

## 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](http://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\*

- |   |   |
|---|---|
| <b>1 INDICATIONS AND USAGE</b>              | <b>10 OVERDOSAGE</b>                                      |
| <b>2 DOSAGE AND ADMINISTRATION</b>          | <b>11 DESCRIPTION</b>                                     |
| 2.1 Dosing Information                      | <b>12 CLINICAL PHARMACOLOGY</b>                           |
| 2.2 Dose Modification                       | 12.1 Mechanism of Action                                  |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>         | 12.2 Pharmacodynamics                                     |
| <b>4 CONTRAINDICATIONS</b>                  | 12.3 Pharmacokinetics                                     |
| <b>5 WARNINGS AND PRECAUTIONS</b>           | <b>13 NONCLINICAL TOXICOLOGY</b>                          |
| 5.1 QT Interval Prolongation                | 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| <b>6 ADVERSE REACTIONS</b>                  | 13.3 Reproductive Toxicology Studies                      |
| 6.1 Clinical Trial Experience               | <b>14 CLINICAL STUDIES</b>                                |
| <b>7 DRUG INTERACTIONS</b>                  | 14.1 Chronic Stable Angina                                |
| 7.1 Effects of Other Drugs on Ranolazine    | 14.2 Lack of Benefit in Acute Coronary Syndrome           |
| 7.2 Effects of Ranolazine on Other Drugs    | <b>15 REFERENCES</b>                                      |
| <b>8 USE IN SPECIFIC POPULATIONS</b>        | <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>               |
| 8.1 Pregnancy                               | <b>17 PATIENT COUNSELING INFORMATION</b>                  |
| 8.3 Nursing Mothers                         |   |
| 8.4 Pediatric Use                           |   |
| 8.5 Geriatric Use                           |   |
| 8.6 Use in Patients with Hepatic Impairment |   |
| 8.7 Use in Patients with Renal Impairment   |   |
| 8.8 Use in Patients with Heart Failure      |   |
| 8.9 Use in Patients with Diabetes Mellitus  |   |

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

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 Ranexa is indicated for the treatment of chronic angina.

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

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Dosing Information**

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

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

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

14 **2.2 Dose Modification**

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

20 **3 DOSAGE FORMS AND STRENGTHS**

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

- 23 • 500 mg tablets are light orange, with CVT500 on one side
- 24 • 1000 mg tablets are pale yellow, with CVT1000 on one side

26 **4 CONTRAINDICATIONS**

27 Ranexa is contraindicated in patients:

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

31 **5 WARNINGS AND PRECAUTIONS**

32 **5.1 QT Interval Prolongation**

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

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

## 38 **6 ADVERSE REACTIONS**

### 39 **6.1 Clinical Trial Experience**

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

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

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

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

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

61 *Cardiac Disorders* – bradycardia, palpitations

62 *Ear and Labyrinth Disorders* – tinnitus, vertigo

63 *Gastrointestinal Disorders* – abdominal pain, dry mouth, vomiting

64 *General Disorders and Administrative Site Adverse Events* – peripheral edema

65 *Respiratory, Thoracic, and Mediastinal Disorders* – dyspnea

66 *Vascular Disorders* – hypotension, orthostatic hypotension

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

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

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

### 74 **Laboratory Abnormalities**

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

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

## 82 **7 DRUG INTERACTIONS**

### 83 **7.1 Effects of Other Drugs on Ranolazine**

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

#### 85 **CYP3A Inhibitors**

86 Do not use Ranexa with strong CYP3A inhibitors, including ketoconazole, itraconazole,  
87 clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir. Ketoconazole  
88 (200 mg twice daily) increases average steady-state plasma concentrations of ranolazine 3.2-fold  
89 [see *Contraindications (4)*].

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

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

#### 97 **P-gp Inhibitors**

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

#### 100 **CYP3A and P-gp Inducers**

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

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

### 105 *CYP2D6 Inhibitors*

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

### 109 *Digoxin*

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

## 111 **7.2 Effects of Ranolazine on Other Drugs**

112 *In vitro* studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of  
113 CYP3A, moderate inhibitors of CYP2D6 and moderate P-gp inhibitors. Ranolazine and its most  
114 abundant metabolites are not known to inhibit the metabolism of substrates for CYP 1A2, 2C8,  
115 2C9, 2C19, or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the  
116 pharmacokinetics of drugs metabolized by these enzymes.

### 117 *Drugs Metabolized by CYP3A*

118 The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each  
119 increased about 2-fold in healthy subjects receiving simvastatin (80 mg once daily) and Ranexa  
120 (1000 mg twice daily). Dose adjustments of simvastatin are not required when Ranexa is  
121 co-administered with simvastatin.

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

### 124 *Drugs Transported by P-gp*

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

### 127 *Drugs Metabolized by CYP2D6*

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

## 131 **8 USE IN SPECIFIC POPULATIONS**

### 132 **8.1 Pregnancy**

133 Pregnancy Category C

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

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

### 140 **8.3 Nursing Mothers**

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

### 145 **8.4 Pediatric Use**

146 Safety and effectiveness have not been established in pediatric patients.

### 147 **8.5 Geriatric Use**

148 Of the chronic angina patients treated with Ranexa in controlled studies, 496 (48%) were  
149  $\geq 65$  years of age, and 114 (11%) were  $\geq 75$  years of age. No overall differences in efficacy  
150 were observed between older and younger patients. There were no differences in safety for  
151 patients  $\geq 65$  years compared to younger patients, but patients  $\geq 75$  years of age on ranolazine,  
152 compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug  
153 discontinuations due to adverse events. In general, dose selection for an elderly patient should  
154 usually start at the low end of the dosing range, reflecting the greater frequency of decreased  
155 hepatic, renal, or cardiac function, and of concomitant disease, or other drug therapy.

### 156 **8.6 Use in Patients with Hepatic Impairment**

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

### 162 **8.7 Use in Patients with Renal Impairment**

163 In patients with varying degrees of renal impairment, ranolazine plasma levels increased up to  
164 50%. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

### 165 **8.8 Use in Patients with Heart Failure**

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

### 170 **8.9 Use in Patients with Diabetes Mellitus**

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

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

### 176 **10 OVERDOSAGE**

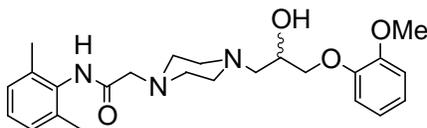
177 High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting.  
178 High intravenous exposure also produces diplopia, paresthesia, confusion, and syncope. In  
179 addition to general supportive measures, continuous ECG monitoring may be warranted in the  
180 event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

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

### 183 **11 DESCRIPTION**

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

186 Ranolazine is a racemic mixture, chemically described as 1-piperazineacetamide, *N*-(2,6-  
187 dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-. It has an empirical formula  
188 of C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>, a molecular weight of 427.54 g/mole, and the following structural formula:



189

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

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

### 199 **12 CLINICAL PHARMACOLOGY**

#### 200 **12.1 Mechanism of Action**

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

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

## 208 **12.2 Pharmacodynamics**

### 209 *Hemodynamic Effects*

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

### 214 *Electrocardiographic Effects*

215 Dose and plasma concentration-related increases in the QTc interval [*see Warnings and*  
216 *Precautions (5.1)*], reductions in T wave amplitude, and, in some cases, notched T waves, have  
217 been observed in patients treated with Ranexa. These effects are believed to be caused by  
218 ranolazine and not by its metabolites. The relationship between the change in QTc and  
219 ranolazine plasma concentrations is linear, with a slope of about 2.6 msec/1000 ng/mL, through  
220 exposures corresponding to doses several-fold higher than the maximum recommended dose of  
221 1000 mg twice daily. The variable blood levels attained after a given dose of ranolazine give a  
222 wide range of effects on QTc. At  $T_{max}$  following repeat dosing at 1000 mg twice daily, the mean  
223 change in QTc is about 6 msec, but in the 5% of the population with the highest plasma  
224 concentrations, the prolongation of QTc is at least 15 msec. In subjects with mild or moderate  
225 hepatic impairment, the relationship between plasma level of ranolazine and QTc is much steeper  
226 [*see Contraindications (4)*].

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

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

## 236 **12.3 Pharmacokinetics**

237 Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable.  
238 For example, at a dose of 1000 mg twice daily, the mean steady-state  $C_{max}$  was 2600 ng/mL with  
239 95% confidence limits of 400 and 6100 ng/mL. The pharmacokinetics of the (+) R- and  
240 (-) S-enantiomers of ranolazine are similar in healthy volunteers. The apparent terminal half-life  
241 of ranolazine is 7 hours. Steady state is generally achieved within 3 days of twice-daily dosing  
242 with Ranexa. At steady state over the dose range of 500 to 1000 mg twice daily,  $C_{max}$  and  
243  $AUC_{0-\tau}$  increase slightly more than proportionally to dose, 2.2- and 2.4-fold, respectively. With

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

### 246 *Absorption and Distribution*

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

252 Food (high-fat breakfast) has no important effect on the C<sub>max</sub> and AUC of ranolazine. Therefore,  
253 Ranexa may be taken without regard to meals. Over the concentration range of 0.25 to  
254 10 µg/mL, ranolazine is approximately 62% bound to human plasma proteins.

### 255 *Metabolism and Excretion*

256 Ranolazine is metabolized mainly by CYP3A and, to a lesser extent, by CYP2D6. Following a  
257 single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and  
258 25% in feces. Ranolazine is metabolized rapidly and extensively in the liver and intestine; less  
259 than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites  
260 has not been well characterized. After dosing to steady state with 500 mg to 1500 mg twice  
261 daily, the four most abundant metabolites in plasma have AUC values ranging from about 5 to  
262 33% that of ranolazine, and display apparent half-lives ranging from 6 to 22 hours.

## 263 **13 NONCLINICAL TOXICOLOGY**

### 264 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

269 There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in  
270 the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m<sup>2</sup>/day) and  
271 50 mg/kg/day for 24 months in mice (150 mg/m<sup>2</sup>/day). These maximally tolerated doses are 0.8  
272 and 0.1 times, respectively, the maximum recommended human dose (MRHD) of 2 grams on a  
273 surface area basis. A published study reported that ranolazine promoted tumor formation and  
274 progression to malignancy when given to transgenic APC (min/+) mice at a dose of 30 mg/kg  
275 twice daily [*see References (15)*]. The clinical significance of this finding is unclear.

### 276 **13.3 Reproductive Toxicology Studies**

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

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

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

283 **14 CLINICAL STUDIES**

284 **14.1 Chronic Stable Angina**

285 CARISA (Combination Assessment of Ranolazine In Stable Angina) was a study in 823 chronic  
 286 angina patients randomized to receive 12 weeks of treatment with twice-daily Ranexa 750 mg,  
 287 1000 mg, or placebo, who also continued on daily doses of atenolol 50 mg, amlodipine 5 mg, or  
 288 diltiazem CD 180 mg. Sublingual nitrates were used in this study as needed.

289 In this trial, statistically significant ( $p < 0.05$ ) increases in modified Bruce treadmill exercise  
 290 duration and time to angina were observed for each Ranexa dose versus placebo, at both trough  
 291 (12 hours after dosing) and peak (4 hours after dosing) plasma levels, with minimal effects on  
 292 blood pressure and heart rate. The changes versus placebo in exercise parameters are presented  
 293 in Table 1. Exercise treadmill results showed no increase in effect on exercise at the 1000 mg  
 294 dose compared to the 750 mg dose.

295 **Table 1 Exercise Treadmill Results (CARISA)**

	<b>Mean Difference from Placebo (sec)</b>	
<b>Study</b>	<b>CARISA (N = 791)</b>	
<b>Ranexa Twice-daily Dose</b>	<b>750 mg</b>	<b>1000 mg</b>
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  $\leq 0.05$     \*\* p-value  $\leq 0.005$

296  
 297 The effects of Ranexa on angina frequency and nitroglycerin use are shown in Table 2.

298

**Table 2 Angina Frequency and Nitroglycerin Use (CARISA)**

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

299

<sup>a</sup> Twice daily

300

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

304 Ranexa has been evaluated in patients with chronic angina who remained symptomatic despite  
 305 treatment with the maximum dose of an antianginal agent. In the ERICA (Efficacy of  
 306 Ranolazine In Chronic Angina) trial, 565 patients were randomized to receive an initial dose of  
 307 Ranexa 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with  
 308 Ranexa 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine  
 309 10 mg once daily. In addition, 45% of the study population also received long-acting nitrates.  
 310 Sublingual nitrates were used as needed to treat angina episodes. Results are shown in Table 3.  
 311 Statistically significant decreases in angina attack frequency ( $p = 0.028$ ) and nitroglycerin use  
 312 ( $p = 0.014$ ) were observed with Ranexa compared to placebo. These treatment effects appeared  
 313 consistent across age and use of long-acting nitrates.

314

**Table 3 Angina Frequency and Nitroglycerin Use (ERICA)**

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

315

<sup>a</sup> 1000 mg twice daily

316

317 **Gender**

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

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

### 323 **Race**

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

### 326 **14.2 Lack of Benefit in Acute Coronary Syndrome**

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

## 333 **15 REFERENCES**

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

## 336 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

- 339 • 500 mg tablets are light orange, with CVT500 on one side
- 340 • 1000 mg tablets are pale yellow, with CVT1000 on one side

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

	<u>Strength</u>	<u>NDC Code</u>
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

342  
343 Store Ranexa tablets at 25°C (77°F) with excursion permitted to 15° to 30°C (59° to 86°F).

## 344 **17 PATIENT COUNSELING INFORMATION**

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

347 Patients should be advised:

- 348 • that Ranexa will not abate an acute angina episode

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

375

376

377

378 Manufactured for:

379 CV Therapeutics, Inc.

380 Palo Alto, CA 94304 USA

381

382 By:

383 DSM Pharmaceuticals, Inc.

384 Greenville, NC 27834 USA

385

386 Patheon Pharmaceuticals Inc.

387 Cincinnati, OH 45237 USA

388

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390 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;  
391 6,620,814; 6,852,724; 6,864,258

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