CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020062Orig1s042

Trade Name: Cardizem CD

Generic Name: Diltiazem HCL

Sponsor: Valeant Pharmaceuticals North America LLC

Approval Date: 06/29/2016

Indication(s): Treatment of hypertension alone or in combination with other antihypertensive medications.

Management of chronic stable angina and angina due to coronary artery spasm.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20062/S-042

SUPPLEMENT APPROVAL

Valeant Pharmaceuticals North America LLC
Attention: Shankar Swaminathan, PhD
Director Regulatory CMC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Dr. Swaminathan:

Please refer to your Supplemental New Drug Application (sNDA) dated 15 September 2015, received 15 September 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cardizem CD (diltiazem hydrochloride) 120, 180, 240, 300 and 360 mg capsules.

This Prior Approval supplemental new drug application provided for an alternate drug product manufacturer for Cardizem CD 360 mg (new formulation and process change) as well as changes in drug substance manufacturers for diltiazem hydrochloride USP. Changes to the Package Insert (PI) and carton/container labeling content were made accordingly. This supplement also provided for revisions to the prescribing information to describe interactions with alcohol, as well as revisions to the Adverse Reactions and Overdose sections of the PI. There were also minor editorial changes throughout.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of

labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 20062/S-042**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

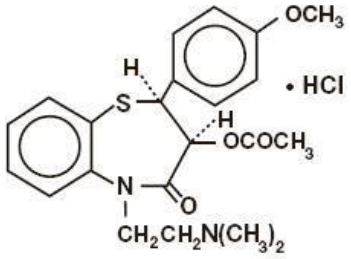
020062Orig1s042

LABELING

CARDIZEM® CD
(diltiazem HCl) Capsules

Rx only

DESCRIPTION
CARDIZEM® (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5*H*)-one, 3-(acetyloxy)-5-[2-(dimethylamino) ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-*cis*-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. CARDIZEM CD is formulated as a once-a-day extended-release capsule containing 120 mg, 180 mg, 240 mg, 300 mg, or 360 mg diltiazem hydrochloride.

Capsules also contain: black iron oxide (300 mg), FD&C Blue #1, gelatin, hypromellose, magnesium stearate, microcrystalline cellulose, polyacrylate dispersion 30%, polysorbate, povidone, simethicone, sucrose stearate, talc, and titanium dioxide.

For oral administration.

CLINICAL PHARMACOLOGY
The therapeutic effects of CARDIZEM CD are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action
Hypertension. CARDIZEM CD produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina. CARDIZEM CD has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal workloads. Diltiazem has

been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels that cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

In hypertensive patients, CARDIZEM CD produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, CARDIZEM CD lowered supine diastolic blood pressure in an apparent linear manner over the entire dose range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were –2.9, –4.5, –6.1, –9.5, and –10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. CARDIZEM CD decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Chronic therapy with CARDIZEM CD produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. CARDIZEM CD reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

In a double-blind, parallel dose-response study of doses from 60 mg to 480 mg once daily, CARDIZEM CD increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69, and 68 seconds, respectively. As doses of CARDIZEM CD were increased, overall angina frequency was decreased. CARDIZEM CD, 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the CARDIZEM CD treatment group was the same as the placebo group.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM to patients in doses of up to 540 mg/day has resulted in small increases in PR interval and on occasion produces abnormal prolongation (see **WARNINGS**).

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. CARDIZEM undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69%

increase in bioavailability in the hepatically impaired patients. A single study in nine patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM CD Capsules. When compared to a regimen of CARDIZEM tablets at steady-state, more than 95% of drug is absorbed from the CARDIZEM CD formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When CARDIZEM CD was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with CARDIZEM tablets and CARDIZEM SR capsules is observed. As the dose of CARDIZEM CD capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area-under-the-curve of 2.7 times. When the dose is increased from 240 mg to 360 mg, there is an increase in the area-under-the-curve of 1.6 times.

In an *in vitro* dissolution study, the release rate of diltiazem from CARDIZEM CD increased significantly as the alcohol percentage in the dissolution medium increased. The effect of alcohol on the release rate may lead to a change in the pharmacokinetics of diltiazem, such as a more rapid absorption and/or an increase in the systemic exposure of diltiazem (see **PRECAUTIONS**, Drug Interactions).

INDICATIONS AND USAGE

CARDIZEM CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

CARDIZEM CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem (see **ADVERSE REACTIONS**).

2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some (see **PRECAUTIONS**).

PRECAUTIONS

General

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. Laboratory parameters of renal and hepatic function should be monitored at regular intervals. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see **ADVERSE REACTIONS**) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Because of the potential for additive effects, slow titration is warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction (see **WARNINGS**). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM (see **WARNINGS**).

Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, titrate anesthetics and calcium blockers slowly.

Benzodiazepines. Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5- to 2.5-fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both midazolam and triazolam.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see **WARNINGS**).

Buspirone. In nine healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5-fold and C_{max} 4.1-fold compared to placebo. The $T_{1/2}$ and T_{max} of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration, and should be based on clinical assessment.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases.

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Clonidine. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with diltiazem. Monitor heart rate in patients receiving concomitant diltiazem and clonidine.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Monitor digoxin levels when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization (see **WARNINGS**).

Quinidine. Diltiazem significantly increases the $AUC_{(0-\infty)}$ of quinidine by 51%, $T_{1/2}$ by 36%, and decreases its CL_{oral} by 33%. Monitor for quinidine adverse effects and adjust the dose accordingly.

Rifampin. Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Avoid coadministration of diltiazem with rifampin or any known CYP3A4 inducer.

Statins. Diltiazem is an inhibitor of CYP3A4 and has been shown to increase significantly the AUC of some statins. The risk of myopathy and rhabdomyolysis with statins metabolized by CYP3A4 may be increased with concomitant use of diltiazem. When possible, use a non-CYP3A4-metabolized statin together with diltiazem; otherwise, monitor for signs and symptoms of any statin related adverse events, and adjust the doses accordingly.

In a healthy volunteer cross-over study (N=10), co-administration of a single 20 mg dose of simvastatin at the end of a 14 day regimen with 120 mg BID diltiazem SR resulted in a 5-fold increase in mean simvastatin AUC versus simvastatin alone. Subjects with increased average steady-state exposures of diltiazem showed a greater fold increase in simvastatin exposure. Computer-based simulations showed that at a daily dose of 480 mg of diltiazem, an 8- to 9-fold mean increase in simvastatin AUC can be expected. If coadministration of simvastatin with diltiazem is required, limit the daily doses of simvastatin to 10 mg and diltiazem to 240 mg.

In a ten-subject randomized, open label, 4-way cross-over study, coadministration of diltiazem (120 mg BID diltiazem SR for 2 weeks) with a single 20 mg dose of lovastatin resulted in 3- to 4-fold increase in mean lovastatin AUC and C_{max} versus lovastatin alone. In the same study, there was no significant change in 20 mg single dose pravastatin AUC and C_{max} during diltiazem

coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Alcohol: Alcohol increases the rate at which CARDIZEM CD releases diltiazem in vitro. This effect may lead to more rapid absorption and an increase in the systemic exposure of diltiazem, and associated dose-related adverse reactions. Avoid consumption of alcohol with CARDIZEM CD (see **CLINICAL PHARMACOLOGY**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of diltiazem 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.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined		
Adverse Reactions	**Cardizem CD (n=607)**	**Placebo (n=301)**
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
Asthenia	1.8%	1.7%

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Congestive heart failure, palpitations, syncope, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see **WARNINGS, Acute Hepatic Injury**), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: acute generalized exanthematous pustulosis, allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, photosensitivity (including lichenoid keratosis and hyperpigmentation at sun-exposed skin

areas), purpura, retinopathy, myopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Because of its extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been reports of diltiazem overdose in amounts ranging from <1 g to 18 g. Of cases with known outcome, most patients recovered and in cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine, as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or norepinephrine).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

Patients controlled on diltiazem alone or in combination with other medications may be switched to CARDIZEM CD capsules at the nearest equivalent total daily dose. Higher doses of CARDIZEM CD may be needed in some patients. Monitor patients closely. Subsequent titration to higher or lower doses may be necessary. There is limited general clinical experience with doses above 360 mg, but doses to 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

Hypertension. Adjust dosage to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, schedule dosage adjustments accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

Angina. Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily. When necessary, titration may be carried out over a 7- to 14-day period.

Concomitant Use with Other Cardiovascular Agents

1. **Sublingual NTG.** May be taken as required to abort acute anginal attacks during CARDIZEM CD (diltiazem hydrochloride) therapy.
2. **Prophylactic Nitrate Therapy.** CARDIZEM CD may be safely coadministered with short- and long-acting nitrates.
3. **Beta-blockers** (see **WARNINGS** and **PRECAUTIONS**).
4. **Antihypertensives.** CARDIZEM CD has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of CARDIZEM CD or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

CARDIZEM® CD
(diltiazem hydrochloride)
Capsules

Strength	Quantity	NDC Number	Description
120 mg	30 btl 90 btl	0187-0795-30 0187-0795-42	Light turquoise blue/light turquoise blue capsule imprinted with cardizem CD and 120 mg on one end.

CARDIZEM® CD **(diltiazem hydrochloride)** **Capsules**			
Strength	**Quantity**	**NDC Number**	**Description**
180 mg	30 btl 90 btl	0187-0796-30 0187-0796-42	Light turquoise blue/blue capsule imprinted with cardizem CD and 180 mg on one end.
240 mg	30 btl 90 btl	0187-0797-30 0187-0797-42	Blue/blue capsule imprinted with cardizem CD and 240 mg on one end.
300 mg	30 btl 90 btl	0187-0798-30 0187-0798-42	Light gray/blue capsule imprinted with cardizem CD and 300 mg on one end.
360 mg	90 btl	0187-0799-42	Light blue/white capsule imprinted with cardizem CD and 360 mg on one end.

Storage Conditions: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Avoid excessive humidity.

Manufactured in Canada by:
Valeant Pharmaceuticals International, Inc.
Steinbach, MB R5G 1Z7 Canada

Distributed by: **Valeant Pharmaceuticals North America LLC**
Bridgewater, NJ 08807, USA

9474000
Rev. 06/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020062Orig1s042

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	020062
Submission Type	Supplement – Prior Approval
Submission Date	09-15-2015
Applicant Name	Valeant Pharmaceuticals North America LLC
Brand Name	Cardizem® CD
Generic Name	Diltiazem Hydrochloride
Indication	Treatment of hypertension and management of chronic stable angina and angina due to coronary artery spasm
Dosage Form	Extended release (b) (4) capsule
Dosage Strength	360 mg
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
Primary Reviewer	Venkateswaran Chithambaram Pillai, PhD
Secondary Reviewer	Sudharshan Hariharan, PhD

TABLE OF CONTENTS

1. BACKGROUND

This prior approval supplement (PAS) submission provides supportive evidence for a change to the drug product manufacturing site and formulation changes. The formulation for Cardizem® CD is being changed to a [(b) (4)] formulation from the original approved [(b) (4)]t formulation. Both the new and approved formulations are capsules filled with extended-release [(b) (4)]. The post-approval formulation change is because the current manufacturer of the approved Cardizem® CD formulation i.e., Sanofi at Kansas City, MO, informed the applicant that they would no longer be able to supply Cardizem® CD. Due to the complexity of the manufacturing process with Cardizem® CD, the applicant considered the technology transfer to a new vendor unfeasible. Instead, the applicant is proposing to switch to an existing facility in Steinbach, Canada, that manufactures an approved generic version of Cardizem® CD (Valeant's approved generic, ANDA 75116, 1999) [(b) (4)]

The proposed clinical program in support of the new formulation of Cardizem® CD consists of (i) bioequivalence study between the new [(b) (4)] and original approved Cardizem® CD [(b) (4)] at 360 mg (V01-DLZM-102), (ii) a food effect study to evaluate the impact of a high fat meal on the pharmacokinetics (PK) of diltiazem following administration of new Cardizem® CD at 360 mg (V01-DLZM-103), and (iii) in vitro dissolution study to evaluate the impact of varying alcohol content on the release performance of diltiazem from the new Cardizem® CD formulation at 360 mg (in vitro alcohol dose dumping).

2. RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP I) accepts the findings of studies V01-DLZM-102 and V01-DLZM-103 and recommends approval of the new Cardizem® CD extended release formulation of diltiazem HCl [(b) (4)] based on bioequivalence to original approved Cardizem® CD [(b) (4)]

3. SUMMARY

- Ninety percent confidence interval of the geometric mean ratio for C_{max} and $AUC_{0\text{-}inf}$ of diltiazem between test (new formulation of Cardizem® CD 360 mg; [(b) (4)] in capsule) and reference (original approved Cardizem® CD 360 mg; [(b) (4)] in capsule) products were contained within the bioequivalence goal posts of 80-125%. Therefore, the new Cardizem® CD formulation is bioequivalent to the original approved Cardizem® CD.

- PK of diltiazem following administration of the test product was similar between fasting and fed conditions. Therefore, the new Cardizem® CD formulation can be administered without regards to meals. This is consistent with the findings for original approved Cardizem® CD (reference product) which also does not have a food effect.

- The overall PK variability of diltiazem is similar between the test and reference products (approx. 40%). The residual variability of diltiazem from the non-replicate crossover study is 21, 16, and 16% for C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$., respectively. An estimate of the true within subject variability of diltiazem for the test product cannot be obtained because a replicate crossover study was not performed.

- The Office of Study Integrity and Surveillance (OSIS) performed bio-analytical site inspection of study V01-DLZM-102 at [redacted] (b) (4) and recommended acceptance of PK data for Agency review.

- The in vitro dissolution study with varying alcohol content was reviewed by the Office of Product Quality (OPQ) and showed potential for alcohol dose dumping. The product insert will be updated with a warning to avoid consumption of alcohol with drug product.

4. APPENDIX (INDIVIDUAL STUDY REVIEWS)

Bioequivalence Study

Study #: V01-DLZM-102	**Study Period:** 15 February 2015 – 04 March 2015
Study Site: (b) (4)	**Investigator:** Eric Sicard, M.D.
Title	An open-label, randomized two-treatment crossover bioequivalence study comparing a new formulation of Cardizem CD 360 mg capsule versus the approved Cardizem CD 360 mg capsule in healthy male and female subjects

Study Design

☑ Bioequivalence	☐ Absolute Bioavailability	☐ Relative Bioavailability

Dose **360 mg** Randomization **Yes** Blinding **No** Type **Fasting** Center **Single**
Period **Two** Population **Healthy volunteers**

	Length (Days)	In Clinical Unit (Yes/No)
Screening	-21 to -3	No
Period	5 days/period for two periods	Yes
Washout	4	No

Treatments:

	Test	Reference
Dosage Form	Cardizem extended release (b) (4) in capsules	Cardizem extended release (b) (4) in capsules
Dosage Strength	360 mg	360 mg
Batch #	14L075P	14K020P
Administration	Oral	Oral

☑ Fast ☐ Fed ☑ With Water ☐ Without Water

Interfering Substances Excluded	None
Sampling Times	0 (pre-dose), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 48 and 60 h after drug administration
PK Parameters	C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$
Statistical/PK Analysis	The pharmacokinetic parameters (C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$) of test and reference formulations of diltiazem were compared by geometric mean ratio (Test/RLD) and 90% confidence interval estimates. Two one-sided tests procedure were used for the construction of 90% confidence intervals for the geometric mean ratios of PK parameters between test and reference formulations. If the confidence intervals for PK parameters of diltiazem were within 80-125%, the test formulation is considered to be bioequivalent to reference formulation. Descriptive statistics were used to summarize the PK parameters.

Analytical Method

Method Type	HPLC-MS/MS	Matrix	Human Plasma
Analytes	Diltiazem, desmethyl diltiazem and desacetyl diltiazem		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Reviewer's comment: Bio-analytical method used for the quantitation of diltiazem, desmethyl diltiazem and desacetyl diltiazem in human plasma were appropriately validated as per Guidance for Industry: Bioanalytical Method Validation.

Results

Study Population

Randomized	Yes
Treated	72 (test)/70(reference)
Completed	68
Discontinued due to AE	1
PK Population/Safety Population	70/(72 (test) & 70 reference)
Age [Median (range)]	33.5 (19-45)
Male/Female	43/29
Race (Caucasian/Black/Asian/Hispanic)	Caucasian: 62 ; Black: 5 ; Asian: 2 ; Other: 3

Pharmacokinetics

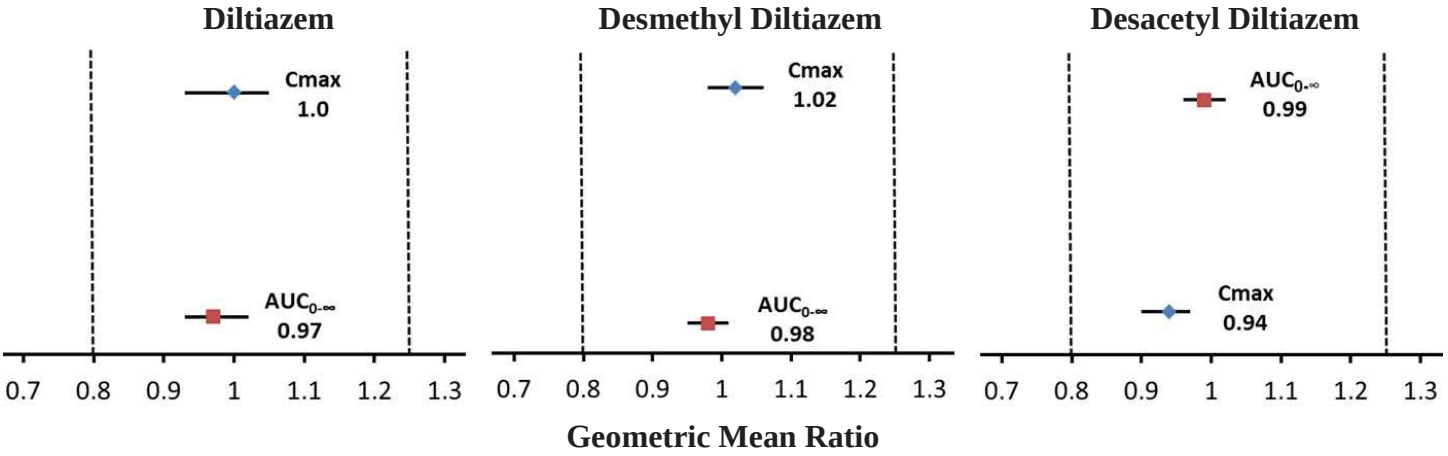


Figure 1: Geometric mean ratio (Test/Reference) for area under the plasma concentration-time curve ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of diltiazem, desmethyl diltiazem and desacetyl diltiazem in healthy volunteers. The error bars represent the 90% CI around GMR.

Pharmacokinetic Parameters

Pharmacokinetic parameters of diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (ng/ml)	160 (41)	160 (38)
AUC_{0-Last} (ng.h/ml)	3020 (40)	3130 (42)
$AUC_{0-\infty}$ (ng.h/ml)	3080 (40)	3190 (41)
T_{max} (h)	12 (8-18)	16 (6-20)
$T_{1/2}$ (h)	7.6 (17%)	7.1 (16%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Pharmacokinetic parameters of desmethyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (ng/ml)	46 (29)	45 (26)
AUC_{0-Last} (ng.h/ml)	1160 (29)	1190 (29)
$AUC_{0-\infty}$ (ng.h/ml)	1190 (29)	1220 (30)
T_{max} (h)	14 (8-24)	16 (6-24)
$T_{1/2}$ (h)	8.9 (16%)	8.5 (15%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

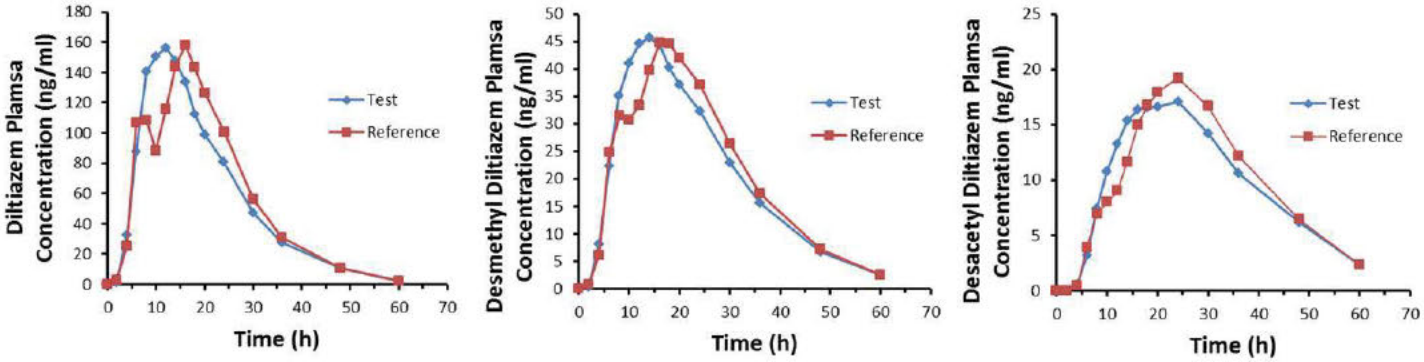
Pharmacokinetic parameters of desacetyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (ng/ml)	16 (71)	17 (79)
$AUC_{0\text{-}Last}$ (ng.h/ml)	449 (88)	458 (94)
$AUC_{0\text{-}\infty}$ (ng.h/ml)	469 (99)	475 (102)
T_{max} (h)	20 (10-36)	24 (16-30)
$T_{1/2}$ (h)	10 (22%)	9.6 (21%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Pharmacokinetic Profile

Figure 2: Average plasma concentration-time profiles of diltiazem, desmethyl diltiazem and desacetyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.



Reviewer's comment: The study design used for this bioequivalence study, collected PK sampling time points and performed statistical analysis are acceptable.

Site Inspection

Requested: ☑ Yes ☐ No **Performed:** ☑ Yes ☐ No ☐ NA

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

Bioequivalence is demonstrated between the test (Cardizem® CD 360 mg [redacted] (b) (4) capsule formulation) and reference (original approved Cardizem® CD 360 mg [redacted] (b) (4) formulation) products.

Food Effect Study

Study #: V01-DLZM-103	**Study Period:** 09 March 2015 – 19 March 2015
Study Site: (b) (4)	**Investigator:** Eric Sicard, M.D.
Title	An open-label, randomized, single-dose, 2-way crossover study to evaluate the impact of a high-fat meal on the pharmacokinetics of diltiazem HCl following administration of a 360 mg capsule dose of diltiazem HCl in healthy male and female subjects
Rationale	To evaluate the impact of high fat meal on the pharmacokinetics of diltiazem following administration of the test product i.e., Cardizem® CD 360 mg (b) (4) capsule formulation.

Study Design

☐ Bioequivalence	☐ Absolute Bioavailability	☑ Relative Bioavailability

Dose **360 mg** Randomization **Yes** Blinding **No** Type **Food effect** Center **Single**
Period **Two** Population **Healthy volunteers**

	Length (Days)	In Clinical Unit (Yes/No)
Screening	-28 to -2	No
Period	4 days/period for two periods	Yes
Washout	4	No

Treatments:

	Test (fed)	Reference (fasted)
Dosage Form	Extended release (b) (4) (b) (4) in capsules	Extended release (b) (4) (b) (4) in capsules
Dosage Strength	360 mg	360 mg
Batch #	14L075P	14L075P
Administration	Oral	Oral

☑ Fast ☑ Fed ☑ With Water ☐ Without Water

Interfering Substances Excluded	None
Sampling Times	0 (pre-dose), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 48 and 60 h after drug administration
PK Parameters	C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$
Statistical/PK Analysis	The pharmacokinetic parameters (C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$) of test and reference formulations of diltiazem were compared by geometric mean ratio (Test/RLD) and 90% confidence interval estimates. Two one-sided tests procedure were used for the construction of 90% confidence intervals for the geometric mean ratios of PK parameters between test and reference formulations. If the confidence intervals for PK parameters of diltiazem were within 80-125%, the test formulation is considered to be bioequivalent to reference formulation. Descriptive statistics were used to summarize the PK parameters.

Analytical Method

Method Type	HPLC-MS/MS	Matrix	Human Plasma
Analytes	Diltiazem, desmethyl diltiazem and desacetyl diltiazem		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Reviewer's comment: Bio-analytical method used for the quantitation of diltiazem, desmethyl diltiazem and desacetyl diltiazem in human plasma were appropriately validated as per Guidance for Industry: Bioanalytical Method Validation.

Results

Study Population

Randomized	Yes
Treated	23 (test) & 22 (reference)
Completed	22
Discontinued Due to AE	0
PK Population/Safety Population	22/23
Age [Median (range)]	29 (22-44)
Male/Female	10/13
Race (Caucasian/Black/Asian/Hispanic)	Caucasian: 18 ; Black: 4 ; Asian: 1

Pharmacokinetics

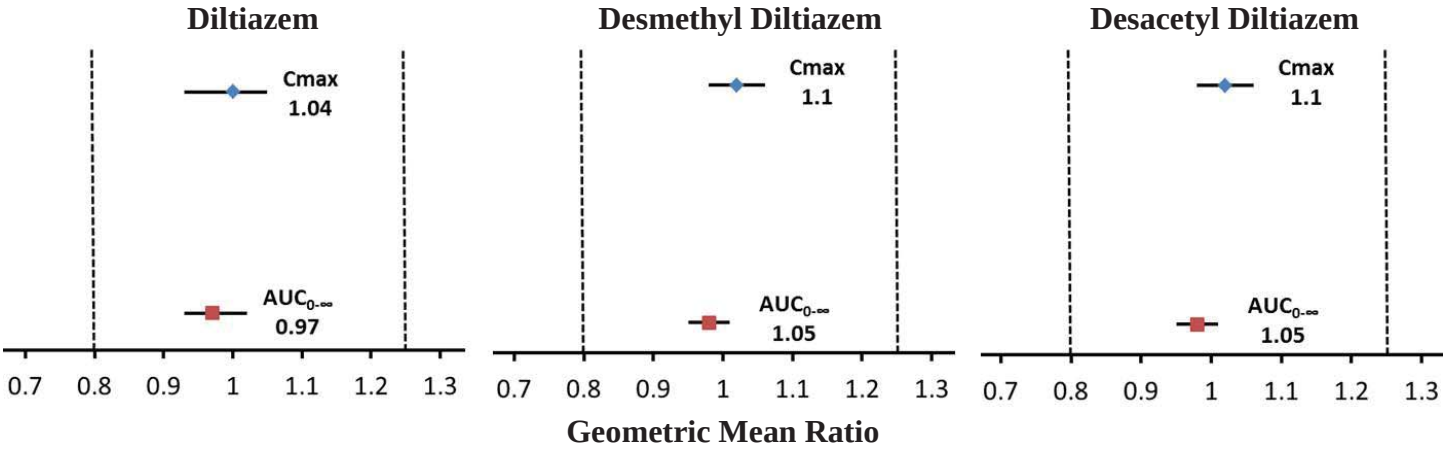


Figure 1: Geometric mean ratio (Test[fed]/Reference[fasted]) for area under the plasma concentration-time curve ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of diltiazem, desmethyl diltiazem and desacetyl diltiazem in healthy volunteers. The error bars represent the 90% CI around GMR.

Pharmacokinetic Parameters

Pharmacokinetic parameters of diltiazem following oral administration of test (fed) and reference (fasted) Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test (fed)	RLD (fasted)
C_{max} (ng/ml)	184 (37)	177 (69)
AUC_{0-Last} (ng.h/ml)	3250 (41)	3350 (49)
$AUC_{0-\infty}$ (ng.h/ml)	3320 (40)	3420 (49)
T_{max} (h)	8 (8-14)	12 (8-16)
$T_{1/2}$ (h)	7.9 (12%)	7.9 (20%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Pharmacokinetic parameters of desmethyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test (fed)	RLD (fasted)
C_{max} (ng/ml)	53 (23)	48 (34)
AUC_{0-Last} (ng.h/ml)	1280 (29)	1210 (30)
$AUC_{0-\infty}$ (ng.h/ml)	1190 (29)	1220 (30)
T_{max} (h)	11 (8-16)	14 (10-16)

$T_{1/2}$ (h)	9.4 (12%)	9.5 (24%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

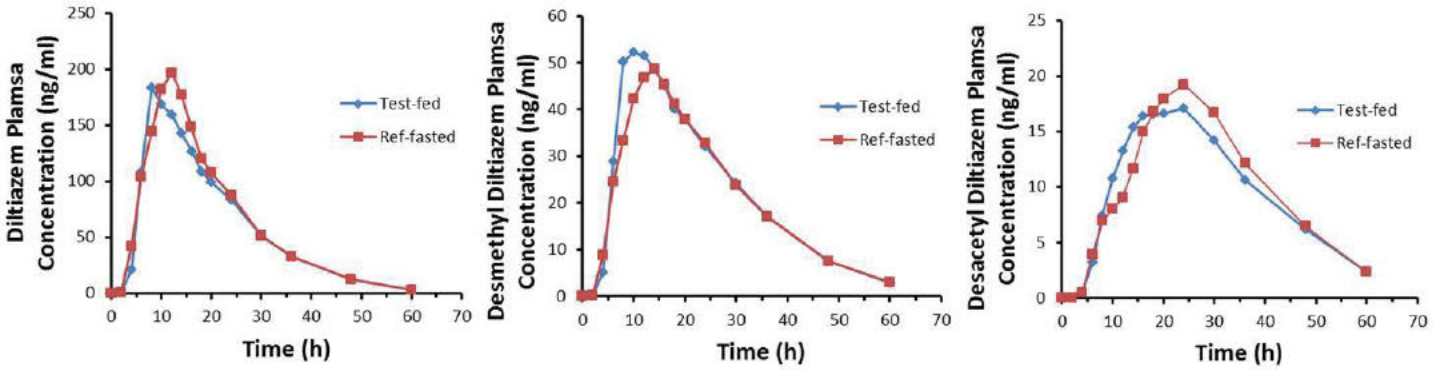
Pharmacokinetic parameters of desacetyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.

Parameter	Geometric mean (% CV)	
	Test (fed)	RLD (fasted)
C_{max} (ng/ml)	14 (50)	16 (59)
$AUC_{0\text{-}Last}$ (ng.h/ml)	397 (70)	428 (74)
$AUC_{0\text{-}\infty}$ (ng.h/ml)	405 (76)	428 (76)
T_{max} (h)	18 (12-30)	20 (10-30)
$T_{1/2}$ (h)	11 (19%)	10.5 (20%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Pharmacokinetic Profile

Figure 2: Average plasma concentration-time profiles of diltiazem, desmethyl diltiazem and desacetyl diltiazem following oral administration of test and reference Cardizem CD 360 mg extended release capsules.



Reviewer's comment: The study design used for the evaluation of food effect on the PK of diltiazem, collected PK sampling time points and performed statistical analysis are acceptable.

Site Inspection

Requested: ☐ Yes ☑ No **Performed:** ☐ Yes ☑ No ☐ NA

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Food has no effect on the pharmacokinetics of diltiazem HCl following administration of Cardizem CD 360 mg (b) (4) in capsule formulation.

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/s/

VENKATESWARAN CHITHAMBARAM PILLAI
06/24/2016

SUDHARSHAN HARIHARAN
06/25/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020062Orig1s042

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

sNDA:	20062/S-042
Drug:	CARDIZEM CD (diltiazem hydrochloride) capsules
Class:	Calcium channel blocker
Applicant:	Valeant Pharmaceuticals North America LLC
Indication: (no change to indication)	CARDIZEM CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications. CARDIZEM CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.
Date of Submission:	15 September 2015
Approval date:	29 June 2016

❖ BACKGROUND

On 15 September 2015, Valeant Pharmaceuticals North America submitted NDA 20062/S-042 which provided for an alternate drug product manufacturer for Cardizem CD 360 mg (new formulation and process change) as well as changes in drug substance manufacturers for diltiazem hydrochloride USP (see description below from the applicant's executive summary). A pharmacokinetic bridging study was conducted (V01-DLZM-102) as well as a meta-analysis (V01-DLZM-900) to support the bridging of the new formulation.

- Drug Substance: Diltiazem Hydrochloride (HCl), USP:
  - The addition of [redacted] (b) (4) as a drug substance manufacturing site – Reference Drug Master File (DMF) [redacted] (b) (4)
  - The addition of [redacted] (b) (4) (manufacturing sites: [redacted] (b) (4) as drug substance manufacturing sites – Reference DMF [redacted] (b) (4)
- Drug Product: Cardizem® CD (diltiazem hydrochloride) Capsules, 360 mg:
  - The addition of Valeant Pharmaceuticals International Inc. [VPII], Steinbach, Manitoba, Canada as a drug product manufacturing site.
  - A new formulation and process change is proposed.

This supplement provides for the manufacturing site transfer for only the 360 mg dose. Per the applicant, the manufacturing site transfer for the lower strengths will be submitted in a subsequent supplement.

This supplement also provided for labeling changes as a result of an in vitro alcohol dose dumping study. The CSR for study V01-DLZM-103, an in vivo food effect study, was also included in this submission. However, the findings from this study did not warrant labeling changes.

❖ LABELING REVIEW

The summary below outlines all changes made to the current approved label as well as the carton/container for the 360 mg dose. The following is a summary of changes that were agreed to by both the Agency and the applicant:

USPI

- Minor editorial changes throughout
- Description section – updates to composition of drug product
- Clinical Pharmacology and Drug Interaction sections – Updated with language pursuant to the in vitro/alcohol interaction study
- Adverse Reactions section – reactions removed that were duplicative with other terms already described, uninformative, or not considered to be caused by drug
- Overdose section – language regarding intravenous calcium has been revised for consistency with other approved diltiazem products
- How Supplied section – removal of 100 count bottles of 120, 180, and 240 mg strengths; change in manufacturer

Carton/Container labeling

Cardizem CD container 360 mg – updated with new manufacturer information

❖ DISCIPLINE REVIEWS

Discipline reviews were conducted by clinical pharmacology (ChithambaramPillai, 25 June 16), biopharmaceutics (Anand, 12 January 2016) and CMC (Raman, 15 March 2016).

❖ INSPECTIONS

The Office of Study Integrity and Surveillance (OSIS) conducted a biopharmaceutical site inspection for Study V01-DLZM-102 and the site was found to be acceptable (Chen, 25 April 2016).

❖ CONCLUSION

The revisions to the PI and carton/container were found acceptable to both the Division and the applicant. The approval letter was signed by Norman Stockbridge, MD, PhD (Director, Division of Cardiovascular & Renal Products) on 29 June 2016.

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/s/

BRIDGET E KANE
06/29/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 25, 2016

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products (DCRP)
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director (acting), Office of Bioequivalence
Office of Generic Drugs

FROM: Kara Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for studies submitted to NDA 020062, (b) (4) (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies V01-DLZM-102, (b) (4) (b) (4) (b) (4).

We recommend that the bioanalytical data for studies V01-DLZM-102, [redacted] (b) (4) [redacted] (b) (4) be accepted for further Agency review.

Studies Audited during this Inspection:

Study number: V01-DLZM-102 (NDA 020062)
Study Title: "An open-label, randomized two-treatment crossover bioequivalence study comparing a new formulation of Cardizem CD 360 mg capsule versus the approved Cardizem CD 360 mg capsule in healthy male and female subjects"
Sample Analysis: March 13 to 24, 2015

Study number: [redacted] (b) (4)
Study Title:
Sample Analysis:

Study number: [redacted] (b) (4)
Study Title:
Sample Analysis:

Study number: [redacted] (b) (4)
Study Title:
Sample Analysis:

Study number: [redacted] (b) (4)
Study Title:
Sample Analysis:

Study number: [redacted] (b) (4)
Study Title:

(b) (4)

Study number: (b) (4)
Study Title:

Sample Analysis:

Study number: (b) (4)
Study Title:

Sample Analysis:

Study number: (b) (4)
Study Title:

Sample Analysis:

OSIS scientists Kara Scheibner, Ph.D. and Xikui Chen, Ph.D. conducted the inspection of the bioanalytical portion of the studies from April 11-15, 2016. The audit covered the bioanalytical method validations and sample analyses for diltiazem, methylphenidate, cinacalcet, exemestane and posaconazole. The audit included a thorough review of facilities and equipment, review of study records and correspondence, and interviews and discussions with (b) (4) management and staff. As a global assessment of the firm's bioanalytical operations, several key components in the study conduct were selected for audit to evaluate the firm's bioanalytical operations since the previous inspection.

At the conclusion of the inspection, no Form FDA 483 was issued at (b) (4).

Recommendation:

Following review of the EIR, the analytical data for studies V01-DLZM-102, (b) (4) (b) (4) were found to be reliable. Therefore, we recommend that the data from the bioanalytical portion of these studies be accepted for further Agency review.

Kara Scheibner, Ph.D.
DGDBE, OSIS

Xikui Chen, Ph.D.
DGDBE, OSIS

Final Classification:

NAI: (b) (4)

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Chen/Scheibner
Draft: XC 04/21/2016
Edit: KS 04/21/2016; MFS 04/21/2016; JC 04/25/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Bioanalytical Sites/ (b) (4)
(b) (4)

FACTS: 11632350

Attachment 1: Applications covered during the inspection

Application (OSIS file #)	FEI	Location
NDA 20062 (BE 7091) [redacted] (b) (4)	3006174712	[redacted] (b) (4)

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/s/

XIKUI CHEN
04/25/2016

SEONGEUN CHO
04/25/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020062Orig1s042

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OSIS Consult
Request for Biopharmaceutical Inspections

Date	22 January 2016
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sharon Turner-Rinehardt, RAC Team Lead (Acting), Project Management Team Office of Study Integrity and Surveillance sharon.turner-rinehardt@fda.hhs.gov
Consulting Office/Division	ODE I /DCRP
Project Manager	Alison Blaus
Application Type	PEPFAR? ☐ Yes ☒ No
	☒ NDA ☐ BLA ☐ ANDA ☐ Biosimilar
Application Number	020062 / s-042
Drug Product	Diltiazem Hydrochloride 360 mg extended release capsule
Sponsor Name	Valeant Pharmaceuticals North America LLC
Sponsor Address	Attn: Vijayata Sharma, Ph.D. Manager, Regulatory Affairs CMC 400 Somerset Corporate Blvd. Bridgewater, NJ 08807
US Agent (if applicable)	n/a
US Agent Address	n/a
Electronic Submission	☒ Yes ☐ No
Goal Date	15 March 2016
Action Goal Date	n/a
Requested Review Goal Date	ASAP

Inspection Request Detail (All fields should be fill out completely)				
Study #1				
Study Number	V01-DLZM-102			
Study Title	An open-label, randomized two-treatment crossover bioequivalence study comparing a new formulation of Cardizem CD 360 mg capsule versus the approved Cardizem CD 360 mg capsule in healthy male and female subjects			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)
☐ Inspection Request - Clinical Site		☒ Inspection Request - Analytical Site		
Facility #1 Name: Address: (Tel) (Fax)		(b) (4)		
Clinical Investigator:		Principal Analytical Investigator:		

(email)	(email)
Check one: ☐ Routine inspection ☐ For cause	Check one: ☒ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☐ Study Report:	☒ Validation Report: (5.3.1.2) ☒ Bioanalytical Report: (5.3.1.2)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director.

I. Appendix

Specific Items To be Addressed During the Inspection
This is a routine inspection for the bioanalytical aspects (method validation and bioanalysis) of the study (V01-DLZM-102) which forms the basis for PK bridge.

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/s/

ALISON L BLAUS
01/25/2016

Blaus, Alison

From: Lyons, Darrell
Sent: Tuesday, December 08, 2015 8:29 AM
To: Blaus, Alison
Subject: RE: N20062S042 IQA DCRP KR

Hi Again,

Since container remains the same with only change in manufacturer name, DMEPA do not need to review.

Thanks,

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

From: Lyons, Darrell
Sent: Tuesday, December 08, 2015 8:16 AM
To: Blaus, Alison
Subject: RE: N20062S042 IQA DCRP KR

Hi Alison,

I'll confirm with DMEPA and get back to you.

Thanks,

Darrell

From: Blaus, Alison
Sent: Monday, December 07, 2015 1:34 PM
To: Lyons, Darrell
Subject: FW: N20062S042 IQA DCRP KR

Hi Darrell

Can you confirm the DMEPA does not need to review changes to a manufacturer names on a container label? These were approved container label and they just changed the manufacturer from one to another.

Thank you –

Alison

From: Dong, Zedong
Sent: Thursday, November 12, 2015 3:54 PM
To: Blaus, Alison; Raman, Kris P; Knight, Yvonne
Cc: Raghavachari, Ramesh; Anand, Om; Chikhale, Elsbeth G; Dorantes, Angelica
Subject: RE: N20062S042 IQA DCRP KR

Thanks, Alison! I am copying the biopharm folks in the email, so they will know that OCP will review the in vivo data. Also, can you please check with DMEPA whether they need to be involved?

Thanks again,

Zedong

From: Blaus, Alison
Sent: Thursday, November 12, 2015 3:49 PM
To: Dong, Zedong; Raman, Kris P; Knight, Yvonne
Cc: Raghavachari, Ramesh
Subject: RE: N20062S042 IQA DCRP KR

Hi Zedong

I'm sorry for the delay! Yes, this should be a PAS and managed by DCRP. I talked to OCP and they will handle the in vivo study while OPQ will handle the in vitro study. Does that sound good?

Thank you for reminding me today –

Alison

From: Dong, Zedong
Sent: Thursday, November 12, 2015 3:30 PM
To: Raman, Kris P; Knight, Yvonne
Cc: Raghavachari, Ramesh; Blaus, Alison
Subject: RE: N20062S042 IQA DCRP KR
Importance: High

Hi Alison,

Just wonder if you have any update whether DCRP would like to manage the supplement. Would really appreciate if you could let us know any decision either way.

Thanks,

Zedong

From: Dong, Zedong
Sent: Tuesday, November 10, 2015 5:16 PM
To: Raman, Kris P; Knight, Yvonne
Cc: Dong, Zedong; Raghavachari, Ramesh; Blaus, Alison
Subject: N20062S042 IQA DCRP KR

Initial Quality Assessment – OLDP Division of Post Marketing Activities I (September, 2015)

NDA Supplement #: 20062/S042

Applicant: Valeant Pharmaceuticals North America LLC

Product: Cardizem

Receipt Date: 09/15/2015 PDUFA Goal Date: 01/15/2015

Final Category: PA

Consults: Biopharmaceutics, Clinical Pharmacology, facility entry into panorama

Comments: The Prior-Approval supplement provides for the addition of two new API suppliers (b) (4) (b) (4), addition of Valeant Pharmaceuticals International Inc. (Steinbach, Manitoba, Canada) as a DP manufacturing site, as well as a new formulation and manufacturing process. The submission also includes reports for in vivo bioequivalence, in vivo food effect, and in vitro alcohol dose dumping evaluations. A revised PI is also provided based on the in vitro dose dumping study.

DCRP project manager (Alison Blaus) was contacted regarding whether DCRP or OPQ should manage the supplement. There is no decision yet from DCRP as of this IQA. I strongly suggest DCRP manage this supplement due to the in vivo BE data (as well as other efficacy and safety information provided in the submission), and the labeling changes based on the in vitro dose dumping study.

Consults from Biopharmaceutics and Clinical Pharmacology are needed. Clinical Pharmacology will also need to decide whether an inspection is needed for the in vivo BE data. The facility information was entered into Panorama, except for excipients testing sites, which seems fine.

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/s/

ALISON L BLAUS
12/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20062/S-042

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Valeant Pharmaceuticals North America, LLC
Attention: Vijayata Sharma, Ph.D.
Manager, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Dr. Sharma:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 20062

SUPPLEMENT NUMBER: 042

PRODUCT NAME: CARDIZEM (diltiazem HCl) Capsules, 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

DATE OF SUBMISSION: 15 September 2015

DATE OF RECEIPT: 15 September 2015

This supplemental application proposes changes to the drug product description as well additional language regarding use of the product with alcohol.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular & Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not

obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please call:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief Project Management Staff
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
12/07/2015