in Documented Coronary Artery Disease

In PREVENT, 825 patients with angiographically documented coronary artery disease were randomized to NORVASC (5–10 mg once daily) or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either NORVASC (5–10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the NORVASC and placebo groups, respectively, for a hazard ratio of 0.691 (95% CI: 0.540–0.884, $p = 0.003$). The primary endpoint is summarized in Figure 1 below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 1). Effects in various subgroups are shown in Figure 2.

In an angiographic substudy (n=274) conducted within CAMELOT, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasound.

Figure 1 - Kaplan-Meier Analysis of Composite Clinical Outcomes for NORVASC versus Placebo

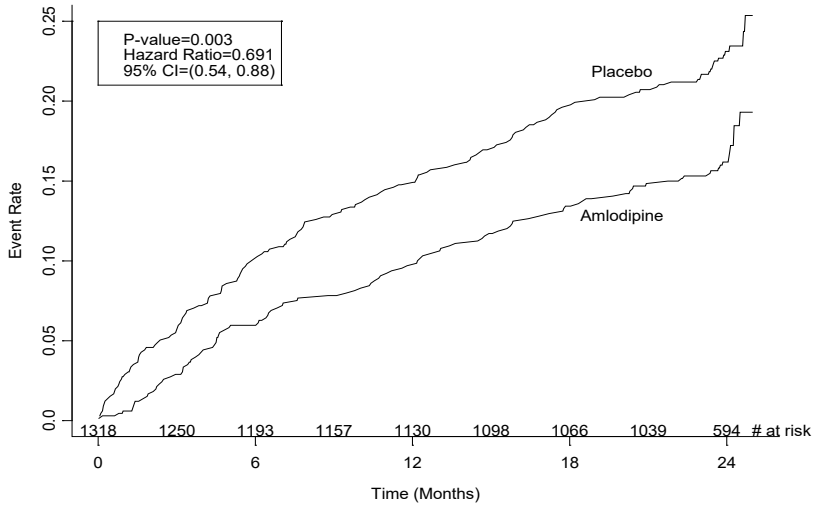
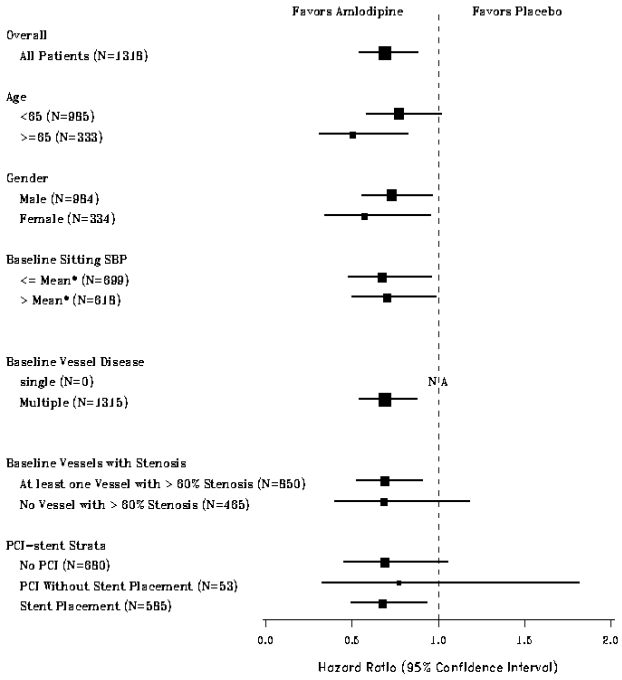


Figure 2 – Effects on Primary Endpoint of NORVASC versus Placebo across Sub-Groups



* The mean sitting baseline SBP is 129 mmHg

Table 1 below summarizes the significant composite endpoint and clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between NORVASC and placebo.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	NORVASC (N=663)	Placebo (N=655)	Risk Reduction (p-value)
Composite CV Endpoint	**110 (16.6)**	**151 (23.1)**	**31% (0.003)**
Hospitalization for Angina*	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization*	78 (11.8)	103 (15.7)	27% (0.033)

* Total patients with these events

14.5 Studies in Patients with Heart Failure

NORVASC has been compared to placebo in four 8–12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of NORVASC 5–10 mg in 1153 patients with NYHA Classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, NORVASC had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on NORVASC and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n=827) or NORVASC (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between NORVASC and placebo in the primary endpoint of all-cause mortality (95% confidence limits from 8% reduction to 29% increase on NORVASC). With NORVASC there were more reports of pulmonary edema.

16 HOW SUPPLIED/STORAGE AND HANDLING

2.5 mg Tablets

NORVASC – 2.5 mg Tablets (amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, diamond, flat-faced, beveled edged engraved with “NORVASC” on one side and “2.5” on the other side and supplied as follows:

NDC 0069-1520-68	Bottle of 90

5 mg Tablets

NORVASC – 5 mg Tablets (amlodipine besylate equivalent to 5 mg of amlodipine per tablet) are white, elongated octagon, flat-faced, beveled edged engraved with both “NORVASC” and “5” on one side and plain on the other side and supplied as follows:

NDC 0069-1530-68	Bottle of 90
NDC 0069-1530-41	Unit Dose package of 100
NDC 0069-1530-72	Bottle of 300

10 mg Tablets

NORVASC – 10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both “NORVASC” and “10” on one side and plain on the other side and supplied as follows:

NDC 0069-1540-68	Bottle of 90
NDC 0069-1540-41	Unit Dose package of 100

Storage

Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP).

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0014-14.0

NORVASC® (amlodipine besylate)

Read this information carefully before you start taking **NORVASC** (NORE-vask) and each time you refill your prescription. There may be new information. This information does not replace talking with your doctor. If you have any questions about **NORVASC**, ask your doctor. Your doctor will know if **NORVASC** is right for you.

What is NORVASC?

NORVASC is a type of medicine known as a calcium channel blocker (CCB). It is used to treat high blood pressure (hypertension) and a type of chest pain called angina. It can be used by itself or with other medicines to treat these conditions.

High Blood Pressure (hypertension)
High blood pressure comes from blood pushing too hard against your blood vessels. **NORVASC** relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure. Drugs that lower blood pressure lower your risk of having a stroke or heart attack.

Angina
Angina is a pain or discomfort that keeps coming back when part of your heart does not get enough blood. Angina feels like a pressing or squeezing pain, usually in your chest under the breastbone. Sometimes you can feel it in your shoulders, arms, neck, jaws, or back. **NORVASC** can relieve this pain.

Who should not use NORVASC?

Do not use **NORVASC** if you are allergic to amlodipine (the active ingredient in **NORVASC**), or to the inactive ingredients. Your doctor or pharmacist can give you a list of these ingredients.

What should I tell my doctor before taking NORVASC?

Tell your doctor about any prescription and non-prescription medicines you are taking, including natural or herbal remedies.
Tell your doctor if you:

- ever had heart disease
- ever had liver problems
- are pregnant, or plan to become pregnant. Your doctor will decide if **NORVASC** is the best treatment for you.
- are breast-feeding. Do not breast-feed while taking **NORVASC**. You can stop breast-feeding or take a different medicine.

How should I take NORVASC?

- Take **NORVASC** once a day, with or without food.
- It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose of **NORVASC** at a time.
- If you miss a dose, take it as soon as you remember. Do not take **NORVASC** if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.
- **Other medicines:** You can use nitroglycerin and **NORVASC** together. If you take nitroglycerin for angina, don't stop taking it while you are taking **NORVASC.**
- While you are taking **NORVASC**, do not stop taking your other prescription medicines, including any other blood pressure medicines, without talking to your doctor.
- If you took too much **NORVASC**, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

What should I avoid while taking NORVASC?

- **Do not** breast-feed. It is not known if **NORVASC** will pass through your milk.
- **Do not** start any new prescription or non-prescription medicines or supplements, unless you check with your doctor first.

What are the possible side effects of NORVASC?

NORVASC may cause the following side effects. Most side effects are mild or moderate:

- swelling of your legs or ankles
- tiredness, extreme sleepiness
- stomach pain, nausea
- dizziness
- flushing (hot or warm feeling in your face)
- arrhythmia (irregular heartbeat)
- heart palpitations (very fast heartbeat)
- muscle rigidity, tremor and/or abnormal muscle movement

It is rare, but when you first start taking **NORVASC** or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to a hospital emergency room.

Tell your doctor if you are concerned about any side effects you experience. These are not all the possible side effects of **NORVASC**. For a complete list, ask your doctor or pharmacist.

How do I store NORVASC?

Keep **NORVASC** away from children. Store **NORVASC** Tablets at room temperature (between 59° and 86°F). Keep **NORVASC** out of the light. Do not store in the bathroom. Keep **NORVASC** in a dry place.

General advice about NORVASC

Sometimes, doctors will prescribe a medicine for a condition that is not written in the patient information leaflets. Only use **NORVASC** the way your doctor told you to. Do not give **NORVASC** to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or doctor for information about **NORVASC**, or you can visit the Pfizer website at **www.pfizer.com** or call 1-800-438-1985.

LAB-0015-8.0
Revised March 2015

APPENDIX G: PACKAGE INSERT FOR CELEBREX® (CELECOXIB) CAPSULES (MAY 2016)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CELEBREX safely and effectively. See full prescribing information for CELEBREX.

CELEBREX® (celecoxib) capsules, for oral use
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)**
- **CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	5/2016
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)	5/2016
Warnings and Precautions, Heart Failure and Edema (5.5)	5/2016

----------INDICATIONS AND USAGE----------

CELEBREX is a nonsteroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Acute Pain (AP) (1.5)
- Primary Dysmenorrhea (PD) (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- OA: 200 mg once daily or 100 mg twice daily (2.2, 14.1)
- RA: 100 to 200 mg twice daily (2.3, 14.2)
- JRA: 50 mg twice daily in patients 10-25 kg. 100 mg twice daily in patients more than 25 kg (2.4, 14.3)
- AS: 200 mg once daily single dose or 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit (2.5, 14.4)
- AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed (2.6, 14.5)

Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). (2.7, 8.6, 12.3)

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers, (2.7, 8.8, 12.3).

----------DOSAGE FORMS AND STRENGTHS----------

CELEBREX (celecoxib) capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to celecoxib, or any components of the drug product or sulfonamides (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of CELEBREX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of CELEBREX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: CELEBREX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue CELEBREX at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

----------ADVERSE REACTIONS----------

Most common adverse reactions in arthritis trials (>2% and >placebo) are: abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking CELEBREX with drugs that interfere with hemostasis. Concomitant use of CELEBREX and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with CELEBREX may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with CELEBREX in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with CELEBREX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of CELEBREX in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. [*see Warnings and Precautions (5.1)*]**
- **CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. [*see Contraindications (4) and Warnings and Precautions (5.1)*]**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events. [*see Warnings and Precautions (5.2)*]**

1. INDICATIONS AND USAGE

CELEBREX is indicated

1.1 Osteoarthritis (OA)

For the management of the signs and symptoms of OA [*see Clinical Studies (14.1)*]

1.2 Rheumatoid Arthritis (RA)

For the management of the signs and symptoms of RA [*see Clinical Studies (14.2)*]

1.3 Juvenile Rheumatoid Arthritis (JRA)

For the management of the signs and symptoms of JRA in patients 2 years and older [*see Clinical Studies (14.3)*]

1.4 Ankylosing Spondylitis (AS)

For the management of the signs and symptoms of AS [*see Clinical Studies (14.4)*]

1.5 Acute Pain

For the management of acute pain in adults [*see Clinical Studies (14.5)*]

1.6 Primary Dysmenorrhea

For the management of primary dysmenorrhea [*see Clinical Studies (14.5)*]

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

These doses can be given without regard to timing of meals.

2.2 Osteoarthritis

For OA, the dosage is 200 mg per day administered as a single dose or as 100 mg twice daily.

2.3 Rheumatoid Arthritis

For RA, the dosage is 100 to 200 mg twice daily.

2.4 Juvenile Rheumatoid Arthritis

For JRA, the dosage for pediatric patients (age 2 years and older) is based on weight. For patients $\geq$10 kg to $\leq$25 kg the recommended dose is 50 mg twice daily. For patients >25 kg the recommended dose is 100 mg twice daily.

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F).

2.5 Ankylosing Spondylitis

For AS, the dosage of CELEBREX is 200 mg daily in single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

2.6 Management of Acute Pain and Treatment of Primary Dysmenorrhea

For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

2.7 Special Populations

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

Poor Metabolizers of CYP2C9 Substrates
In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.

In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [*see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)*].

3. DOSAGE FORMS AND STRENGTHS
CELEBREX (celecoxib) capsules:
50 mg white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body.
100 mg white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body.
200 mg white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body.
400 mg white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body.

4. CONTRAINDICATIONS
CELEBREX is contraindicated in the following patients:
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to celecoxib, any components of the drug product [see *Warnings and Precautions (5.7, 5.9)*].
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*].
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*].
- In patients who have demonstrated allergic-type reactions to sulfonamides.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [*see Clinical Studies (14.6)*].

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients
Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Celebrex in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Celebrex is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs, including celecoxib cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with CELEBREX. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [see Clinical Studies (14.6)].

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue CELEBREX until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue CELEBREX immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including CELEBREX can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [see *Clinical Studies (14.6)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of celecoxib may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

In the CLASS study [*see Clinical Studies (14.6)*], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively.

Avoid the use of CELEBREX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If CELEBREX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia**,** heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors or the ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. The renal effects of CELEBREX may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating CELEBREX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of CELEBREX [*see Drug Interactions (7)*]. Avoid the use of CELEBREX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If CELEBREX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic- hypoadosteronism state.

5.7 Anaphylactic Reactions
Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. Celebrex is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people [see *Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if any anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, CELEBREX is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When CELEBREX is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
Serious skin reactions have occurred following treatment with Celebrex, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CELEBREX at the first appearance of skin rash or any other sign of hypersensitivity. CELEBREX is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Premature Closure of Fetal Ductus Arteriosus
Celecoxib may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

5.11 Hematological Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with CELEBREX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs, including CELEBREX, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.12 Masking of Inflammation and Fever
The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.14 Disseminated Intravascular Coagulation (DIC)
Because of the risk of disseminated intravascular coagulation with use of CELEBREX in pediatric patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, and inform patients and their caregivers to report symptoms as soon as possible.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Of the CELEBREX-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Pre-marketing Controlled Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral Edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-Accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central, Peripheral Nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis					
Rhinitis	2.3%	1.1%	1.7%	1.6%	2.6%
Sinusitis	2.0%	1.3%	2.4%	2.3%	0.6%
Upper Respiratory Infection	5.0%	4.3%	4.0%	5.4%	5.8%
	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

CBX = CELEBREX 100 – 200 mg twice daily or 200 mg once daily; NAP = Naproxen 500 mg twice daily;
DCF = Diclofenac 75 mg twice daily;
IBU = Ibuprofen 800 mg three times daily.

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse reactions occurred in 0.1 - 1.9% of patients treated with CELEBREX (100 - 200 mg twice daily or 200 mg once daily):

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Hypersensitivity, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, paresthesia, vertigo

Hearing and vestibular: Deafness, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary: Hepatic enzyme increased (including SGOT increased, SGPT increased)

Metabolic and nutritional: BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Musculoskeletal: Arthralgia, arthrosis, myalgia, synovitis, tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia,

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, cough, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients:

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

General: Sepsis, sudden death

Liver and biliary: Cholelithiasis

Hemic and lymphatic: Thrombocytopenia

Nervous: Ataxia, suicide *[see Drug Interactions (7.1)]*

Renal: Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study [see *Special Studies* (14.6)]

Hematological Events: The incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients on CELEBREX 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three times daily 1.9%. The lower incidence of events with CELEBREX was maintained with or without aspirin use [*see Clinical Pharmacology (12.2)*].

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

Juvenile Rheumatoid Arthritis Study

In a 12-week, double-blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg twice daily, 82 patients were treated with celecoxib 6 mg/kg twice daily, and 83 patients were treated with naproxen 7.5 mg/kg twice daily. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness (Table 2). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice daily had no observable deleterious effect on growth and development during the course of the 12-week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of JRA among treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg twice daily. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

Table 2: Adverse Events Occurring in ≥5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

	All Doses Twice Daily		
System Organ Class Preferred Term	**Celecoxib 3 mg/kg N=77**	**Celecoxib 6 mg/kg N=82**	**Naproxen 7.5 mg/kg N=83**
Any Event	**64**	**70**	**72**
Eye Disorders	**5**	**5**	**5**
Gastrointestinal	**26**	**24**	**36**
Abdominal pain NOS	4	7	7
Abdominal pain upper	8	6	10
Vomiting NOS	3	6	11
Diarrhea NOS	5	4	8
Nausea	7	4	11
General	**13**	**11**	**18**
Pyrexia	8	9	11
Infections	**25**	**20**	**27**
Nasopharyngitis	5	6	5
Injury and Poisoning	**4**	**6**	**5**
Investigations*	**3**	**11**	**7**
Musculoskeletal	**8**	**10**	**17**
Arthralgia	3	7	4
Nervous System	**17**	**11**	**21**
Headache NOS	13	10	16
Dizziness (excl vertigo)	1	1	7
Respiratory	**8**	**15**	**15**
Cough	7	7	8
Skin & Subcutaneous	**10**	**7**	**18**

* Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

Other Pre-Approval Studies

Adverse Events from Ankylosing Spondylitis Studies: A total of 378 patients were treated with CELEBREX in placebo- and active-controlled AS studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the AS studies were similar to those reported in the OA/RA studies.

Adverse Events from Analgesia and Dysmenorrhea Studies: Approximately 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

The APC and PreSAP Trials

Adverse reactions from long-term, placebo-controlled polyp prevention studies: Exposure to CELEBREX in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years [*see Special Studies Adenomatous Polyp Prevention Studies (14.6)*].

Some adverse reactions occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks; see *Adverse events from* CELEBREX *pre-marketing controlled arthritis trials*, above). The adverse reactions for which these differences in patients treated with CELEBREX were greater as compared to the arthritis pre-marketing trials were as follows:

	CELEBREX (400 to 800 mg daily) N = 2285	**Placebo N=1303**
Diarrhea	10.5%	7.0%
Gastroesophageal reflux disease	4.7%	3.1%
Nausea	6.8%	5.3%
Vomiting	3.2%	2.1%
Dyspnea	2.8%	1.6%
Hypertension	12.5%	9.8%
Nephrolithiasis	2.1%	0.8%

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking CELEBREX, at an incidence greater than placebo in the long-term polyp prevention studies, and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders*:* Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth*:* Labyrinthitis

Cardiac disorders*:* Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders*:* Deep vein thrombosis

Reproductive system and breast disorders*:* Ovarian cyst

Investigations*:* Blood potassium increased, blood sodium increased, blood testosterone decreased

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CELEBREX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Cardiovascular*:* Vasculitis, deep venous thrombosis

General: Anaphylactoid reaction, angioedema

Liver and biliary*:* Liver necrosis, hepatitis, jaundice, hepatic failure

Hemic and lymphatic: Agranulocytosis, aplastic anemia, pancytopenia, leucopenia

Metabolic: Hypoglycemia, hyponatremia

Nervous*:* Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage

Renal*:* Interstitial nephritis

7. DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with celecoxib.

Table 3: Clinically Significant Drug Interactions with Celecoxib

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of Celecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of CELEBREX with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*]. In two studies in healthy volunteers, and in patients with osteoarthritis and established heart disease respectively, celecoxib (200-400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100-325 mg).
Intervention:	Concomitant use of CELEBREX and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. CELEBREX is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of CELEBREX and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of CELEBREX and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, , patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of CELEBREX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of Celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of CELEBREX and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of CELEBREX and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Celebrex has no effect on methotrexate pharmacokinetics.
Intervention:	During concomitant use of CELEBREX and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of CELEBREX and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of CELEBREX and cyclosporine, monitor patients for signs of worsening renal function.

NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of Celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*].
Intervention:	The concomitant use of Celecoxib with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of CELEBREX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of CELEBREX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
CYP2C9 Inhibitors or inducers	
Clinical Impact:	Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g. fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of celecoxib.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers. [*see Clinical Pharmacology (12.3)*].
CYP2D6 substrates	
Clinical Impact:	*In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6 (e.g. atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates. [*see Clinical Pharmacology (12.3)*].
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with CELEBREX may increase the risk of GI ulceration or bleeding.
Intervention	Monitor patients with concomitant use of CELEBREX with corticosteroids for signs of bleeding [see Warnings and Precautions (5.2)].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Pregnancy category D from 30 weeks of gestation onward.

Risk Summary

Use of NSAIDs, including CELEBREX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

There are no adequate and well-controlled studies of CELEBREX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of CELEBREX during labor or delivery. In animal studies, NSAIDs, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

The available data do not establish the presence or absence of developmental toxicity related to the use of Celebrex.

Animal data

Celecoxib at oral doses ≥150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in

pre-implantation and post-implantation losses at oral doses ≥50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg twice daily). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

8.2 Lactation

Risk Summary
Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of CELEBREX in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when CELEBREX is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CELEBREX and any potential adverse effects on the breastfed infant from the CELEBREX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including CELEBREX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including CELEBREX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use
CELEBREX is approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [*(see Boxed Warning, Warnings and Precautions (5.12), and Clinical Studies (14.3)*].

The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). When NSAIDs including celecoxib are used in patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see *Dosage and Administration (2.4), Warnings and Precautions (5.12), Adverse Reactions (6.3), Animal Toxicology (13.2), Clinical Studies (14.3)*].

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see *Poor Metabolizers of CYP2C9 substrates (8.8)*].

8.5 Geriatric Use
Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13*)].

Of the total number of patients who received CELEBREX in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients [*see Warnings and Precautions (5.4, 5.6)*].

8.6 Hepatic Impairment
The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)*].

8.7 Renal Impairment
CELEBREX is not recommended in patients with severe renal insufficiency [*see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)*].

8.8 Poor Metabolizers of CYP2C9 Substrates
In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer CELEBREX starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)*].

10. OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occured, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

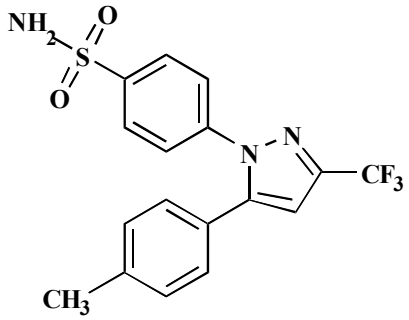
No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11. DESCRIPTION

CELEBREX (celecoxib) capsule is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is $C_{17}H_{14}F_3N_3O_2S$, and it has the following chemical structure:



Celecoxib is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range.

The inactive ingredients in CELEBREX include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CELECOXIB has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

Celecoxib is a potent inhibitor of prostaglandin synthesis in vitro. Celecoxib concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

Platelets

In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of CELEBREX.

Fluid Retention

Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

12.3 Pharmacokinetics

Celecoxib exhibits dose-proportional increase in exposure after oral administration up to 200 mg twice daily and less than proportional increase at hgher doses. It has extensive distribution and high protein binding. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

Absorption
Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose-proportional up to 200 mg twice daily; at higher doses there are less than proportional increases in C_{max} and AUC *[see Food Effects]*. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 4.

Table 4
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
C_{max}, ng/mL	**T_{max}, hr**	**Effective $t_{1/2}$, hr**	**V_{ss}/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects
When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

Coadministration of CELEBREX with an aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX, at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in Cmax, Tmax or $t_{1/2}$ after administration of capsule contents on applesauce [*see Dosage and Administration (2)*].

Distribution
In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Metabolism
Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

Excretion
Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Specific Populations

Geriatric
At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose [*see Dosage and Administration (2.7) and Use in Specific Populations (8.5)*].

Pediatric
The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient.

Twice-daily administration of 50 mg capsules to JRA patients weighing ≥12 to ≤25 kg and 100 mg capsules to JRA patients weighing >25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (*see Dosage and Administration (2.4).* Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.

Race
Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Impairment
A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Dosage and Administration (2.6) and Use in Specific Populations (8.6)*].

Renal Impairment
In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELEBREX is not recommended in patients with severe renal insufficiency [*see Warnings and Precautions (5.6)*].

Drug Interaction Studies
In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

In vivo studies have shown the following:

Aspirin
When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Lithium
In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with CELEBREX 200 mg twice daily as compared to subjects receiving lithium alone [*see Drug Interactions (7)*].

Fluconazole
Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole [*see Drug Interactions (7)*].

Other Drugs
The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, [*see Drug Interactions (7)*], phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [*see Dosage and Administration (2.6), Use in Specific Populations (8.8)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2-to 4-times the human exposure as measured by the AUC_{0-24} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg twice daily) for two years.

Mutagenesis
Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Impairment of Fertility
Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC_{0-24}). At ≥50 mg/kg/day (approximately 6-times human exposure based on the AUC_{0-24} at 200 mg twice daily) there was increased preimplantation loss.

13.2 Animal Toxicology
An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

14. CLINICAL STUDIES

14.1 Osteoarthritis

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

14.2 Rheumatoid Arthritis

CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg twice daily and 200 mg twice daily were similar in effectiveness and both were comparable to naproxen 500 mg twice daily.

Although CELEBREX 100 mg twice daily and 200 mg twice daily provided similar overall effectiveness, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100-200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 years to 17 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with currently inactive systemic features), received one of the following treatments: celecoxib 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The response rates were based upon the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates at week 12 were 69%, 80% and 67% in the celecoxib 3 mg/kg twice daily, celecoxib 6 mg/kg twice daily, and naproxen 7.5 mg/kg twice daily treatment groups, respectively.

The efficacy and safety of CELEBREX for JRA have not been studied beyond six months. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [(*see Boxed Warning, Warnings and Precautions (5.12)*)].

14.4 Ankylosing Spondylitis

CELEBREX was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg CELEBREX doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to CELEBREX 400 mg, 53%, than to CELEBREX 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in at least three of the four following domains: patient global pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

14.5 Analgesia, including Primary Dysmenorrhea

In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses [*see Dosage and Administration (2.6)*] of CELEBREX provided pain relief within 60 minutes.

14.6 Special Studies

Adenomatous Polyp Prevention Studies

Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with CELEBREX: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated):

- In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.
- In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three-years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.

Celecoxib Long-Term Arthritis Safety Study (CLASS)
This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on CELEBREX and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively [*see Warnings and Precautions (5.4)*].

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with CELEBREX 400 mg twice daily are described in Table 4. Table 4 also displays results for patients less than or greater than 65 years of age. The difference in rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 5: Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

All Patients	
CELEBREX alone (n=3105)	0.78
CELEBREX with ASA (n=882)	2.19
Patients <65 Years	
CELEBREX alone (n=2025)	0.47
CELEBREX with ASA (n=403)	1.26
Patients ≥65 Years	
CELEBREX alone (n=1080)	1.40
CELEBREX with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

Endoscopic Studies
The correlation between findings of short-term endoscopic studies with CELEBREX and the relative incidence of clinically significant serious upper GI events with long-term use has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials [*see Warnings and Precautions (5.4) and Clinical Studies (14.6)*]

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial [*see Clinical Studies (14.6)*].

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 OA and RA patients in whom baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of CELEBREX (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all doses of CELEBREX the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with CELEBREX and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (≤ 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

16. HOW SUPPLIED/STORAGE AND HANDLING

CELEBREX (celecoxib) 50 mg capsules are white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body, supplied as:

NDC Number	Size
0025-1515-01	bottle of 60

CELEBREX (celecoxib) 100 mg capsules are white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX (celecoxib) 200 mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

CELEBREX (celecoxib) 400 mg capsules are white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body, supplied as:

NDC Number	Size
0025-1530-02	bottle of 60
0025-1530-01	carton of 100 unit dose

Storage
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]

17. PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop CELEBREX and seek immediate medical therapy [*see Warnings and Precautions (5.3), Use in Specific Populations (8.6)*].

Heart Failure and Edema
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7*)].

Serious Skin Reactions
Advise patients to stop CELEBREX immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9)*].

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including CELEBREX, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity
Inform pregnant women to avoid use of CELEBREX and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of CELEBREX with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see *Warnings and Precautions (5.2*) and *Drug Interactions (7)*]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with CELEBREX until they talk to their healthcare provider [see *Drug Interactions (7)*].

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Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs" or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy**
- are breastfeeding or plan to breast feed**.**

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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APPENDIX H: SAMPLE SIZE AND EFFICACY ANALYSIS

H.1 Results from Study No. KIT-302-03-01

H.1.1 Study No. KIT-302-03-01 documented that while celecoxib had only minor effects on BP, and amlodipine reduced BP significantly, adding celecoxib to the amlodipine increased the BP reduction. The mean changes in SBP_{day}, DBP_{day}, SBP_{night}, and DBP_{night} from baseline to end of therapy are listed below.

Changes in Blood Pressure from Baseline to End of Therapy (Mean ± Standard Deviation mmHg)

	SBP_{day}	DBP_{day}	SBP_{night}	DBP_{night}
Placebo	-2.1 ± 8.2	-0.3 ± 5.4	-1.4 ± 9.2	0.0 ± 6.2
Celecoxib	-0.5 ± 8.8	-1.5 ± 5.1	-1.7 ± 12.3	0.3 ± 7.1
Amlodipine	-8.8 ± 8.1	-5.5 ± 5.1	-6.4 ± 11.4	-3.2 ± 7.8
Amlodipine + Celecoxib	-10.6 ± 9.2	-7.5 ± 6.4	-10.5 ± 10.6	-7.0 ± 8.6

H.2 Margin

H.2.1 The sample size is to be based on the hypothesis that the mean reduction in SBP_{day} from Day 0 to Day 14 of subjects in the Amlodipine+Celecoxib group (arm 1) minus half the mean reduction in SBP_{day} from Day 0 to Day 14 of subjects in the Amlodipine+Placebo group (arm 2) is at least 0.

H.2.2 The margin is based on a mean reduction of 8.8 mmHg in SBP_{day} for the Amlodipine+Placebo group and a mean reduction of 10.6 mmHg for the Amlodipine+Celecoxib group as seen in the previous study, KIT-302-03-01.

H.2.3 To ensure that at least half the effect is maintained, a value of $10.6 – 0.5(8.8) = 6.2$ mmHg should be set for *d* (anticipated mean difference) in the sample size formula (see Section 10.9 for formula).

H.3 Standard Deviation

H.3.1 The standard deviation for SBP_{day} with Amlodipine+Placebo was observed to be 8.1 mmHg in the previous study (Study No. KIT-302-03-01).

H.3.2 The standard deviation for SBP_{day} with Amlodipine+Celecoxib was observed to be 9.2 mmHg in the previous study (Study No. KIT-302-03-01).

H.3.3 The pooled standard deviation for the power and sample size justification is 8.7 mm Hg.

H.4 Preliminary Estimate

H.4.1 It is suggested that a preliminary analysis is carried out at n = 27 per group. This is based on $\alpha = 0.025$, $\beta = 0.2$ and a conservative estimate of s = 8.7. To further optimize the probability of success the actual number is to be increased to 45 per group.

APPENDIX I: CHILD-PUGH CLASSIFICATION OF LIVER CIRRHOSIS

The Child-Pugh score is based on five clinical measures of liver disease. Each measure is scored 1-3 as outlined in the table below.

Measure	1 Point	2 Points	3 Points
Bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
Prothrombin time (s prolonged)	<4	4-6	>6
Ascites	None	Mild	Marked
Encephalopathy	None	Mild	Marked

Chronic liver disease is classified into Child-Pugh Classes A to C based on the added score from above. Subjects with Child-Pugh Class B or C cirrhosis will be excluded from this trial.

Points	Class
5-6	A
7-9	B
10-15	C

References

Child CG, Turcotte JG. 1964. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders. 50-64.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. 1973. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 60(8):646–649.