CORZYNA™ (ranolazine)

HEALTHCARE PROVIDER FACT SHEET

(download additional copies at www.kyepharma.com)

See also the full product monograph available at www.kyepharma.com.

Dose Reductions

Dose reductions of CORZYNA™ are required when CORZYNA™ is taken with:

- Moderate CYP3A4 inhibitors
- P-gp inhibitors

Caution Required

Use CORZYNA™ with caution in patients:

- Taking P-gp inhibitors
- Taking drugs that affect electrolyte levels
- ≥75 years of age
- With angina and heart failure NYHA Class I to IV

Risk Factors for Torsade de Pointes

- Female gender
- Age ≥65 years
- Baseline QT/QTc interval prolongation
- Genetic variants affecting cardiac ion channels or regulatory proteins
- Congenital long QT syndromes
- Concomitant use of drugs known to prolong QT interval
- History of arrhythmias
- Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders)
- Bradycardia
- Acute neurological events

SERIOUS WARNINGS AND PRECAUTIONS

CORZYNA™ has been shown to prolong the QT interval (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections below). Doses of 1000 mg twice daily of CORZYNA™ should not be exceeded.

INDICATIONS

CORZYNA™ 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.

CONTRAINDICATIONS

CORZYNA™ is contraindicated in patients:

- taking strong inhibitors of CYP3A4
- taking Class IA or Class III antiarrhythmics
- taking inducers of CYP3A4
- with severe renal impairment (i.e., eGFR ≤30 mL/min/1.73m^2)
- with moderate or severe hepatic impairment
- with a hypersensitivity to ranolazine or any of the excipients

DOSAGE AND ADMINISTRATION

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 is 1000 mg twice daily. Take CORZYNA™ with or without meals.

Dose adjustments may be needed when CORZYNA™ is taken in combination with certain other drugs (see DRUG INTERACTIONS section below and blue box on the left).

WARNINGS AND PRECAUTIONS

QT Interval Prolongation:

- Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner. 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.
- Rare events of Torsade de Pointes and ventricular fibrillation have been reported during post-market use.
- The risk of Torsade de Pointes during treatment with ranolazine can be mitigated through dose reduction and/or avoidance of its use in patients with certain underlying risk factors or taking certain concomitant medications.
  - Concomitant use with Class IA and Class III antiarrhythmics is contraindicated (e.g., quinidine, procainamide, disopyramide, sotalol, ibutilide, amiodarone, dronedarone)
  - Doses of 1000 mg twice daily should not be exceeded
  - CORZYNA™ is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir, grapefruit juice)
  - Concomitant administration with other drugs that prolong 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.
  - Risk factors for Torsade de Pointes (refer to list 'Risk Factors for Torsade de Pointes' in blue column to the left)
- 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.
  - 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.

Strong CYP3A4 Inhibitors
- Clarithromycin
- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Nelfinavir
- Ritonavir
- Indinavir
- Saquinavir
- Grapefruit juice

Class IA and Class III Antiarrhythmics
- Quinidine
- Procainamide
- Disopyramide
- Sotalol
- Ibutilide
- Amiodarone
- Dronedarone

CYP3A4 Inducers
- Phenytoin
- Rifampicin
- Rifabutin
- Rifapentine
- Phenobarbital
- Carbamazepine
- St. John's wort

Moderate CYP3A4 Inhibitors
- Diltiazem
- Verapamil
- Erythromycin
- Fluconazole

P-gp Inhibitors & Transporters
- Cyclosporine
- Verapamil
- Digoxin

CYP2D6 Inhibitors & Substrates
- Digoxin
- Paroxetine
- Metoprolol
- Propafenone
- Flecainide
- Tricyclic antidepressants
- Antipsychotics
- Dextromethorphan

CYP3A4 Substrates
- Simvastatin
- Lovastatin
- Atorvastatin
- Cyclosporine
- Tacrolimus
- Sirolimus
- Everolimus

OCT2 Substrates
- Metformin
- Pindolol
- Varenicline

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Renal Impairment:
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).

DRUG INTERACTIONS
- Strong CYP3A4 inhibitors: Contraindicated
- Class IA and Class III antiarrhythmics: Contraindicated
- CYP3A4 inducers: Contraindicated
- Moderate CYP3A4 inhibitors: Limit maximum dose of CORZYNA™ to 500 mg twice daily.
- P-gp inhibitors and transporters: Careful dose titration of ranolazine is required. Down-titration of CORZYNA™ may be required if initiating these therapies.
- CYP2D6 inhibitors and substrates: Careful dose titration of ranolazine is required in patients taking CYP2D6 inhibitors. Higher plasma levels of ranolazine may also occur in patients who are poor metabolizers of CYP2D6.
- CYP3A4 substrates: 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 and CYP3A4 substrates with a narrow therapeutic range may be required.
- OCT2 substrates: Use of metformin should be limited to 1700 mg daily if used with CORZYNA™ 1000 mg twice daily.

USE IN SPECIAL POPULATIONS
Geriatric patient population:
- Patients ≥75 years of age had a higher incidence of adverse events
- Patients may have increased ranolazine exposure due to greater frequency of impairment of hepatic, renal, and cardiac function, or various comorbidities and/or concomitant drug use that may be present.
- Dose selection should be carried out with caution.

Pregnant and Lactating Women:
- There is no available data on the use of CORZYNA™ in pregnant and lactating 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.
- A decision should be made whether to forego breastfeeding in patients taking CORZYNA™ or to discontinue CORZYNA™ treatment.

Renal impairment:
- CORZYNA™ is contraindicated in severe renal impairment.
- Careful dose titration is recommended in patients with mild to moderate renal impairment.
- The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.
- Monitor renal function prior to initiation and periodically in patients treated with CORZYNA™. Discontinue CORZYNA™ if acute renal failure develops.

Hepatic impairment:
- CORZYNA™ is contraindicated in patients with moderate to severe hepatic impairment.
- Careful dose titration is recommended in patients with mild hepatic impairment.

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