Product Monograph

Including Patient Medication Information

[Pr]**CORZYNA**™

ranolazine extended-release tablets

For oral use

375 mg, 500 mg, 750 mg and 1000 mg of ranolazine

Antianginal

Kye Pharmaceuticals Inc.

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Date of Authorization:
2025-06-30

Control Number: 264421

Recent Major Label Changes

4. Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	06/2025

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

CORZYNA (ranolazine extended-release tablets) is indicated, as add-on therapy, for symptomatic treatment of adult 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 7.1.4 Geriatrics and 8.5 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 9 Drug Interactions)
- patients taking Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmics (e.g., sotalol, ibutilide, amiodarone, dronedarone)
- patients taking inducers of CYP 3A4, e.g., rifampicin, phenobarbital, carbamazepine, St. John's wort (see 9 Drug Interactions)
- patients with severe renal impairment, i.e., eGFR ≤30 mL/min/1.73m2
- patients with moderate or severe hepatic impairment (see 7 Warnings and Precautions, Hepatic/ Biliary/ Pancreatic)
- patients with a hypersensitivity to ranolazine or any of the excipients (see 6 Dosage Forms, Strengths, Composition, and Packaging)

3. Serious Warnings and Precautions Box

- CORZYNA has been shown to prolong the QT interval (see 2. Contraindications; 7. Warnings and Precautions, Cardiovascular, QT Interval Prolongation; 8.5. Post- Market Adverse Reactions; 9. Drugs Interactions; 10.2. Pharmacodynamics, Electrocardiographic Effects)
- Doses of 1000 mg twice daily of CORZYNA should not be exceeded.

4. Dosage and Administration

4.1. Dosing Considerations

- Limit the maximum dose of CORZYNA to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors
- Use of P-gp inhibitors may increase exposure to CORZYNA.

4.2. Recommended Dose and Dosage Adjustment

- Initiate CORZYNA dosing at 375 mg or 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 9.4. Drug-Drug Interaction).
- 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 (see 2. Contraindications)
- Use of P-gp inhibitors, such as cyclosporine, may increase exposure to CORZYNA (see 9.4. Drug-Drug Interactions).

4.4. Administration

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

4.5. 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. Overdose

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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Extended-release Tablets, 375 mg, 500 mg, 750 mg, and 1000 mg	HPMC 2910/ Hypromellose, hydroxypropylcellulose, iron oxide red, iron oxide yellow, macrogol/PEG, lactose monohydrate, magnesium stearate, copolymer based on ethyl acrylate and methacrylic acid, microcrystalline cellulose, polysorbate 80, polyvinyl alcohol, purified water, sodium hydroxide, sodium lauryl sulfate, talc, titanium dioxide, triacetin.

Description

CORZYNA 375 mg tablets are white or off-white coloured, biconvex film coated, oblong shaped tablets debossed with "375" on one side and plain on the other side available in cartons of 60.

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 750 mg tablets are white or off-white coloured, biconvex film coated, oblong shaped tablets embossed with "750" on one side and plain on the other side available in cartons 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

General

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 9. 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 2. Contraindications).

Cardiovascular

QT Interval Prolongation

Ranolazine blocks I_{Kr} and prolongs the QT_C interval in a dose-related manner (see 10.2. 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 8.5. 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 2. Contraindications and 9. Drug Interactions). Use of CORZYNA should be avoided in patients with QT prolongation, acquired long QT syndrome and most forms of congenital long QT syndrome as well as those patients on QT prolonging drugs.

QTc 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 QTc-prolonging drug. Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc 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.

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.

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.

While taking CORZYNA, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination if they are experiencing any of these effects.

Endocrine and Metabolism

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.

Hepatic/Biliary/Pancreatic

CORZYNA is contraindicated in patients with moderate to severe liver impairment (see 2. 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 10.2. Pharmacodynamics). Careful dose titration is recommended in patients with mild hepatic impairment.

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 10.2. 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.

Renal

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 2. 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.

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.

Monitor renal function after initiation and periodically in patients with renal impairment (CrCL <60 mL/min) (see 2. Contraindications).

7.1. Special Populations

7.1.1. Pregnancy

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. Breastfeeding

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 ≥75 years of age who were treated with ranolazine had a higher incidence of adverse events, serious adverse events (see 8.3. 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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

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%). 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.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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.

Table 2 - Summary of Treatment Emergent Adverse Events Reported by ≥ 3% of Subjects in the MARISA Trial*

System organ class/preferred term	Ranolazine n = 191 (%)			Placebo n = 191 (%)
	500 mg	1000 mg	1500 mg	
Gastrointestinal disorders				
Constipation	0	1.7	4.3	0
Nausea	< 1	1.1	8.6	0
General and other disorders				
Dizziness	1.1	5.0	12.3	1.1
Headache	< 1	1.1	2.7	2.2
Asthenia	0	1.7	6.4	2.2
Sweating	0	0	2.7	0

*The MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) Trial involved 191 patients with effort angina who were randomized in a double-blind, four-period crossover study of sustained-release ranolazine or placebo received b.i.d.

Table 3 – Summary of Treatment Emergent Adverse Events Reported by ≥ 1% of Subjects in the ERICA Trial#

System organ class/preferred term	Ranolazine n = 281 (%)	Placebo n = 284 (%)
Cardiovascular disorders		
Peripheral edema	5.7	2.8
Tachycardia	1.1	0.4
Gastrointestinal disorders		
Constipation	8.9	1.8
Nausea	2.8	0.7
General and other disorders		
Dizziness	3.9	2.5

System organ class/preferred term	Ranolazine n = 281 (%)	Placebo n = 284 (%)
Headache	2.8	2.5

[#] The ERICA (Efficacy of Ranolazine in Chronic Angina) Trial was a double-blind placebo-controlled study in 565 patients with coronary disease and ≥ 3 anginal attacks/ week who were randomized to 1,000 mg ranolazine or placebo twice a day for 6 weeks.

8.3. 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 ≥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 7.1.4. Geriatrics).

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

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 2. Contraindications).

8.5. 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. Serious Drug Interactions

- Concomitant use of CORZYNA with strong CYP 3A4 inhibitors, CYP 3A4 inducers and Class IA and Class III antiarrhythmics is contraindicated (see 2. Contraindications).

9.2. Drug Interactions Overview

The concomitant administration of CORZYNA with other drugs known to prolong the QT interval or induce Torsade de Pointes should be avoided.

Drugs that can decrease serum electrolyte levels should be used with caution with CORZYNA.

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. The potential for dose-related adverse events (e.g. nausea, dizziness) may be increased with higher plasma concentrations of ranolazine. Limit the dose of CORZYNA to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors. Careful dose titration of ranolazine is required in patients treated with P-gp inhibitors and CYP 2D6 inhibitors.

CYP 3A4 Substrates

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. The plasma levels of simvastatin 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 9.4. 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.

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.

Ranolazine and its various metabolites are not known to inhibit the metabolism of CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes.

9.3. Drug-Behaviour Interactions

The interaction of CORZYNA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 – Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Strong CYP 3A4 Inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nelfinavir, ritonavir, indinavir, saquinavir and grapefruit juice)	CT	Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (e.g., nausea, dizziness) may also increase with increased plasma concentrations. Concomitant treatment with ketoconazole 200 mg twice daily increased the AUC of ranolazine by 3.0- to 3.9-fold during ranolazine treatment.	Strong CYP 3A4 inhibitors are contraindicated (see 2. Contraindications and 10.3. Pharmacokinetics).
Moderate CYP 3A4 Inhibitors (e.g., including, but not limited to, diltiazem, verapamil, aprepitant, erythromycin, and fluconazole	CT	Causes dose-dependent increases in average ranolazine steady-state concentrations of 1.5- to 2.4-fold. Diltiazem (180–360 mg daily) and verapamil (120 mg three times daily) increase ranolazine steady-state plasma concentrations about 2-fold.	Careful dose titration of ranolazine is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors. Limit the dose of CORZYNA to 500 mg twice daily in patients taking moderate CYP 3A4 inhibitors, and down titration of CORZYNA may be required (see 4. Dosage and Administration; 7. Warnings and Precautions, General, CYP3A4, CYP2D6, and P-gp system inhibitors, and 10.3 Pharmacokinetics).
P-gp Inhibitors (e.g., Cyclosporine, Verapamil, Digoxin)	CT	Increase plasma levels of ranolazine. Verapamil (120 mg three times daily) increases ranolazine steady- state concentrations 2.2-fold. Plasma concentrations of ranolazine are not significantly altered by concomitant use	Concomitant use of CORZYNA with P-gp inhibitors may increase ranolazine concentrations. Use CORZYNA with caution in these patients, limiting dose increases. Careful dose titration of CORZYNA is recommended in patients treated with P-gp

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
		with digoxin at 0.125 mg once daily.	inhibitors. Down-titration of CORZYNA may be required if initiating these therapies. (see 7. Warnings and Precautions, General, CYP3A4, CYP2D6, and P-gp system inhibitors; 10.3 Pharmacokinetics).
CYP 3A4 Inducers (e.g., rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort)	CT	Rifampicin (600 mg once daily) decreases ranolazine steady-state concentrations (1000 mg twice daily) by approximately 95%.	Concomitant use of CORZYNA with CYP 3A4 inducers is contraindicated (see 2. Contraindications and 10.3. Pharmacokinetics).
Anti-arrhythmic Medicines and Other Medicinal Products that may Prolong the QT interval	CT	CORZYNA causes QTc prolongation, concomitant use with anti-arrhythmic medicines may prolong the QT interval.	(see 7. Warnings and Precautions, Cardiovascular and 10.2. Pharmacodynamics, Electrocardiographic Effects). 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.

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Class IA (e.g. procainamide, disopyramide) and Class III (e.g.: sotalol, ibutilide, amiodarone, dronedarone) Antiarrhythmics	C	CORZYNA causes QTc prolongation, concomitant use with anti-arrhythmic medicines may prolong the QT interval.	Concomitant use with Class I antiarrhythmics and Class III antiarrhythmics is contraindicated (see 2. Contraindications).
Drugs that Affect Electrolyte Levels Thiazide and related diuretics (e.g. Laxatives and enemas; Amphotericin B; High-dose corticosteroids; Proton Pump inhibitors)	CT	Electrolyte disturbances may increase the risk of QT interval prolongation in patients prone to this condition.	Drugs that can decrease serum electrolyte levels should be used with caution with CORZYNA (see 7. Warnings and Precautions, Cardiovascular, QT Interval Prolongation).
Drugs Metabolized by CYP 3A4 CYP 3A4 substrates e.g.: (Lovastatin; Atorvastatin) CYP 3A4 substrates with narrow therapeutic range: (e.g. Cyclosporine; Tacrolimus Sirolimus; Everolimus)	CT	Increased plasma concentrations of tacrolimus, a CYP3A4 substrate, have been observed in patients after ranolazine administration. It is recommended that tacrolimus blood levels are monitored when co- administering CORZYNA and tacrolimus and that tacrolimus dosage is adjusted accordingly. This is also recommended for other CYP3A4 substrates with a narrow therapeutic range (e.g., cyclosporine, sirolimus, everolimus).	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 CYP3A4 substrates (e.g. lovastatin, atorvastatin) and CYP3A4 substrates with a narrow therapeutic range may be required as CORZYNA may increase plasma concentrations of these drugs (see 10.3. Pharmacokinetics)

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Drugs Transported by P-gp (e.g., Digoxin)	CT	An increase in plasma digoxin concentrations by an average of 1.5-fold has been reported when CORZYNA and digoxin are co-administered. Therefore, digoxin levels should be monitored following initiation and termination of ranolazine therapy.	Careful dose titration of ranolazine is recommended in patients treated with P-gp inhibitors. Down-titration of CORZYNA may also be required. The dose of digoxin may be adjusted (see 10.3. Pharmacokinetics)
Drugs Metabolized by CYP 2D6 (e.g., Tricyclic antidepressants, antipsychotics)	CT	CORZYNA is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine. The potent CYP2D6 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 1.2-fold. No dose adjustment is required. At the dose level 500 mg twice daily, co-administration of a potent inhibitor of CYP2D6 could result in an increase in ranolazine AUC of about 62%.	Since the exposure to CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics may be increased during co-administration with CORZYNA, lower doses of these drugs may be required (see 10.3. Pharmacokinetics).

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Drugs Transported by OCT2 (e.g.: Metformin, pindolol and varenicline)	CT	Plasma exposure of metformin (1000 mg twice daily) increased 1.4- and 1.8- fold in subjects with type 2 diabetes mellitus when co-administered with CORZYNA. Metformin exposure was not significantly increased when given with CORZYNA 500 mg twice daily (see 10.3. Pharmacokinetics)	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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5. Drug-Food Interactions

Grapefruit, grapefruit juice, and grapefruit-containing products should not be ingested while receiving CORZYNA (see 2. Contraindications). These foods inhibit CYP 3A4 and increase plasma concentrations of ranolazine.

9.6. Drug-Herb Interactions

Concomitant use of CORZYNA with CYP 3A4 inducers St. John's wort is contraindicated. Interactions with other herbal products have not been established (see 9.4 Drug-Drug Interactions, Table 4)

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. 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 2. Contraindications, 7 Warnings and Precautions, Cardiovascular, QT Interval Prolongation, 9 Drug Interactions). In a double-blind, randomized, placebo- controlled, parallel-design ECG assessment study, healthy subjects (N=10/group) were treated with a supratherapeutic 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.

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).

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 AUC0-τ 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 ^{14}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 9. Drug Interactions).

Food (high-fat breakfast) has no important effect on the C_{max} 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.

11. Storage, Stability, and Disposal

Store CORZYNA at 15°C to 30°C.

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

Part 2: Scientific Information

13. Pharmaceutical Information

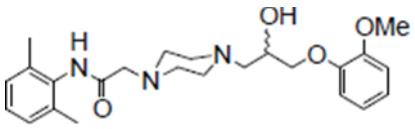
Drug Substance

Non-proprietary name of the drug substance(s): Ranolazine

Chemical name: 1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-±,

Molecular formula and molecular mass: $C_{24}H_{33}N_3O_4$; 427.54 g/mol

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.

14. Clinical Trials

14.1. Clinical Trials by Indication

As an add on to first-line antianginal therapies.

Table 5 – Summary of Patient Demographics for Clinical Trials with Ranolazine, when used as add-on to first-line antianginal therapies

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (SD)	Sex
CARISA*	Randomized, Double-bling, placebo-controlled	1.Ranolazine 750 mg bid for 12 weeks	823 patients with symptomatic	64 yrs (9.3)	638 M 185 F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (SD)	Sex
		2. Ranolazine 1000 mg bid for 12 weeks 3. Placebo bid for 12 weeks	chronic angina		
ERICA[#]	Randomized, Double blind, placebo-controlled	Ranolazine 1000 mg bid or placebo for 6 weeks	565 patients with coronary disease and ≥ 3 anginal attacks/week	62 yrs (8.7)	409 M 155 F
MARISA[£]	Randomized, Double blind, placebo controlled four period crossover	Ranolazine 500 mg, 1000 mg or 1500 mg bid or placebo for 1 week	191 patients with effort angina	64 yrs (9.4)	140 M 51 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.

[£]In the MARISA trial provides limited data with ranolazine assessed as a monotherapy. One- hundred and ninety-one patients were randomised to treatment with ranolazine 500 mg twice daily, 1000 mg twice daily, 1500 mg twice daily, and matching placebo, each for 1 week in a crossover design. Ranolazine was significantly superior to placebo in prolonging exercise time, time to angina, and time to 1 mm ST segment depression at all doses studied with an observed dose-response relationship. Improvement of exercise duration was statistically significant compared to placebo for all three doses of ranolazine from 24 seconds at 500 mg twice daily to 46 seconds at 1500 mg twice daily, showing a dose-related response.

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 Table 6, below.

Table 6 - Exercise Treadmill Results at Week 12 in the CARISA Trial

	CARISA Trial				
	Ranolazine		Placebo (N =258)	Mean[a] treatment difference (SE)	
	750 mg (N = 272)	1000 mg (N = 261)		750 mg	1000 mg
Primary endpoint					
Exercise Duration, mean change from baseline, seconds					
Trough	115.4	115.8	91.7	23.7[b] (10.9)	24[b] (11.0)
Peak	99.4	91.5	65.4	34[c] (10.7)	26.1[c] (10.8)
Key secondary endpoints					
Time to Angina, mean change from baseline, seconds					
Trough	145.1	146.2	114.3	29.7[b] (12.1)	26.0[b] (12.2)
Peak	126.9	126.8	88.9	38.0[c] (12.4)	37.9[c] (12.6)
Time to 1 mm ST-Segment Depression, mean change from baseline, seconds					
Trough	145.1	146.2	125.1	19.9 (12.2)	21.1 (12.4)
Peak	100.0	93.8	59.2	40.8[c] (11.8)	34.5[c] (11.9)

a. Mean difference from placebo based on analysis of variance model, including effects for baseline, pooled site, background therapy, and treatment, adjusted for randomization stratification factors

b. Statistically significant under multiplicity control for ranolazine vs placebo ($p < 0.05$)

c. Statistically significant under multiplicity control for ranolazine vs placebo ($p \leq 0.005$)

The effects of ranolazine on angina frequency and nitroglycerin use are shown in Table 7. A baseline frequency of 4.5 anginal episodes per week were observed in all treatment groups.

Table 7 - Angina Frequency and Nitroglycerin Use in the CARISA Trial

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

[a] Twice daily

Tolerance to 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 8, 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 8 – Results of Key Endpoints at 6-week Duration in Subjects with Stable Coronary Disease in Angina Frequency and Nitroglycerin Use in the ERICA Trial

	ERICA Trial		
	Ranolazine[a] (N = 277)	**Placebo (N = 281)**	**p-value[b]**
Primary endpoint			
Weekly angina frequency (attacks/ week)			
Trimmed mean ± SE	2.88 ± 0.19	3.31 ± 0.22	0.028
Median	2.18	2.43	--
Secondary endpoint			
Weekly nitroglycerin consumption (doses/ week)			
Trimmed mean ± SE	2.03 ± 0.20	2.68 ± 0.22	0.014
Median	1.34	1.67	--

a. 1000 mg twice daily
b. Based on Cochran-Mantel Haenszel mean scores test using rank scores, stratifying by pooled site
SE = Standard error

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.

14.2. Comparative Bioavailability Studies

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 9.

Table 9 – Summary Table of the Comparative Bioavailability Data

Ranolazine (1 x 1000 mg) From measured data Geometric mean Arithmetic mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (ng•h/mL)	20,346.5 24,189.7 (53.8)	18,678.5 22,135.1 (54.3)	108.9	99.1 - 119.5
AUC_I (ng•h/mL)	20,681.7 24,552.4 (53.9)	19,414.7 22,645.7 (52.7)^	106.7	98.2 - 116.0
C_{MAX} (ng/ mL)	1479.6 1617.8 (42.6)	1369.5 1515.4 (45.7)	108.0	100.3 - 116.4
T_{MAX}[3] (h)	5.33 (1.00 – 24.00)	5.03 (1.00 – 24.02)		
$T_{½}$[4] (h)	5.10 (38.2)	4.75 (33.0)^		

[1] CORZYNA (ranolazine) Extended-Release Tablets, 1000 mg (Kye Pharmaceuticals Inc.)
[2] RANEXA (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc.), marketed in the United States.
[3] Expressed as the median (range) only.
[4] Expressed as the arithmetic mean (CV %) only.
^N = 62

An open label, randomized, two-period, crossover, single (1 x 750 mg) oral dose comparative bioavailability study of CORZYNA (ranolazine) Extended-Release Tablets, 750 mg (Kye Pharmaceuticals Inc.) and RANEXA (ranolazine) Extended-Release Tablets, 750 mg (Menarini International Operations Luxembourg S.A., marketed in Europe) was conducted in healthy, adult, male and female subjects under fasting conditions. The results of the 64 subjects who completed the study are summarized in Table 10.

Table 10 – Summary Table of the Comparative Bioavailability Data

Ranolazine (1 x 750 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	8998.6 10396.0 (56.59)	9065.6 10481.1 (59.92)	99.2	92.9 – 105.9
- AUCI (ng h/mL)	9161.6 10636.6 (58.85)	9,231.0 10,647.1 (59.29)	99.2	92.8 – 106.0
C_{max}	798.6	758.8	105.3	96.6 – 114.4
(ng/mL)	875.6 (40.39)	858.9 (49.42)		
Tmax[3] (h)	4.51 (2.00 – 12.00)	5.50 (1.00 – 16.00)		
$T_{1/2}$[4] (h)	5.40 (49.70)	5.69 (75.60)		

1. CORZYNA (ranolazine) Extended-Release Tablets, 750 mg (Kye Pharmaceuticals Inc.)
2. RANEXA (ranolazine) Extended-Release Tablets, 750 mg (Menarini – Von Heyden GmbH), marketed in Europe
3. Expressed as the median (range)
4. Expressed as the arithmetic mean (CV%) only

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 11.

Table 11 – Summary Table of the Comparative Bioavailability Data

Ranolazine (1 x 1000 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	18,851.1 20,769.2 (45.2)	18,763.3 20,470.0 (42.3)	100.6	94.86 – 106.68

Ranolazine (1 x 1000 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_I (ng·h/mL)	19,298.5 21,307.0 (45.6)^	19,024.8 20,729.7 (42.3)	101.0	95.10 – 107.18
C_{max} (ng/mL)	1396.9 1497.3 (38.7)	1422.0 1517.0 (38.5)	98.3	91.99 – 105.09
T_{max}[3](h)	5.67 (3.00 – 24.00)	5.67 (4.02 – 24.03)		
$T_{½}$[4] (h)	5.01(76.8)^	4.50 (41.6)		

[1] CORZYNA (ranolazine) Extended-Release Tablets, 1000 mg (Kye Pharmaceuticals Inc.)
[2] RANEXA (ranolazine) Extended-Release Tablets, 1000 mg (Gilead Sciences, Inc.), marketed in the United States
[3] Expressed as the median (range)
[4] Expressed as the arithmetic mean (CV%) only
^N = 58

An open label, randomized, two-treatment, two-sequence, two-period, crossover, single (1 x 750 mg) oral dose comparative bioavailability study of CORZYNA (ranolazine) Extended- Release Tablets, 750 mg (Kye Pharmaceuticals Inc.) and RANEXA (ranolazine) Extended- Release Tablets, 750 mg (Menarini International Operations Luxembourg S.A., marketed in Europe) was conducted in healthy, adult, male and female subjects under fed conditions. The results of the 58 subjects who completed the study are summarized in Table 12.

Table 12– Summary Table of the Comparative Bioavailability Data

Ranolazine (1 x 750 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T	8,453	8,359	101.1	97.1– 105.3
(ng·h/mL)	9,427 (48.93)	9,313 (50.46)		
AUC_I	9,467[5]	9,880[5]	95.5	88.7 – 102.9
(ng·h/mL)	10,392 (44.62)[5]	10,911 (47.62)[5]		
C_{max}	680	696	97.7	91.7 – 104.1
(ng/mL)	741 (43.19)	751 (40.97)		

Ranolazine (1 x 750 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
T_{max}[3](h)	4.50 (2.00 – 16.02)	5.55 (2.50 – 12.00)		
$T_{½}$[4] (h)	6.79 (3.78)	8.97 (6.87)		

[1] CORZYNA (ranolazine) Extended-Release Tablets, 750 mg (Kye Pharmaceuticals Inc.)
[2] RANEXA (ranolazine) Extended-Release Tablets, 750 mg (Menarini – Von Heyden GmbH), marketed in Europe
[3] Expressed as the median (range)
[4] Expressed as the arithmetic mean (CV%) only
[5] N = 55

16. Non-Clinical Toxicology

Genotoxicity 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.

Carcinogenicity There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m^2/day) and 50 mg/kg/day for 24 months in mice (150 mg/m^2/day). These maximally tolerated doses are 0.8 and 0.1 times, respectively, the 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.

Reproductive and developmental toxicology

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

Pr CORZYNA™

Ranolazine Extended-Release Tablets

This Patient Medication Information is written for the person who will be taking **CORZYNA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **CORZYNA**, talk to a healthcare professional.

Serious warnings and precautions box

- 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 CORZYNA is 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 CORZYNA works:

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

The ingredients in CORZYNA are:

Medicinal ingredient(s): Ranolazine

Non-medicinal ingredients: HPMC 2910/hypromellose, hydroxypropylcellulose, iron oxide red, iron oxide yellow, macrogol/PEG, lactose monohydrate, magnesium stearate, copolymer based on ethyl acrylate and methacrylic acid, microcrystalline cellulose, polysorbate 80, polyvinyl alcohol, purified water, sodium hydroxide, sodium lauryl sulfate, talc, titanium dioxide, triacetin.

CORZYNA comes in the following dosage form(s):

Extended-release Tablets: 375 mg, 500 mg, 750 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, indinavir, 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 if you:

- take medicines (prescription, over-the-counter (OTC) and natural health products)
- have or have a family history of a heart problem, called 'QT prolongation' or 'long QT syndrome'
- 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)
- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if CORZYNA will harm your unborn baby
- 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.

Serious drug interactions

Serious drug interactions with CORZYNA include:

- strong CYP 3A4 inhibitors: (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nelfinavir, ritonavir, indinavir, saquinavir and grapefruit juice) are contraindicated.
- CYP 3A4 inducers (e.g., rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort) are contraindicated, and
- Class IA (e.g. procainamide, disopyramide) and Class III antiarrhythmics (e.g.: sotalol, ibutilide, amiodarone, dronedarone) are contraindicated.

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.
- **Do not** take more than 500 mg twice a day if you also take medicines such as diltiazem, verapamil, erythromycin, and fluconazole (moderate *CYP 3A4 inhibitors*)

Usual dose:

375 mg, 500 mg, 750 mg, or 1000 mg twice a day.

Overdose:

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

If you think you, or a person you are caring for, have taken too much CORZYNA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

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.

Side effects may include:

- Dizziness
- Headache
- Constipation
- Nausea

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
QT prolongation (changes in the electrical activity of your heart): dizziness, feeling faint or			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
lightheaded, heart beating irregularly or fast, seizures			
Kidney failure in people who already 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, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare 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).

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

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 the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.kyepharma.com; or by calling 1-888-822-7126.

This leaflet was prepared by Kye Pharmaceuticals Inc.

Date of Authorization: 2025-06-30