CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-526/S-007

Trade Name: Ranexa

Generic Name: Ranolazine

Sponsor: CV Therapeutics

Approval Date: March 26, 2009

Indications: For the treatment of chronic angina. Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526/S-007

CV Therapeutics
Attention: Carol D. Karp
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your supplemental new drug application dated November 25, 2008, received November 26, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Ranexa (ranolazine) 500 mg Extended-Release (ER) Tablets.

This supplemental new drug application provides CMC information to support the registration of Patheon as a second supplier of the 500 mg tablet. We also note minor revisions to the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and **USE IN SPECIFIC POPULATIONS** sections of the labeling.

We have completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert) submitted November 25, 2008. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-526 S-007."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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 Mr. John David, Regulatory Project Manager at (301) 796-1059.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: enclosed labeling (text for the package insert)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

3/26/2009 07:46:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Ranexa (ranolazine) extended-release tablets
Initial U.S. Approval: 2006

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

Indications and Usage (1)	11/2008
Contraindications (4)	11/2008

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

Ranexa is indicated for the treatment of chronic angina. (1)

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

500 mg twice daily and increase to 1000 mg twice daily, based on clinical symptoms (2.1)

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

Extended-release tablets: 500 mg, 1000 mg (3)

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

- Use with strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir) (4, 7.1)
- Use with CYP3A inducers (e.g., rifampin, phenobarbital) (4, 7.1)
- Use in patients with clinically significant hepatic impairment (4, 8.6)

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

- QT interval prolongation: Can occur with ranolazine. Little data available on high doses, long exposure, use with QT interval-prolonging drugs, or potassium channel variants causing prolonged QT interval. (5.1)

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

Most common adverse reactions (> 4% and more common than with placebo) are dizziness, headache, constipation, nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact CV Therapeutics at 1-877-CVT-7171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- CYP3A inhibitors: Do not use Ranexa with strong CYP3A inhibitors. With moderate 3A inhibitors (e.g., diltiazem, verapamil, erythromycin), limit maximum dose of Ranexa to 500 mg twice daily. (7.1)
- CYP3A inducers: Do not use Ranexa with CYP3A inducers. (7.1)
- P-gp inhibitors (e.g., cyclosporine): May need to lower Ranexa dose based on clinical response. (7.1)
- Drugs transported by P-gp or metabolized by CYP2D6 (e.g., digoxin, tricyclic antidepressants): May need reduced doses of these drugs when used with Ranexa. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ranexa is indicated for the treatment of chronic angina.

Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Initiate Ranexa dosing at 500 mg twice daily and increase to 1000 mg twice daily, as needed, based on clinical symptoms. Take Ranexa with or without meals. Swallow Ranexa tablets whole; do not crush, break, or chew.

The maximum recommended daily dose of Ranexa is 1000 mg twice daily.

If a dose of Ranexa is missed, take the prescribed dose at the next scheduled time; do not double the next dose.

2.2 Dose Modification

Dose adjustments may be needed when Ranexa is taken in combination with certain other drugs *[see Drug Interactions (7.1)]*. Limit the maximum dose of Ranexa to 500 mg twice daily in patients on diltiazem, verapamil, and other moderate CYP3A inhibitors. Down-titrate Ranexa based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine.

3 DOSAGE FORMS AND STRENGTHS

Ranexa is supplied as film-coated, oblong-shaped, extended-release tablets in the following strengths:

- 500 mg tablets are light orange, with CVT500 on one side
- 1000 mg tablets are pale yellow, with CVT1000 on one side

4 CONTRAINDICATIONS

Ranexa is contraindicated in patients:

- Taking strong inhibitors of CYP3A *[see Drug Interactions (7.1)]*
- Taking inducers of CYP3A *[see Drug Interactions (7.1)]*
- With clinically significant hepatic impairment *[see Use in Specific Populations (8.6)]*

5 WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation

Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.

Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death *[see Clinical Studies (14.2)]*. However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval.

6 ADVERSE REACTIONS

6.1 Clinical Trial 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.

A total of 2,018 patients with chronic angina were treated with ranolazine in controlled clinical trials. Of the patients treated with Ranexa, 1,026 were enrolled in three double-blind, placebo-controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks duration. In addition, upon study completion, 1,251 patients received treatment with Ranexa in open-label, long-term studies; 1,227 patients were exposed to Ranexa for more than 1 year, 613 patients for more than 2 years, 531 patients for more than 3 years, and 326 patients for more than 4 years.

At recommended doses, about 6% of patients discontinued treatment with Ranexa because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on Ranexa than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on Ranexa than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term treatment studies, a similar adverse reaction profile was observed.

The following additional adverse reactions occurred at an incidence of 0.5 to 2.0% in patients treated with Ranexa and were more frequent than the incidence observed in placebo-treated patients:

Cardiac Disorders – bradycardia, palpitations

Ear and Labyrinth Disorders – tinnitus, vertigo

Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting

General Disorders and Administrative Site Adverse Events – peripheral edema

Respiratory, Thoracic, and Mediastinal Disorders – dyspnea

Vascular Disorders – hypotension, orthostatic hypotension

Other (< 0.5%) but potentially medically important adverse reactions observed more frequently with Ranexa than placebo treatment in all controlled studies included: angioedema, renal failure,

eosinophilia, blurred vision, confusional state, hematuria, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

A large clinical trial in acute coronary syndrome patients was unsuccessful in demonstrating a benefit for Ranexa, but there was no apparent proarrhythmic effect in these high-risk patients *[see Clinical Trials (14.2)]*.

Laboratory Abnormalities

Ranexa produces small reductions in hemoglobin A1c. Ranexa is not a treatment for diabetes.

Ranexa produces elevations of serum creatinine by 0.1 mg/dL, regardless of previous renal function. The elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of Ranexa, and is not accompanied by changes in BUN. In healthy volunteers, Ranexa 1000 mg twice daily had no effect upon the glomerular filtration rate. The elevated creatinine levels are likely due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Ranolazine

Ranolazine is primarily metabolized by CYP3A and is a substrate of P-glycoprotein (P-gp).

CYP3A Inhibitors

Do not use Ranexa with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir. Ketoconazole (200 mg twice daily) increases average steady-state plasma concentrations of ranolazine 3.2-fold *[see Contraindications (4)]*.

Limit the dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products. Diltiazem (180–360 mg daily) and verapamil (120 mg three times daily) increase ranolazine steady-state plasma concentrations about 2-fold *[see Dosage and Administration (2.2)]*.

Weak CYP3A inhibitors such as simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

P-gp Inhibitors

Down-titrate Ranexa based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine *[see Dosage and Administration (2.2)]*.

CYP3A and P-gp Inducers

Avoid co-administration of Ranexa and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort. Rifampin (600 mg once daily)

decreases the plasma concentration of ranolazine (1000 mg twice daily) by approximately 95% by induction of CYP3A and, probably, P-gp.

CYP2D6 Inhibitors

The potent CYP2D6 inhibitor, paroxetine (20 mg once daily), increases ranolazine concentrations 1.2-fold. No dose adjustment of Ranexa is required in patients treated with CYP2D6 inhibitors.

Digoxin

Digoxin (0.125 mg) does not significantly alter ranolazine levels.

7.2 Effects of Ranolazine on Other Drugs

In vitro studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A, moderate inhibitors of CYP2D6 and moderate P-gp inhibitors. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Drugs Metabolized by CYP3A

The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each increased about 2-fold in healthy subjects receiving simvastatin (80 mg once daily) and Ranexa (1000 mg twice daily). Dose adjustments of simvastatin are not required when Ranexa is co-administered with simvastatin.

The pharmacokinetics of diltiazem is not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg three times daily and Ranexa 1000 mg twice daily.

Drugs Transported by P-gp

Ranexa (1000 mg twice daily) causes a 1.5-fold elevation of digoxin plasma concentrations. The dose of digoxin may have to be adjusted.

Drugs Metabolized by CYP2D6

Ranolazine or its metabolites partially inhibit CYP2D6. There are no studies of concomitant use of Ranexa with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotics, but lower doses of CYP2D6 substrates may be required.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

In animal studies, ranolazine at exposures 1.5 (rabbit) to 2 (rat) times the usual human exposure caused maternal toxicity and misshapen sternebrae and reduced ossification in offspring. These doses in rats and rabbits were associated with an increased maternal mortality rate *[see Reproductive Toxicology Studies (13.3)]*. There are no adequate well-controlled studies in

pregnant women. Ranexa should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether ranolazine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ranolazine in nursing infants, decide whether to discontinue nursing or to discontinue Ranexa, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the chronic angina patients treated with Ranexa in controlled studies, 496 (48%) were ≥ 65 years of age, and 114 (11%) were ≥ 75 years of age. No overall differences in efficacy were observed between older and younger patients. There were no differences in safety for patients ≥ 65 years compared to younger patients, but patients ≥ 75 years of age on ranolazine, compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. In general, dose selection for an elderly patient should usually start 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.

8.6 Use in Patients with Hepatic Impairment

Ranexa is contraindicated in patients with clinically significant hepatic impairment. Plasma concentrations of ranolazine were increased by 30% in patients with mild (Child-Pugh Class A) and by 60% in patients with moderate (Child-Pugh Class B) hepatic impairment. This was not enough to account for the 3-fold increase in QT prolongation seen in patients with mild to severe hepatic impairment *[see Contraindications (4)]*.

8.7 Use in Patients with Renal Impairment

In patients with varying degrees of renal impairment, ranolazine plasma levels increased up to 50%. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

8.8 Use in Patients with Heart Failure

Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. Ranexa had minimal effects on heart rate and blood pressure in patients with angina and heart failure NYHA Class I to IV. No dose adjustment of Ranexa is required in patients with heart failure.

8.9 Use in Patients with Diabetes Mellitus

A population pharmacokinetic evaluation of data from angina patients and healthy subjects showed no effect of diabetes on ranolazine pharmacokinetics. No dose adjustment is required in patients with diabetes.

Ranexa produces small reductions in HbA1c in patients with diabetes, the clinical significance of which is unknown. Ranexa should not be considered a treatment for diabetes.

10 OVERDOSAGE

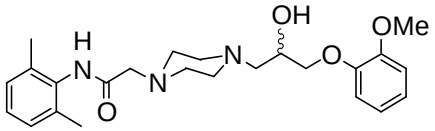
High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting. High intravenous exposure also produces diplopia, paresthesia, confusion, and syncope. In addition to general supportive measures, continuous ECG monitoring may be warranted in the event of overdose.

Since ranolazine is about 62% bound to plasma proteins, hemodialysis is unlikely to be effective in clearing ranolazine.

11 DESCRIPTION

Ranexa (ranolazine) is available as a film-coated, non-scored, extended-release tablet for oral administration.

Ranolazine is a racemic mixture, chemically described as 1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-. It has an empirical formula of $C_{24}H_{33}N_3O_4$, a molecular weight of 427.54 g/mole, and the following structural formula:



Ranolazine is a white to off-white solid. Ranolazine is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Ranexa tablets contain 500 mg or 1000 mg of ranolazine and the following inactive ingredients: carnauba wax, hypromellose, magnesium stearate, methacrylic acid copolymer (Type C), microcrystalline cellulose, polyethylene glycol, sodium hydroxide, and titanium dioxide. Additional inactive ingredients for the 500 mg tablet include polysorbate 80 and FD&C Yellow No. 6 Lake; additional inactive ingredients for the 1000 mg tablet include lactose monohydrate, triacetin, and Iron Oxide Yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current (I_{Na}). However, the relationship of this inhibition to angina symptoms is uncertain.

The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of I_{Kr}, which prolongs the ventricular action potential.

12.2 Pharmacodynamics

Hemodynamic Effects

Patients with chronic angina treated with Ranexa in controlled clinical studies had minimal changes in mean heart rate (< 2 bpm) and systolic blood pressure (< 3 mm Hg). Similar results were observed in subgroups of patients with CHF NYHA Class I or II, diabetes, or reactive airway disease, and in elderly patients.

Electrocardiographic Effects

Dose and plasma concentration-related increases in the QTc interval *[see Warnings and Precautions (5.1)]*, reductions in T wave amplitude, and, in some cases, notched T waves, have been observed in patients treated with Ranexa. These effects are believed to be caused by ranolazine and not by its metabolites. The relationship between the change in QTc and ranolazine plasma concentrations is linear, with a slope of about 2.6 msec/1000 ng/mL, through exposures corresponding to doses several-fold higher than the maximum recommended dose of 1000 mg twice daily. The variable blood levels attained after a given dose of ranolazine give a wide range of effects on QTc. At T_{max} following repeat dosing at 1000 mg twice daily, the mean change in QTc is about 6 msec, but in the 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 msec. In subjects with mild or moderate hepatic impairment, the relationship between plasma level of ranolazine and QTc is much steeper *[see Contraindications (4)]*.

Age, weight, gender, race, heart rate, congestive heart failure, diabetes, and renal impairment did not alter the slope of the QTc-concentration relationship of ranolazine.

No proarrhythmic effects were observed on 7-day Holter recordings in 3,162 acute coronary syndrome patients treated with Ranexa. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with Ranexa (80%) versus placebo (87%), including ventricular tachycardia ≥ 3 beats (52% versus 61%). However, this difference in arrhythmias did not lead to a reduction in mortality, a reduction in arrhythmia hospitalization, or a reduction in arrhythmia symptoms.

12.3 Pharmacokinetics

Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable. For example, at a dose of 1000 mg twice daily, the mean steady-state C_{max} was 2600 ng/mL with 95% confidence limits of 400 and 6100 ng/mL. The pharmacokinetics of the (+) R- and (-) S-enantiomers of ranolazine are similar in healthy volunteers. The apparent terminal half-life of ranolazine is 7 hours. Steady state is generally achieved within 3 days of twice-daily dosing with Ranexa. At steady state over the dose range of 500 to 1000 mg twice daily, C_{max} and $AUC_{0-\tau}$ increase slightly more than proportionally to dose, 2.2- and 2.4-fold, respectively. With

twice-daily dosing, the trough:peak ratio of the ranolazine plasma concentration is 0.3 to 0.6. The pharmacokinetics of ranolazine is unaffected by age, gender, or food.

Absorption and Distribution

After oral administration of Ranexa, peak plasma concentrations of ranolazine are reached between 2 and 5 hours. After oral administration of ^{14}C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from Ranexa tablets relative to that from a solution of ranolazine is 76%. Because ranolazine is a substrate of P-gp, inhibitors of P-gp may increase the absorption of ranolazine.

Food (high-fat breakfast) has no important effect on the C_{max} and AUC of ranolazine. Therefore, Ranexa may be taken without regard to meals. Over the concentration range of 0.25 to 10 μg/mL, ranolazine is approximately 62% bound to human plasma proteins.

Metabolism and Excretion

Ranolazine is metabolized mainly by CYP3A and, to a lesser extent, by CYP2D6. Following a single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and 25% in feces. Ranolazine is metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites has not been well characterized. After dosing to steady state with 500 mg to 1500 mg twice daily, the four most abundant metabolites in plasma have AUC values ranging from about 5 to 33% that of ranolazine, and display apparent half-lives ranging from 6 to 22 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ranolazine tested negative for genotoxic potential in the following assays: Ames bacterial mutation assay, Saccharomyces assay for mitotic gene conversion, chromosomal aberrations assay in Chinese hamster ovary (CHO) cells, mammalian CHO/HGPRT gene mutation assay, and mouse and rat bone marrow micronucleus assays.

There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m^2/day) and 50 mg/kg/day for 24 months in mice (150 mg/m^2/day). These maximally tolerated doses are 0.8 and 0.1 times, respectively, the maximum recommended human dose (MRHD) of 2 grams on a surface area basis. A published study reported that ranolazine promoted tumor formation and progression to malignancy when given to transgenic APC (min/+) mice at a dose of 30 mg/kg twice daily *[see References (15)]*. The clinical significance of this finding is unclear.

13.3 Reproductive Toxicology Studies

Animal reproduction studies with ranolazine were conducted in rats and rabbits.

There was an increased incidence of misshapen sternebrae and reduced ossification of pelvic and cranial bones in fetuses of pregnant rats dosed at 400 mg/kg/day (2 times the MRHD on a surface area basis). Reduced ossification of sternebrae was observed in fetuses of pregnant

rabbits dosed at 150 mg/kg/day (1.5 times the MRHD on a surface area basis). These doses in rats and rabbits were associated with an increased maternal mortality rate.

14 CLINICAL STUDIES

14.1 Chronic Stable Angina

CARISA (Combination Assessment of Ranolazine In Stable Angina) was a study in 823 chronic angina patients randomized to receive 12 weeks of treatment with twice-daily Ranexa 750 mg, 1000 mg, or placebo, who also continued on daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg. Sublingual nitrates were used in this study as needed.

In this trial, statistically significant ($p < 0.05$) increases in modified Bruce treadmill exercise duration and time to angina were observed for each Ranexa dose versus placebo, at both trough (12 hours after dosing) and peak (4 hours after dosing) plasma levels, with minimal effects on blood pressure and heart rate. The changes versus placebo in exercise parameters are presented in Table 1. Exercise treadmill results showed no increase in effect on exercise at the 1000 mg dose compared to the 750 mg dose.

Table 1 Exercise Treadmill Results (CARISA)

	Mean Difference from Placebo (sec)	
Study	**CARISA (N = 791)**	
Ranexa Twice-daily Dose	**750 mg**	**1000 mg**
Exercise Duration		
Trough	24*	24*
Peak	34**	26*
Time to Angina		
Trough	30*	26*
Peak	38**	38**
Time to 1 mm ST-Segment Depression		
Trough	20	21
Peak	41**	35**

* p-value ≤ 0.05 ** p-value ≤ 0.005

The effects of Ranexa on angina frequency and nitroglycerin use are shown in Table 2.

Table 2 Angina Frequency and Nitroglycerin Use (CARISA)

		Placebo	Ranexa 750 mg[a]	Ranexa 1000 mg[a]
Angina Frequency (attacks/week)	N	258	272	261
	Mean	3.3	2.5	2.1
	p-value vs placebo	—	*0.006*	*< 0.001*
Nitroglycerin Use (doses/week)	N	252	262	244
	Mean	3.1	2.1	1.8
	p-value vs placebo	—	*0.016*	*< 0.001*

[a] Twice daily

Tolerance to Ranexa did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of Ranexa.

Ranexa has been evaluated in patients with chronic angina who remained symptomatic despite treatment with the maximum dose of an antianginal agent. In the ERICA (Efficacy of Ranolazine In Chronic Angina) trial, 565 patients were randomized to receive an initial dose of Ranexa 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with Ranexa 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine 10 mg once daily. In addition, 45% of the study population also received long-acting nitrates. Sublingual nitrates were used as needed to treat angina episodes. Results are shown in Table 3. Statistically significant decreases in angina attack frequency ($p = 0.028$) and nitroglycerin use ($p = 0.014$) were observed with Ranexa compared to placebo. These treatment effects appeared consistent across age and use of long-acting nitrates.

Table 3 Angina Frequency and Nitroglycerin Use (ERICA)

		Placebo	Ranexa[a]
Angina Frequency (attacks/week)	N	281	277
	Mean	4.3	3.3
	Median	2.4	2.2
Nitroglycerin Use (doses/week)	N	281	277
	Mean	3.6	2.7
	Median	1.7	1.3

[a] 1000 mg twice daily

Gender

Effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In CARISA, the improvement in Exercise Tolerance Test (ETT) in females was about 33% of that in males at the 1000 mg twice-daily dose level. In ERICA, where the primary endpoint

was angina attack frequency, the mean reduction in weekly angina attacks was 0.3 for females and 1.3 for males.

Race

There were insufficient numbers of non-Caucasian patients to allow for analyses of efficacy or safety by racial subgroup.

14.2 Lack of Benefit in Acute Coronary Syndrome

In a large (n = 6,560) placebo-controlled trial (MERLIN-TIMI 36) in patients with acute coronary syndrome, there was no benefit shown on outcome measures. However, the study is somewhat reassuring regarding proarrhythmic risks, as ventricular arrhythmias were less common on ranolazine *[see Clinical Pharmacology (12.2)]*, and there was no difference between Ranexa and placebo in the risk of all-cause mortality (relative risk ranolazine:placebo 0.99 with an upper 95% confidence limit of 1.22).

15 REFERENCES

M.A. Suckow et al. The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC (min/+) mice. Cancer Letters 209(2004):165−9.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ranexa is supplied as film-coated, oblong-shaped, extended-release tablets in the following strengths:

- 500 mg tablets are light orange, with CVT500 on one side
- 1000 mg tablets are pale yellow, with CVT1000 on one side

Ranexa (ranolazine) extended-release tablets are available in:

	Strength	**NDC Code**
Unit-of-Use Bottle (60 Tablets)	500 mg	67159-112-03
Pharmacy Bottle (500 Tablets)	500 mg	67159-112-04
Unit-of-Use Bottle (60 Tablets)	1000 mg	67159-114-03
Pharmacy Bottle (500 Tablets)	1000 mg	67159-114-04

Store Ranexa tablets at 25°C (77°F) with excursion permitted to 15° to 30°C (59° to 86°F).

17 PATIENT COUNSELING INFORMATION

To ensure safe and effective use of Ranexa, the following information and instructions should be communicated to the patient when appropriate.

Patients should be advised:

- that Ranexa will not abate an acute angina episode

- to inform their physician of any other medications when taken concurrently with Ranexa, including over-the-counter medications
- that Ranexa may produce changes in the electrocardiogram (QTc interval prolongation)
- to inform their physician of any personal or family history of QTc prolongation, congenital long QT syndrome, or if they are receiving drugs that prolong the QTc interval such as Class Ia (e.g., quinidine) or Class III (e.g., dofetilide, sotalol, amiodarone) antiarrhythmic agents, erythromycin, and certain antipsychotics (e.g., thioridazine, ziprasidone)
- that Ranexa should not be used in patients who are receiving drugs that are strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir)
- that initiation of treatment with Ranexa should be avoided during administration of inducers of CYP3A (e.g., rifampin, rifabutin, rifapentin, barbiturates, carbamazepine, phenytoin, St. John's wort)
- to inform their physician if they are receiving drugs that are moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin) or P-gp inhibitors (e.g., cyclosporine)
- that grapefruit juice or grapefruit products should be limited when taking Ranexa
- that Ranexa should generally not be used in patients with clinically significant liver impairment
- that doses of Ranexa higher than 1000 mg twice daily should not be used
- that if a dose is missed, the usual dose should be taken at the next scheduled time. The next dose should not be doubled
- that Ranexa may be taken with or without meals
- that Ranexa tablets should be swallowed whole and not crushed, broken, or chewed
- to contact their physician if they experience fainting spells while taking Ranexa
- that Ranexa may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile, or machinery, or engage in activities requiring mental alertness or coordination

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Manufactured for:
CV Therapeutics, Inc.
Palo Alto, CA 94304 USA

By:
DSM Pharmaceuticals, Inc.
Greenville, NC 27834 USA

Patheon Pharmaceuticals Inc.
Cincinnati, OH 45237 USA

U.S. Patent Numbers 6,303,607; 6,369,062; 6,479,496; 6,503,911; 6,525,057; 6,562,826; 6,617,328; 6,620,814; 6,852,724; 6,864,258

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

LABELING REVIEW

RHPM Review of Product Draft Labeling

Application: NDA 21-526 S-007 SLR

Applicant: CV Therapeutics, Inc.

Submission Date: November 25, 2009
Receipt Date: November 26, 2009

Product Name: Ranexa (ranolazine extended-release tablets)

Background: CV Therapeutics, Inc. (CVT) submitted NDA 21-526 S-007 SLR to revise the current labeling for the 500 mg extended-release (ER) tablet, which was approved for the treatment of chronic angina on November 5, 2008.

The sponsor notes that CMC information to support the registration of Patheon as a second supplier of the 500 mg tablet is provided. Although an additional dosage strength, a 1000 mg tablet, was approved on 12 February 2007, (b) (4)

The approved 500 mg tablet is currently manufactured by DSM Pharmaceuticals, Inc. (DSM), Greenville, North Carolina. This NDA Supplement (S-007) includes supportive chemistry, manufacturing, and controls (CMC) information to provide for Patheon Pharmaceuticals Inc. (Patheon), Cincinnati, Ohio, as a second supplier for Ranexa 500 mg ER tablet. The 500 mg tablet from Patheon has the same formulation as the approved 500 mg tablet manufactured by DSM. The sponsor conducted a human bioequivalence (BE) study (CVT 301-22) to compare the Patheon 500 mg (Test) tablet against the currently-approved 500 mg (Reference) tablet manufactured by DSM. The 500 mg Reference tablet (Lot 3H3026A) that was used in CVT 301-22 is the same lot that was used in the pivotal clinical study CVT 3037 (ERICA). Results of CVT 301-22 show that the 500 mg tablet manufactured by Patheon is bioequivalent to the 500 mg tablet manufactured by DSM.

Ranolazine drug substance, 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy3-(2-methoxyphenoxy) propyl]-, (±)-, used in the Patheon tablet is manufactured by the current drug substance manufacturer, (b) (4) , using the same manufacturing process and specifications that have been filed in the approved NDA 21-526.

Review: CV Therapeutics, Inc. submitted package insert labeling with revisions that add Patheon as a second supplier for the 500 mg tablet and the labeling also includes administrative changes:

1. Under "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" the ***WARNINGS AND PRECAUTIONS*** section was revised from:

- QT interval prolongation: Can occur with ranolazine. (b) (4) available on high doses, long exposure, use with QT interval-prolonging drugs, or potassium channel variants causing prolonged QT interval. (5.1)

to:

- QT interval prolongation: Can occur with ranolazine. Little data available on high doses, long exposure, use with QT interval-prolonging drugs, or potassium channel variants causing prolonged QT interval. (5.1)

2. Under "**USE IN SPECIFIC POPULATIONS**" the **Pregnancy** section was revised from:

Pregnancy Category C

In animal studies, ranolazine at exposures 1.5 (rabbit) to 2 (rat) times the usual human exposure caused maternal toxicity and misshapen sternebrae and reduced ossification in offspring. These doses in rats and rabbits were associated with an increased maternal mortality rate (b) (4) There are no adequate well-controlled studies in pregnant women. Ranexa should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

to:

Pregnancy Category C

In animal studies, ranolazine at exposures 1.5 (rabbit) to 2 (rat) times the usual human exposure caused maternal toxicity and misshapen sternebrae and reduced ossification in offspring. These doses in rats and rabbits were associated with an increased maternal mortality rate *[see Reproductive Toxicology Studies (13.3)]*. There are no adequate well-controlled studies in pregnant women. Ranexa should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

3. The following second supplier was added:

By:

DSM Pharmaceuticals, Inc.
Greenville, NC 27834 USA

Patheon Pharmaceuticals Inc.
Cincinnati, OH 45237 USA

Comments/Recommendations: CV Therapeutics, Inc. labeling was last approved November 5, 2008. A CMC review dated March 18, 2009 is in DFS and Dr. Marroum will also enter a review.

An approval letter for S-007 will be drafted for Dr. Stockbridge's signature.

_____
John David
Regulatory Health Project Manager

dr: jd/2-6-09
f: jd/3-26-09

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/s/

John David
3/26/2009 07:43:30 AM
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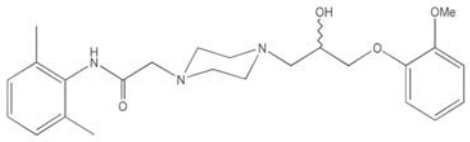
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. ORGANIZATION: 110 (OND managed)	2. NDA Number 21-526
3. Name and Address of Applicant (City & State) CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304		4. Supplement(s) Number(s) Date(s) SCM-007 11/26/08
5. Drug Name Ranexa®	6. Nonproprietary Name Ranolazine	7. Amendments - Dates
8. Supplement Provides For: Patheon Pharmaceuticals Inc., Cincinnati, Ohio, as a second supplier for Ranexa 500 mg ER tablets		
9. Pharmacological Category Treatment of Chronic Angina	10. How Dispensed Rx	11. Related NDAs
12. Dosage Form(s) Extended Release Tablets	13. Potencies 500 mg and 1000 mg	
14. Chemical Name and Structure: 1-Piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-  Molecular Formula: $C_{24}H_{33}N_3O_4$ Molecular Weight: 427.54		15. Records/Reports Current Yes X No Reviewed Yes No X
16. Comments: This is a PA supplement. The applicant is proposing for the addition of Patheon Pharmaceuticals Inc., Cincinnati, Ohio, as a second supplier for Ranexa 500 mg ER tablets. The stability data generated at the proposed site supports the addition of Patheon Pharmaceuticals as a second supplier for Ranexa 500 mg ER tablets. An overall acceptable recommendation was received from the Office of Compliance on February 25, 2009 for the proposed site, Patheon Pharmaceuticals Inc., Cincinnati, Ohio (see attachment on page 12).		
17. Conclusions and Recommendations: The supplement is "Approved" from CMC perspective.		
18. Reviewer:		
Name: Kris Raman, Ph.D.	Signature:	Date Completed: 3/9/09

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/s/

Kris Raman
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CHEMIST

Jim Vidra
3/18/2009 01:03:57 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S-007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

NDA#	21526 S047
Drug	Ranolazine
Formulation	ER Tablets
Type	Addition of manufacturing site
Sponsor	CV Therapeutics
Letter Date	November 25th 2008
Reviewer/Team Leader	Patrick Marroum Ph.D.

Background:

The approved 500 mg ranolazine tablet is currently manufactured by DSM Pharmaceuticals Inc in Greenville North Carolina. In this submission the sponsor would like to add a second manufacturing site for the 500 mg strength Patheon Pharmaceuticals Inc in Cincinnati Ohio.
-In support for the addition of this manufacturing site the sponsor conducted a bioequivalence study comparing the 500 mg tablet manufactured at DSM to the 500 mg tablet manufactured at Patheon.

RESULTS:

The results of the bioequivalence study show that the 500 mg ranolazine tablets manufactured at DSM Pharmaceuticals are bioequivalent to the 500 mg tablets manufactured at Patheon.

RECOMMENDATION:

Since the 500 mg tablets manufactured at Patheon are bioequivalent to the 500 mg tablets manufactured at DSM, Patheon pharmaceuticals should be approved as a second manufacturer for the 500 mg ranolazine tablets. (b) (4)

_____ Date_____
Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

Study CVT 301-22: A four period, replicate design, randomized, open label, crossover study of ranolazine ER in healthy adult male subjects to evaluate the bioequivalence of the current 500 mg and Second supplier of 500 mg tablets

Investigators: (b) (6)

Objectives:
To evaluate the bioequivalence of 500 mg ER tablets manufactured by a second supplier against the current ranolazine ER 500 mg tablets following single doses to healthy adult male subjects. The secondary objectives were to characterize the safety and additional pharmacokinetic parameters of single oral doses of 500 mg manufactured by the 2nd supplier in healthy adult male subjects.

Study Design:
This was a single center, randomized open label replicate design crossover study in healthy adult males between the ages of 18 to 45 years. Subjects were randomly assigned to one of 2 treatment sequences and received single oral doses of 500 mg of ranolazine under fasting conditions on four separate occasions with each subject receiving each supplier tablets twice. Each subject fasted for at least 6 hours before and 4 hours after each dose intake and remained confined in the clinic for 48 hours after each dose of ranolazine. A total of 42 subjects were randomized and 32 completed the study.
Plasma samples for measurement of ranolazine concentrations were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, 42 and 48 hours post dose.

Formulation:
Test: 500 mg ER ranolazine manufactured at Patheon Pharmaceuticals (Cincinnati Ohio) lot # 3054538R, batch size (b) (4).
Reference: 500 mg ER ranolazine manufactured at DSM pharmaceuticals (Greenville North Carolina lot # 3H3026A, batch size (b) (4)

Data Analysis:

Standard pharmacokinetic parameters were calculated using non compartmental methods. AUC and CMAX were analyzed using the confidence interval approach. The logarithm of AUC and CMAX were analyzed using ANOVA with fixed factors for sequence, period and treatment and a random effect for subjects nested within sequence. From this ANOVA model, least squares mean estimated for the LN of AUC and LN of CMAX for each treatment, the estimated treatment difference (second supplier – current supplier) and a 90 % confidence interval for the treatment difference were calculated. The estimated difference and confidence interval were exponentiated to obtain a point estimate and 90 % CI for relative bioavailability.

Analytical Method:

Plasma samples were analyzed for ranolazine using an LC API/MS/MS method that uses [redacted] as an internal standard. The method was further refined to improve the limit of detection to 10 ng/ml by using a protein extraction step. All the samples that were below 50 ng/ml were analyzed by the modified improved method.
The inter-day precision ranged from [redacted] at 800 ng/ml to [redacted] at 100 ng/ml. The inter-day accuracy ranged from [redacted]
As for the improved method, the inter-day precision ranged from [redacted] at 4000 ng/ml to [redacted] at 100 ng/ml. The inter-day accuracy expressed as % recovery ranged from [redacted] at 4000 ng/ml to [redacted] at 100 ng/ml.

Results:

Table 1 shows a summary of the relevant PK parameters of interest while Figure 1 gives the plasma concentration time profile for the test and reference. Table 2 gives a summary of the statistical analysis with the corresponding 90 % confidence intervals.

Figure 1 depicts mean ranolazine plasma concentration-time profiles for the Reference and Test tablets. Each treatment profile represents the overall mean of the two replicates periods combined.

Figure 1 **Mean Ranolazine Plasma Concentrations**

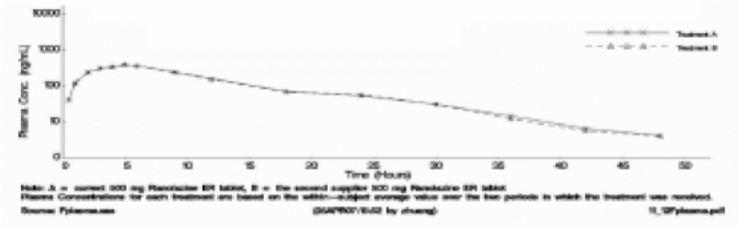

Table 5 **Summary of Pharmacokinetic Parameters**

Parameter Mean (± SD)	Treatment A Reference Material			Treatment B Test Material		
	A1 (n = 40)	A2 (n = 39)	A (n = 40)	B1 (n = 41)	B2 (n = 38)	B (n = 41)
C_{max} (ng/mL)	649 (386)	697 (334)	669 (307)	714 (356)	673 (312)	691 (299)
AUC_{0-t} (ng*h/mL)	6858 (3271)	7231 (3001)	6951 (2954)	6941 (3203)	7046 (3121)	6955 (3027)
$AUC_{0-\infty}$ (ng*h/mL)	6690 (3207)	7068 (2967)	6798 (2895)	6838 (3182)	6775 (3113)	6672 (3014)
t_{max} (h)	5.1 (1.6)	4.5 (1.7)	4.8 (1.2)	5.1 (1.3)	4.7 (1.5)	4.9 (1.1)
Elimination half-life (h)	6.4 (3.1)	5.9 (2.2)	6.2 (2.0)	7.5 (5.7)	7.2 (3.6)	7.3 (3.5)
Elimination rate constant (/h)	0.1 (0.1)	0.1 (0.0)	0.1 (0.0)	0.1 (0.1)	0.1 (0.1)	0.1 (0.0)

TABLE 1

Table 6 **Statistical Analysis of Pharmacokinetic Parameters**

Parameter	Treatment	LS Mean	Ratio of 2nd Supplier vs Current Supplier	90% CI for the Ratio
C_{max} (ng/mL)	A	598.80	--	--
	B	621.81	1.04	0.951–1.133
AUC_{last} (ng*h/mL)	A	6335.06	--	--
	B	6291.78	0.99	0.948–1.041

A = current supplier ranolazine ER 500 mg tablet; B = second supplier ranolazine ER 500 mg tablet
Derived from Section 14.2.4

TABLE 2.

Conclusion:

The 500 mg ranolazine tablets manufactured at Patheon are bioequivalent to the 500 mg tablets manufactured at DSM Pharmaceuticals.

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/s/

Patrick Marroum
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BIOPHARMACEUTICS