

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **CORZYNA™**

Ranolazine Extended-Release Tablets

Extended-Release Tablets, 500 and 1000 mg, Oral

Antianginal

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## RECENT MAJOR LABEL CHANGES

Initial: December 2020

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

CORZYNA™ (ranolazine extended-release tablets) is indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium channel blockers.

#### 1.1 Pediatrics

**Pediatrics (<18 years):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (≥75 years):** Evidence from clinical studies suggests that use of ranolazine in patients 75 years of age or older is associated with an increased incidence of adverse events (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics and ADVERSE REACTIONS, Post-Market Adverse Reactions).

### 2 CONTRAINDICATIONS

CORZYNA™ is contraindicated in patients:

- taking strong inhibitors of CYP 3A4, e.g., ketoconazole, clarithromycin, protease inhibitors such as nelfinavir, grapefruit juice (see DRUG INTERACTIONS)
- taking Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmics (e.g., sotalol, ibutilide, amiodarone, dronedarone)
- taking inducers of CYP 3A4, e.g., rifampicin, phenobarbital, carbamazepine, St. John's wort (see DRUG INTERACTIONS)
- with severe renal impairment, i.e., eGFR ≤30 mL/min/1.73m<sup>2</sup>
- with moderate or severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment)
- with a hypersensitivity to ranolazine or any of the excipients (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)

### 3 SERIOUS WARNINGS AND PRECAUTIONS

#### Serious Warnings and Precautions

CORZYNA™ has been shown to prolong the QT interval (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation*, ADVERSE REACTIONS, Post-Market Adverse Reactions, DRUG INTERACTIONS, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, *Electrocardiographic Effects*). Doses of 1000 mg twice daily of CORZYNA™ should not be exceeded.

## **4 DOSAGE AND ADMINISTRATION**

### **4.1 Recommended Dose and Dosage Adjustment**

Initiate CORZYNA™ dosing at 500 mg twice daily and increase to 1000 mg twice daily, as needed, based on clinical symptoms.

The maximum recommended daily dose of CORZYNA™ is 1000 mg twice daily.

Dose adjustments may be needed when CORZYNA™ is taken in combination with certain other drugs (see DRUG INTERACTIONS, Drug-Drug Interactions). Limit the maximum dose of CORZYNA™ to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors such as diltiazem and verapamil. Use of CORZYNA™ with strong CYP 3A4 inhibitors is contraindicated. Use of P-gp inhibitors, such as cyclosporine, may increase exposure to CORZYNA™ (see DRUG INTERACTIONS, Drug-Drug Interactions).

### **4.2 Administration**

Take CORZYNA™ with or without meals. Swallow CORZYNA™ tablets whole; do not crush, break, or chew. Titrate CORZYNA™ based on clinical response.

### **4.3 Missed Dose**

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

## **5 OVERDOSAGE**

Hypotension, QT prolongation, bradycardia, myoclonic activity, severe tremor, unsteady gait/incoordination, dizziness, nausea, vomiting, dysphasia, and hallucinations have been seen in cases of oral overdose of ranolazine. In cases of extreme overdose of CORZYNA™, fatal outcomes have been reported. In clinical studies, high intravenous exposure resulted in 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.

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| For management of a suspected drug overdose, contact your regional poison control centre. |
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## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition           | Non-medicinal Ingredients  |
|-------------------------|--|--|
| Oral                    | Extended-release Tablets, 500 mg and 1000 mg | Hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, Opadry® II 85F570040 beige, Opadry® II 32K520117 yellow, purified water, sodium hydroxide. |

CORZYNA™ 500 mg tablets are light orange coloured, film coated, oblong shaped tablets debossed with “C49” on one side and plain on the other side available in bottles of 60.

CORZYNA™ 1000 mg tablets are yellow coloured, film coated, oblong shaped tablets debossed with “C48” on one side and plain on the other side available in bottles of 60.

## 7 WARNINGS AND PRECAUTIONS

### Cardiovascular

#### QT Interval Prolongation

Ranolazine blocks  $I_{Kr}$  and prolongs the  $QT_c$  interval in a dose-related manner (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, *Electrocardiographic Effects*).

Although overall experience in large clinical trials that evaluated ranolazine following acute coronary syndrome did not show an increased risk of symptomatic documented arrhythmias, including ventricular tachycardia or sudden death, rare events of Torsade de Pointes and ventricular fibrillation have been reported during post-market use (see ADVERSE REACTIONS, Post-Market Adverse Reactions). CORZYNA™ should not be used at doses above 1000 mg twice daily. CORZYNA™ is contraindicated with Class IA and Class III antiarrhythmics and strong inhibitors of CYP 3A4 (see CONTRAINDICATIONS and DRUG INTERACTIONS). Use of CORZYNA™ should be avoided in patients with acquired long QT syndrome and most forms of congenital long QT syndrome.

$QT_c$  prolongation can lead to an increased risk of Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, Torsade de Pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised if administering CORZYNA™ to patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a  $QT_c$ -prolonging drug. Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following: female gender; age  $\geq 65$  years; baseline prolongation of the  $QT/QT_c$  interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; concomitant use of drugs known to prolong  $QT$  interval; history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; and acute neurological events.

### *Monitoring and Laboratory Tests*

ECG evaluations should be performed at baseline prior to initiating therapy with CORZYNA™ and repeated periodically during treatment with CORZYNA™ to monitor for QTc prolongation (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, *Electrocardiographic Effects*). Electrolyte levels (potassium, calcium, and magnesium) should be assessed at baseline and monitored periodically during treatment with CORZYNA™. Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to initiating or continuing CORZYNA™ treatment.

### **CYP 3A4, CYP 2D6, and P-glycoprotein (P-gp) System Inhibitors**

Limit the dose of CORZYNA™ to 500 mg twice daily in patients taking moderate inhibitors of CYP 3A4 (e.g., diltiazem, verapamil, erythromycin, fluconazole). Careful dose titration of ranolazine is required in patients treated with P-gp inhibitors (e.g., cyclosporine, verapamil) and CYP 2D6 inhibitors (e.g., digoxin) (see DRUG INTERACTIONS). Higher plasma levels of ranolazine may also occur in patients who are poor metabolisers of CYP 2D6.

Concomitant use of strong CYP 3A4 inhibitors is contraindicated (see CONTRAINDICATIONS).

### **Driving and Operating Machinery**

CORZYNA may cause dizziness, blurred vision, confusional state, abnormal coordination and hallucinations, which may affect the ability to drive and use machinery.

### **Renal**

Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] <30 mL/min) while taking ranolazine. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen [BUN]), discontinue CORZYNA™ and treat appropriately (see WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment).

Monitor renal function after initiation and periodically in patients with renal impairment (CrCL <60 mL/min) (see CONTRAINDICATIONS).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

There are no adequate well-controlled studies in pregnant women. In animal studies, ranolazine at exposures 1.5- (rabbit) to 2- (rat) times the usual human exposure caused maternal toxicity, misshapen sternebra, and reduced ossification in offspring. These doses in rats and rabbits were associated with increased maternal mortality.

CORZYNA™ should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

### **7.1.2 Breast-feeding**

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, a decision should be made whether to forego breastfeeding in patients taking CORZYNA™ or to discontinue CORZYNA™ treatment.

### 7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

No overall differences in efficacy were observed between older and younger patients. However, patients  $\geq 75$  years of age who were treated with ranolazine had a higher incidence of adverse events, serious adverse events (see ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions), and drug discontinuations due to adverse events. In general, dose selection for these patients should be carried out with caution, given the greater frequency of impairment of hepatic, renal, and cardiac function, or various comorbidities and/or concomitant drug use that may be present.

### 7.1.5 Hepatic Impairment

CORZYNA™ is contraindicated in patients with moderate to severe liver impairment (see CONTRAINDICATIONS). In a study of patients with cirrhosis, the  $C_{max}$  of ranolazine was increased 30% in patients with mild (Child-Pugh Class A) hepatic impairment, but increased 80% in patients with moderate (Child-Pugh Class B) hepatic impairment, when compared to patients without hepatic impairment. This increase was not enough to account for the 3-fold increase in QT prolongation seen in these patients with cirrhosis having mild to moderate hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Careful dose titration is recommended in patients with mild hepatic impairment.

### 7.1.6 Renal Impairment

A pharmacokinetic study of ranolazine in subjects with severe renal impairment ( $CrCL < 30$  mL/min) was stopped when 2 of 4 subjects developed acute renal failure after receiving ranolazine 500 mg twice daily for 5 days in the lead-in phase followed by 1000 mg twice a day (1 dose in one subject and 11 doses in the other). Increases in creatinine, BUN, and potassium were observed in 3 subjects during the 500 mg lead-in phase. One subject required hemodialysis, while the other 2 subjects improved upon drug discontinuation.

CORZYNA™ is contraindicated in severe renal impairment (see CONTRAINDICATIONS). Monitor renal function prior to initiation and periodically in patients treated with CORZYNA™. Discontinue CORZYNA™ if acute renal failure develops.

In a separate study,  $C_{max}$  was increased between 40% and 50% in patients with mild or moderate renal impairment, compared to patients with no renal impairment, suggesting a similar increase in exposure in these two patient populations with pre-existing renal failure. Careful dose titration is recommended in patients with mild to moderate renal impairment. The pharmacokinetics of ranolazine have not been assessed in patients on dialysis.

### 7.1.7 Heart Failure

Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. Ranolazine had minimal effects on heart rate and blood pressure in patients with angina and heart failure NYHA Class I to IV. No general dose adjustment of CORZYNA™ is required in patients with heart failure, although dosing should be carried out with caution.



### 7.1.8 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.

## 8 ADVERSE REACTIONS

### 8.1 Clinical Trial Adverse Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Of the patients with chronic stable angina pectoris treated with ranolazine, 1026 were enrolled in three double-blind, placebo-controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks' duration. Twelve hundred and fifty-one (1251) patients received treatment with ranolazine in open-label, long-term studies, of which, 1227 patients were exposed to ranolazine 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 ranolazine 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 in ranolazine-treated patients than placebo-treated patients were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), and asthenia, constipation, headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily were poorly tolerated and are not recommended.

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

### 8.2 Less Common Clinical Trial Adverse Reactions

The following additional adverse reactions occurred at an incidence of 0.5% to 4.0% in patients treated with ranolazine and were more frequent than the incidence observed in placebo-treated patients:

*Cardiac Disorders:* bradycardia, palpitations

*Ear and Labyrinth Disorders:* tinnitus, vertigo

*Eye Disorders:* blurred vision

*Gastrointestinal Disorders:* abdominal pain, dry mouth, vomiting, dyspepsia

*General Disorders and Administrative Site Adverse Events:* asthenia, peripheral edema

*Metabolism and Nutrition Disorders:* anorexia, hyponatremia

*Nervous System Disorders:* syncope

*Psychiatric Disorders:* anxiety, confusional state

*Renal and Urinary Disorders:* hematuria

*Respiratory, Thoracic, and Mediastinal Disorders:* dyspnea

*Skin and Subcutaneous Tissue Disorders:* hyperhidrosis, pruritus, urticaria

*Vascular Disorders:* hypotension, orthostatic hypotension

Less common (<0.5%) but potentially important adverse reactions that were observed more frequently with ranolazine than placebo treatment in controlled studies included: angioedema, renal failure, eosinophilia, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

Increases of serum creatinine and hepatic enzymes have been seen on occasion.

In a large clinical trial in patients treated after acute coronary syndrome that was unsuccessful in demonstrating clinical outcome benefit for ranolazine, neither were there apparent proarrhythmic effects nor adverse cardiac outcomes observed overall in these high-risk patients. In another large clinical trial that assessed patients with chronic stable angina and incomplete revascularisation following percutaneous coronary intervention (PCI), the overall incidence of major adverse cardiovascular events, which consisted of all-cause mortality, stroke and heart failure hospitalisations, did not differ between patients treated with ranolazine and placebo. However, in patients  $\geq 75$  years of age in this study, this composite of major adverse cardiovascular events was increased over placebo (HR 1.79; 95% C.I. 1.06-3.06),  $p=0.03$  (see WARNINGS AND PRECAUTIONS, Geriatrics).

### **8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**

Ranolazine treatment produces elevations of serum creatinine by about 0.1 mg/dL in patients with preserved renal function, likely because of inhibition of creatinine's tubular secretion. In general, the elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of ranolazine, and is not accompanied by changes in BUN. In healthy volunteers, ranolazine 1000 mg twice daily had no effect upon the glomerular filtration rate. More marked and progressive increases in serum creatinine, associated with increases in BUN or potassium, indicating acute renal failure, have been reported after initiation of ranolazine in patients with severe renal impairment (see CONTRAINDICATIONS).

### **8.4 Post-Market Adverse Reactions**

*The following adverse reactions have been identified during post-approval use of ranolazine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably establish a causal relationship to drug exposure:*

*Cardiovascular Disorders* – QT interval prolongation, Torsade de Pointes, ventricular fibrillation

*Nervous System Disorders* – Abnormal coordination, diplopia, gait disturbance, myoclonus, paresthesia, tremor, and other serious neurologic adverse events have been reported to occur in patients taking ranolazine. The onset of events was often associated with an increase in ranolazine dose or exposure. Many patients reported symptom resolution following drug discontinuation or dose decrease.

*Metabolism and Nutrition Disorders* – Cases of hypoglycemia have been reported in diabetic patients taking antidiabetic medication.

*Musculoskeletal Disorders* - Rhabdomyolysis has been observed in patients receiving ranolazine concomitantly with simvastatin.

*Psychiatric Disorders* – hallucination

*Renal and Urinary Disorders* – dysuria, urinary retention

*Skin and Subcutaneous Tissue Disorders* – angioedema, pruritus, rash

## **9 DRUG INTERACTIONS**

### **9.1 Drug-Drug Interactions**

#### Effects of Other Drugs on Ranolazine

##### *Strong CYP 3A4 Inhibitors*

Strong CYP 3A4 inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, nelfinavir, ritonavir, indinavir, saquinavir and grapefruit juice are contraindicated (see CONTRAINDICATIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

##### *Moderate CYP 3A4 Inhibitors*

Limit the dose of CORZYNA™ to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors, including, but not limited to, diltiazem, verapamil, erythromycin, and fluconazole (see WARNINGS AND PRECAUTIONS, CYP 3A4, CYP 2D6, and P-gp System Inhibitors, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

##### *P-gp Inhibitors*

Concomitant use of CORZYNA™ with P-gp inhibitors, such as cyclosporine, may increase ranolazine concentrations. Use CORZYNA™ with caution in these patients, limiting dose increases (see WARNINGS AND PRECAUTIONS, CYP 3A4, CYP 2D6, and P-gp System Inhibitors and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

##### *CYP 3A4 Inducers*

Concomitant use of CORZYNA™ with CYP 3A4 inducers, such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort is contraindicated (see CONTRAINDICATIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

*Anti-arrhythmic Medicines and Other Medicinal Products that may Prolong the QT interval*  
CORZYNA™ causes QTc interval prolongation (see WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation* and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, *Electrocardiographic Effects*). Concomitant use with Class IA antiarrhythmics (e.g., procainamide, disopyramide) and Class III antiarrhythmics (e.g., sotalol, ibutilide, amiodarone, dronedarone) is contraindicated (see CONTRAINDICATIONS). The concomitant administration of CORZYNA™ with other drugs known to prolong the QT interval or induce Torsade de Pointes should be avoided. Current information sources should be consulted for lists of drugs that prolong the QTc interval.

While the patient is using CORZYNA™, other QTc-prolonging drugs should be discontinued and alternative concomitant drugs that do not prolong the QTc interval should be chosen instead.

#### *Drugs that Affect Electrolyte Levels*

Drugs that can decrease serum electrolyte levels should be used with caution with CORZYNA™ (see WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation*). Electrolyte disturbances may increase the risk of QT interval prolongation in patients prone to this condition. Such drugs include, but are not limited to, the following: thiazide and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; and proton pump inhibitors.

#### *Drug-Food Interactions*

Grapefruit, grapefruit juice, and grapefruit-containing products should not be ingested while receiving CORZYNA™ (see CONTRAINDICATIONS). These foods inhibit CYP 3A4 and increase plasma concentrations of ranolazine.

#### Effects of Ranolazine on Other Drugs

##### *Drugs Metabolized by CYP 3A4*

Limit the dose of simvastatin in patients on any dose of CORZYNA™ to 20 mg once daily, when ranolazine is co-administered. Dose adjustment of other sensitive CYP 3A4 substrates (e.g., lovastatin, atorvastatin) and CYP 3A4 substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus, everolimus) may be required as CORZYNA™ may increase plasma concentrations of these drugs (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

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

Careful dose titration of ranolazine is recommended in patients treated with P-gp inhibitors. Down-titration of CORZYNA™ may also be required. Concomitant use of ranolazine and digoxin results in increased exposure to digoxin. The dose of digoxin may have to be adjusted (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

##### *Drugs Metabolized by CYP 2D6*

Since the exposure to CYP 2D6 substrates, such as tricyclic antidepressants and antipsychotics, may be increased during co-administration with CORZYNA™, lower doses of these drugs may be required (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

##### *Drugs Transported by OCT2*

In patients with type 2 diabetes mellitus, concomitant use of CORZYNA™ 1000 mg twice daily and metformin results in increased plasma levels of metformin. When CORZYNA™ 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Monitor blood glucose levels and risks associated with high exposures of metformin.

Metformin exposure was not significantly increased when given with CORZYNA™ 500 mg twice daily (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

The mechanism of action of ranolazine's antianginal effects has not been determined, but these effects do not depend on reductions in heart rate or blood pressure. Treatment with ranolazine does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. At therapeutic concentrations, ranolazine inhibits the cardiac late sodium current ( $I_{Na}$ ). However, the relationship of this inhibition to treatment effects of anginal symptoms is not certain.

The QT prolongation effect of ranolazine appears to be due, at least in part, to its inhibition of  $I_{Kr}$ , which prolongs the ventricular action potential.

### 10.2 Pharmacodynamics

#### Hemodynamic Effects

In controlled clinical trials, patients with chronic stable angina treated with ranolazine, either alone, or in combination with other anti-anginal medications, 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 NYHA Class I or II heart failure, diabetes, reactive airway disease, and in elderly patients.

#### Electrocardiographic Effects

Ranolazine causes a concentration-dependent prolongation of the QTc interval (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation*, and DRUG INTERACTIONS). In a double-blind, randomized, placebo-controlled, parallel-design ECG assessment study, healthy subjects (N=10/group) were treated with a suprathreshold dose of ranolazine at 1500 mg BID or placebo for three days. On the basis of a pharmacokinetic-pharmacodynamic model of the relationship between ranolazine concentrations and the placebo- and baseline-adjusted QTcF interval, the magnitude of the QTcF prolongation at maximal plasma concentrations obtained following recommended therapeutic doses of CORZYNA™ 500 mg BID and 1000 mg BID was predicted to be 16.3 msec (90% CI 10.1, 22.6) and 33.4 msec (90% CI 22.7, 44.6), respectively, using geometric mean steady-state  $C_{max}$  values of ranolazine 1450 ng/mL obtained for the 500 mg BID dose, and 3590 ng/mL for the 1000 mg BID dose, from another trial of 14 healthy subjects that used a crossover study design.

### 10.3 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 ranolazine. At steady-state over the dose range of 500 to 1000 mg twice daily, the  $C_{max}$  and  $AUC_{0-\tau}$  increase slightly more than proportionally to dose, at 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 are unaffected by age, gender, or food.

**Absorption:** After oral administration of extended-release ranolazine, peak plasma concentrations are reached between 2 and 5 hours. After oral administration of <sup>14</sup>C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine 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 (see DRUG INTERACTIONS).

Food (high-fat breakfast) has no important effect on the C<sub>max</sub> and AUC of ranolazine. Therefore, food does not affect the rate and extent of absorption of CORZYNA™.

**Distribution:** Over the concentration range of 0.25 to 10 µg/mL, ranolazine is approximately 62% bound to human plasma proteins, mainly to α-1 acid glycoprotein, and weakly to albumin.

**Metabolism:** Ranolazine is metabolized mainly by CYP 3A4 and, to a lesser extent, by CYP 2D6. 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.

**Elimination:** Following a single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and 25% in feces.

## Drug Interactions

### Effect of Other Drugs on Ranolazine

*In vitro* data indicate that ranolazine is a substrate of cytochrome CYP 3A4, and, to a lesser extent, of CYP 2D6. Ranolazine is also a substrate of P-glycoprotein. The potential for dose-related adverse events (e.g., nausea, dizziness) may be increased with higher plasma concentrations of ranolazine.

#### *Strong CYP 3A4 Inhibitors*

Do not use CORZYNA™ with strong CYP 3A4 inhibitors, including itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, and nefazodone (see CONTRAINDICATIONS). Grapefruit juice is also a potent CYP 3A4 inhibitor. Ketoconazole (200 mg twice daily) increases average steady-state plasma concentrations of ranolazine 3.9-fold (see DRUG INTERACTIONS, Drug-Drug Interactions).

#### *Moderate CYP 3A4 Inhibitors*

Limit the dose of CORZYNA™ to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors, including diltiazem, verapamil, aprepitant, erythromycin, and fluconazole. 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).

#### *Weak CYP 3A4 Inhibitors*

The weak CYP 3A4 inhibitors simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

### *CYP 3A4 Inducers*

Rifampin 600 mg once daily decreases ranolazine steady-state concentrations (1000 mg twice daily) by approximately 95% (see DRUG INTERACTIONS, Drug-Drug Interactions).

Concomitant use of CORZYNA™ with CYP 3A4 inducers is contraindicated (see CONTRAINDICATIONS).

### *CYP 2D6 Inhibitors*

Ranolazine is partially metabolised by CYP 2D6, therefore, inhibitors of this enzyme may potentially increase plasma concentrations of ranolazine. The potent CYP 2D6 inhibitor, paroxetine, at a dose of 20 mg once daily, increased steady-state plasma concentrations of ranolazine 1000 mg twice daily by an average of 20% in healthy volunteers. No dose adjustment of CORZYNA™ is required in patients treated with CYP 2D6 inhibitors.

### *P-glycoprotein inhibitors*

Ranolazine is a substrate of P-glycoprotein. Inhibitors of P-gp (e.g., cyclosporin, verapamil) increase plasma levels of ranolazine. Verapamil (120 mg three times daily) increases ranolazine steady-state concentrations 2.2-fold. Careful dose titration of ranolazine is recommended in patients treated with P-gp inhibitors. Down-titration of CORZYNA™ may be required if initiating these therapies.

### *Digoxin*

Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin at 0.125 mg once daily.

### Effect of Ranolazine on Other Drugs

*In vitro* studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of CYP 3A4 and may increase plasma concentrations of other CYP 3A4 substrates. Ranolazine and this metabolite are moderate inhibitors of CYP 2D6, as well as moderate inhibitors of P-gp. *In vitro*, ranolazine has also been shown to be an inhibitor of OCT2. Ranolazine and its various metabolites are not known to inhibit the metabolism of CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes.

### *CYP 3A4 Substrates*

The plasma levels of simvastatin, a CYP 3A4 substrate, and its active metabolite are increased 2-fold in healthy volunteers receiving simvastatin 80 mg once daily, along with ranolazine 1000 mg twice daily (see DRUG INTERACTIONS, Drug-Drug Interactions). Mean exposure to atorvastatin 80 mg once daily is increased by about 40% following co-administration with ranolazine 1000 mg twice daily in healthy volunteers. However, in a single subject the exposure to atorvastatin and metabolites was increased by ~400% in the presence of ranolazine.

### *Diltiazem*

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

### *P-gp Substrates*

#### Digoxin

Ranolazine increases digoxin concentrations by an average of 1.5-fold in healthy volunteers receiving ranolazine 1000 mg twice daily and digoxin 0.125 mg once daily. Digoxin levels should be monitored following initiation of CORZYNA™ therapy, and regularly during such co-administration (see DRUG INTERACTIONS, Drug-Drug Interactions).

### *CYP 2D6 Substrates*

Ranolazine is a moderate inhibitor of CYP 2D6. Ranolazine 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. Therefore, the exposure to metoprolol or other CYP 2D6 substrates (e.g., propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co-administration with CORZYNA™, and dose adjustment of these medicinal products may be required. In extensive metabolizers of dextromethorphan, a substrate of CYP 2D6, ranolazine inhibits partially the formation of the main metabolite dextrorphan.

### *Drugs transported by the Organic Cation Transporter-2 (OCT2)*

Plasma exposure of metformin 1000 mg twice daily increased 1.4- and 1.8-fold in patients with type 2 diabetes when co-administered with CORZYNA™ 500 mg and 1000 mg twice daily, respectively. When metformin is co-administered with CORZYNA™ 1000 mg twice daily, limit metformin dosing to 1700 mg/day. The exposure of other OCT2 substrates, including, but not limited to, pindolol and varenicline, may be affected to a similar degree (see DRUG INTERACTIONS, Drug-Drug Interactions).

### *Pharmacodynamic Interactions*

Concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Examples of such drugs include, but are not limited to, certain antiarrhythmics (e.g., quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g., imipramine, doxepin, amitriptyline).

## **11 STORAGE, STABILITY AND DISPOSAL**

Shelf-life of CORZYNA™: 24 months.

Store CORZYNA™ at 15 to 30°C.

Any unused product or waste material should be disposed of as biohazardous waste.

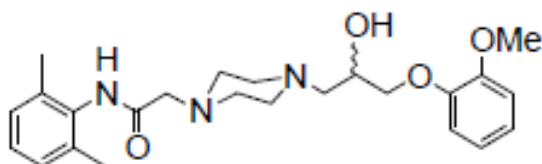


## PART II: SCIENTIFIC INFORMATION

### 12 PHARMACEUTICAL INFORMATION

#### Drug Substance

|                    |   |
|--------------------|---|
| Proper name:       | Ranolazine  |
| Chemical name:     | 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)- |
| Molecular formula: | C <sub>24</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>                                 |
| Molecular Mass:    | 427.54 g/mole   |



Structural formula:

Physicochemical properties:

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. Ranolazine exhibits low solubility across the pH range of 1.2 to 7.5, except in 0.1N HCl.

| Ranolazine drug substance solubility in physiological buffers |                     |
|---|---------------------|
| Medium  | Solubility in mg/ml |
| 0.1N HCl  | 15.6609             |
| 0.01N HCl   | 2.0066              |
| pH 4.5 Acetate buffer   | 1.6712              |
| pH 6.8 Phosphate buffer                                       | 0.2355              |
| Purified water  | 0.1306              |
| pH 7.5 Phosphate buffer                                       | 0.1446              |

Ranolazine exhibits polymorphic Form I.

## 13 CLINICAL TRIALS

### 13.1 Trial Design and Study Demographics

**Table 2 - Summary of patient demographics for clinical trials with ranolazine, when used as add-on to first-line antianginal therapies**

| Study   | Trial design                                 | Dosage, route of administration and duration   | Study subjects (n)   | Mean age | Sex            |
|---------|--|--|--|----------|----------------|
| CARISA* | Randomized, Double blind, placebo-controlled | 1. Ranolazine 750 mg bid for 12 weeks<br>2. Ranolazine 1000 mg bid for 12 weeks<br>3. Placebo bid for 12 weeks | 823 patients with symptomatic chronic angina                         | 64 yrs   | 638 M<br>185 F |
| ERICA#  | Randomized, Double blind, placebo-controlled | Ranolazine 1000 mg bid or placebo for 6 weeks  | 565 patients with coronary disease and $\geq$ 3 anginal attacks/week | 62 yrs   | 409 M<br>155 F |

\*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 extended-release ranolazine 750 mg, 1000 mg, or placebo, who also continued on fixed daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg. Sublingual nitrates were used in this study as needed.

#In the ERICA (Efficacy of Ranolazine in Chronic Angina) trial, 565 patients were randomized to receive an initial dose of extended-release ranolazine 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with extended-release ranolazine 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine at a dose of 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.

### 13.2 Study Results

In the CARISA trial, statistically significant ( $p < 0.05$ ) increases in modified Bruce treadmill exercise duration and time to angina were observed at Week 12 for each ranolazine dose versus placebo, at both trough (12 hours after dosing),  $p < 0.05$ , and peak (4 hours after dosing),  $p < 0.005$ , with minimal effects on blood pressure and heart rate. At trough, mean exercise duration was 416 seconds at baseline in this study, while mean time to onset of angina at baseline was 326 seconds, and mean time to ECG ischemia at baseline was 303 seconds. At peak, mean exercise duration was 467 seconds at baseline in this study, while mean time to onset of angina at baseline was 387 seconds, and mean time to ECG ischemia at baseline was 405 seconds.

The changes versus placebo in exercise parameters are presented in **Error! Reference source not found.**, below.

**Table 3 - Exercise Treadmill Results at Week 12 in the CARISA Trial**

| Study  | CARISA (N=791) |        |                                    |         |                                    |
|--|----------------|--------|------------------------------------|---------|------------------------------------|
|  | Placebo        | 750 mg | Mean Difference from Placebo (sec) | 1000 mg | Mean Difference from Placebo (sec) |
| Exercise Duration, mean change from baseline, seconds                  |                |        |                                    |         |                                    |
| Trough   | 91.7           | 115.4  | 24 <sup>a</sup>                    | 115.8   | 24 <sup>a</sup>                    |
| Peak   | 65.4           | 99.4   | 34 <sup>b</sup>                    | 91.5    | 26 <sup>b</sup>                    |
| Time to Angina, mean change from baseline, seconds                     |                |        |                                    |         |                                    |
| Trough   | 114.3          | 144.0  | 30 <sup>a</sup>                    | 140.3   | 26 <sup>a</sup>                    |
| Peak   | 88.9           | 126.9  | 38 <sup>b</sup>                    | 126.8   | 38 <sup>b</sup>                    |
| Time to 1 mm ST-Segment Depression, mean change from baseline, seconds |                |        |                                    |         |                                    |
| Trough   | 125.1          | 145.1  | 20                                 | 146.2   | 21                                 |
| Peak   | 59.2           | 100.0  | 41 <sup>b</sup>                    | 93.8    | 35 <sup>b</sup>                    |

<sup>a</sup> p-value ≤0.05; <sup>b</sup> p-value ≤0.005

The effects of ranolazine on angina frequency and nitroglycerin use are shown in Table 4. A baseline frequency of 4.5 anginal episodes per week were observed in all treatment groups.

**Table 4 - Angina Frequency and Nitroglycerin Use-in the CARISA Trial**

|                                 |                    | Placebo | Ranolazine 750 mg <sup>a</sup> | Ranolazine 1000 mg <sup>a</sup> |
|---------------------------------|--------------------|---------|--------------------------------|---------------------------------|
| 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                          |

<sup>a</sup> Twice daily

Tolerance to ranolazine 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 ranolazine.

In the ERICA trial, ranolazine has been evaluated in patients with chronic angina who remained symptomatic despite treatment with the maximum dose of an antianginal agent. Results from this trial are shown in

Table 5, below. Statistically significant decreases in trimmed mean weekly anginal episodes were observed at 2.9 and 3.3 ( $p=0.03$ ), for ranolazine and placebo, respectively. Trimmed mean weekly consumption of rescue (short-acting) nitroglycerin use was also significantly reduced, at 2.0 and 2.7 ( $p=0.01$ ), respectively. Trimmed mean values excluded individual patient values in the top and bottom 2% of values measured. These treatment effects appeared consistent across age and use of long-acting nitrates.

**Table 5 - Angina Frequency and Nitroglycerin Use in the ERICA Trial**

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

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

#### Gender

Overall, effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In the CARISA trial, 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 the ERICA trial, 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 subgroups.

### **Comparative Bioavailability Studies**

#### Fasting Conditions

An open label, randomized, two-treatment, two-period, two-sequence, single (1 x 1000 mg) oral dose, crossover comparative bioavailability study of CORZYNA™ (ranolazine) Extended-Release Tablets, 1000 mg (KYE Pharmaceuticals Inc.) and RANEXA® (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc., marketed in the United States) was conducted in healthy, adult, Asian male subjects under fasting conditions. The results of the 63 subjects who completed the study are summarized in Table 6.

**Table 6 – Summary Table of the Comparative Bioavailability Data**

| Ranolazine<br>(1 x 1000 mg)<br>From measured data<br>Geometric Mean<br>Arithmetic Mean (CV%) |                             |  |                            |                         |
|--|-----------------------------|--|----------------------------|-------------------------|
| Parameter  | Test <sup>1</sup>           | Reference <sup>2</sup>                   | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>T</sub><br>(ng·h/mL)  | 20,346.5<br>24,189.7 (53.8) | 18,678.5<br>22,135.1 (54.3)              | 108.9                      | 99.1 - 119.5            |
| AUC <sub>I</sub><br>(ng·h/mL)  | 20,681.7<br>24,552.4 (53.9) | 19,414.7<br>22,645.7 (52.7) <sup>^</sup> | 106.7                      | 98.2 - 116.0            |
| C <sub>max</sub><br>(ng/mL)  | 1479.6<br>1617.8 (42.6)     | 1369.5<br>1515.4 (45.7)                  | 108.0                      | 100.3 - 116.4           |
| T <sub>max</sub> <sup>3</sup> (h)  | 5.33 (1.00 – 24.00)         | 5.03 (1.00 – 24.02)                      |                            |                         |
| T <sub>1/2</sub> <sup>4</sup> (h)  | 5.10 (38.2)                 | 4.75 (33.0) <sup>^</sup>                 |                            |                         |

<sup>1</sup> CORZYNA™ (ranolazine) Extended-Release Tablets, 1000 mg (KYE Pharmaceuticals Inc.)

<sup>2</sup> RANEXA® (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc.), marketed in the United States

<sup>3</sup> Expressed as the median (range)

<sup>4</sup> Expressed as the arithmetic mean (CV%) only

<sup>^</sup>N = 62

#### High-Fat, High-Calorie Fed Conditions

An open label, randomized, two-treatment, two-period, two-sequence, single (1 x 1000 mg) oral dose, crossover, comparative bioavailability study of CORZYNA™ (ranolazine) Extended-Release Tablets, 1000 mg (KYE Pharmaceuticals Inc.) and RANEXA® (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc., marketed in the United States) was conducted in healthy, adult, Asian male subjects under high-fat, high-calorie fed conditions. The results of the 59 subjects who completed the study are summarized in Table 7.

**Table 7 – Summary Table of the Comparative Bioavailability Data**

| Ranolazine<br>(1 x 1000 mg)<br>From measured data<br>Geometric Mean<br>Arithmetic Mean (CV%) |  |                             |                            |                         |
|--|--|-----------------------------|----------------------------|-------------------------|
| Parameter  | Test <sup>1</sup>                        | Reference <sup>2</sup>      | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>T</sub><br>(ng·h/mL)  | 18,851.1<br>20,769.2 (45.2)              | 18,763.3<br>20,470.0 (42.3) | 100.6                      | 94.86 – 106.68          |
| AUC <sub>I</sub><br>(ng·h/mL)  | 19,298.5<br>21,307.0 (45.6) <sup>^</sup> | 19,024.8<br>20,729.7 (42.3) | 101.0                      | 95.10 – 107.18          |
| C <sub>max</sub><br>(ng/mL)  | 1396.9<br>1497.3 (38.7)                  | 1422.0<br>1517.0 (38.5)     | 98.3                       | 91.99 – 105.09          |
| T <sub>max</sub> <sup>3</sup> (h)  | 5.67 (3.00 – 24.00)                      | 5.67 (4.02 – 24.03)         |                            |                         |
| T <sub>1/2</sub> <sup>4</sup> (h)  | 5.01(76.8) <sup>^</sup>                  | 4.50 (41.6)                 |                            |                         |

<sup>1</sup> CORZYNA™ (ranolazine) Extended-Release Tablets, 1000 mg (KYE Pharmaceuticals Inc.)

<sup>2</sup> RANEXA® (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc.), marketed in the United States

<sup>3</sup> Expressed as the median (range)

<sup>4</sup> Expressed as the arithmetic mean (CV%) only

<sup>^</sup>N = 58

## 14 NON-CLINICAL TOXICOLOGY

### Carcinogenesis

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<sup>2</sup>/day) and 50 mg/kg/day for 24 months in mice (150 mg/m<sup>2</sup>/day). These maximally tolerated doses are 0.8 and 0.1 times, respectively, the daily maximum recommended human dose (MRHD) of 2000 mg 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. The clinical significance of this finding is unclear.

### Mutagenesis

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.

### Impairment of Fertility

In male and female rats, oral administration of ranolazine that produced exposures (AUC) approximately 3-fold or 5-fold higher, respectively, than the MRHD had no effect on fertility.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### **PrCORZYNA™ Ranolazine Extended-release Tablets**

Read this carefully before you start taking CORZYNA™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about CORZYNA™.

#### **Serious Warnings and Precautions**

CORZYNA™ can change the electrical activity (prolong the QT interval) of your heart. You should not take more than 1000 mg of CORZYNA™ twice a day.

#### **What is CORZYNA™ used for?**

CORZYNA™ is a medicine used to treat chest pain (stable angina) in adults. It is used along with other medicines in patients:

- who cannot tolerate other antianginal therapies or for whom other antianginal therapies do not work to control their chest pain (this includes beta-blockers and calcium channel blockers)

#### **How does CORZYNA™ work?**

How CORZYNA™ works to treat your symptoms of angina is not exactly known.

#### **What are the ingredients in CORZYNA™?**

Medicinal ingredients: Ranolazine

Non-medicinal ingredients: Hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, Opadry® II 85F570040 beige, Opadry® II 32K520117 yellow, purified water, sodium hydroxide.

#### **CORZYNA™ comes in the following dosage forms:**

Extended-release Tablets: 500 mg and 1000 mg

#### **Do not use CORZYNA™ if you:**

- are allergic to ranolazine or to any of the other ingredients in CORZYNA™ (see list of non-medicinal ingredients above)
- have severe kidney disease
- have moderate to severe liver disease
- take any of the following medicines. These can have serious interactions with CORZYNA™.
  - for arrhythmias: quinidine, procainamide, disopyramide, sotalol, ibutilide, amiodarone, dronedarone
  - for a fungal infection: ketoconazole, itraconazole, voriconazole, posaconazole
  - for an infection: clarithromycin
  - for depression: nefazodone
  - for HIV: nelfinavir, ritonavir, lopinavir, saquinavir
  - for tuberculosis (TB): rifampicin, rifabutin, rifapentine
  - for seizures: phenobarbital, phenytoin, carbamazepine
  - St. John's wort
- eat grapefruit, drink grapefruit juice or take products that contain grapefruit



**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CORZYNA™. Talk about any health conditions or problems you may have, including:**

- all of the medicines you take (prescription, over-the-counter (OTC) and natural health products)
- if you have or have a family history of a heart problem, called 'QT prolongation' or 'long QT syndrome'
- if you have low electrolyte levels (such as low potassium, magnesium or calcium), conditions that can cause low electrolyte levels (such as persistent vomiting and eating disorders) or are taking medicines that can affect your electrolyte levels such as:
  - diuretics
  - laxatives
  - enemas
  - high dose corticosteroids
  - medicines for acid reflux or gastroesophageal reflux disease (GERD)
- if you have liver problems
- if you have kidney problems
- if you are pregnant or plan to become pregnant. It is not known if CORZYNA™ will harm your unborn baby
- if you are breastfeeding or plan to breastfeed. It is not known if CORZYNA™ passes into your breast milk. Your doctor will decide if you should breastfeed or if you should stop treatment with CORZYNA™

**Other warnings you should know about:**

**Patients over 75 years of age:** You may be more sensitive to experiencing side effects.

**Monitoring and Laboratory tests:** Before you start treatment with CORZYNA™ and periodically during treatment your doctor should:

- perform electrocardiograms (ECGs) to monitor your heart
- do blood tests to check your electrolyte levels
- check your kidney and liver function

**Driving and using machinery:** You should avoid driving a car, using machinery or doing tasks that require you to be alert until you know how CORZYNA™ affects you. CORZYNA™ may cause:

- dizziness
- blurred vision
- you to feel confused
- hallucinations: hearing, seeing or sensing things that are not there

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

The following may also interact with CORZYNA™:

- medicines for heart problems including arrhythmias: such as digoxin, propafenone, flecainide
- medicines for bacterial, viral or fungal infection: such as erythromycin, rifampicin, rifabutin, rifapentine, fluconazole
- medicines to prevent organ rejection after a transplant: such as cyclosporine, sirolimus, everolimus

- medicines used to lower your cholesterol: such as simvastatin, lovastatin, atorvastatin
- medicines for high blood pressure: such as metoprolol, diltiazem, verapamil
- medicines for depression: such as imipramine, doxepin, amitriptyline
- metformin – used to treat high blood sugar (diabetes)
- tacrolimus – used to treat eczema

**How to take CORZYNA™:**

Take CORZYNA™:

- exactly as your doctor tells you
- **do not** crush, break or chew the tablet. Swallow it whole.
- **do not** take more than 1000 mg twice a day

**Usual adult dose:** 500 mg or 1000 mg twice a day.

**Overdose:**

If you think you have taken too much CORZYNA™, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Signs of an overdose include:

- low blood pressure
- slow heart rate
- muscle twitches
- shaking
- feeling unsteady or confused
- dizziness
- nausea and vomiting
- trouble speaking / understanding
- hallucinations

**Missed Dose:**

If you miss a dose, wait and take the next dose at your regular time. Do not double your dose to make up for the missed dose.

**What are possible side effects from using CORZYNA™?**

These are not all the possible side effects you may have when taking CORZYNA™. If you experience any side effects not listed here, tell your healthcare professional.

| <b>Serious side effects and what to do about them</b> |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect                                      | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| <b>COMMON</b>   |                                      |              |   |
| Dizziness   | ✓                                    |              |   |
| Headache  | ✓                                    |              |   |
| Constipation  | ✓                                    |              |   |
| Nausea  | ✓                                    |              |   |
| <b>LESS COMMON</b>                                    |                                      |              |   |
| QT prolongation (changes in the                       |                                      |              | ✓   |

|   |  |   |  |
|---|--|---|--|
| electrical activity of your heart):<br>dizziness, feeling faint or<br>lightheaded, heart beating irregularly<br>or fast, seizures |  |   |  |
| Kidney failure in people who already<br>have severe kidney problems   |  | ✓ |  |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

Store at room temperature (15°C – 30°C).  
Keep out of reach and sight of children.

### If you want more information about CORZYNA™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website [www.kyepharma.com](http://www.kyepharma.com), or by calling 1-888-822-7126.

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