Angiwell-XR® Tablets انجی ویل۔ایکس آر ٹیبلیٹس

(Ranolazine)

QUALITATIVE & QUANTITATIVE COMPOSITION

Angiwell-XR 500 mg Tablets

Each extended release tablet contains:

Ranolazine.....500 mg

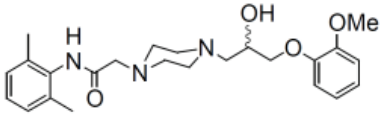
Angiwell-XR 1000 mg Tablets

Each extended release tablet contains:

Ranolazine.....1000 mg

DESCRIPTION

Angiwell–XR (Ranolazine) is available as a film-coated, non-scored, extended-release tablet for oral administration. Ranolazine is a racemic mixture, chemically described as 1-piperazineacetamide,N-(2,6dimethylphenyl)-4-[2-hydroxy -3-(2-methoxyphenoxy)propyl]-, (±)-. It has an empirical formula of $C_{24}H_{33}N_3O_4$, a molecular weight of 427.54 g/mole, and the following structural formula:



Ranolazine is 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.

CLINICAL INFORMATION

Indication

Angiwell–XR (Ranolazine) is indicated for the treatment of chronic angina.

Angiwell–XR (Ranolazine) Tablets may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

Dosage and Administration

Initiate Angiwell–XR (Ranolazine) Tablet 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 Angiwell–XR (Ranolazine) Tablet is 1000 mg twice daily. If a dose of Angiwell–XR (Ranolazine) Tablet is missed, take the prescribed dose at the next scheduled time do not double the next dose.

Dosage Adjustment

Pediatric Use

Safety and effectiveness is not known in pediatric patients.

Administration Requirements

Take Angiwell–XR (Ranolazine) Tablet with or without meals. Swallow Angiwell–XR (Ranolazine) Tablet whole; do not crush, break, or chew.

Contraindications

Ranolazine Tablet is contraindicated in patients:

- Taking strong inhibitors of CYP3A
- Taking inducers of CYP3A
- With liver cirrhosis

Warnings and Precausions

QT Interval Prolongation

Ranolazine blocks IKr and prolongs the QTc interval in a dose-related manner. Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death. However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, potassium channel variants resulting in a long QT interval, in patients with a family history of (or congenital) long QT syndrome, or in patients with known acquired QT interval prolongation.

Renal Failure

Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) while taking Ranolazine tablets. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen [BUN]), discontinue Ranolazine Tablet and treat appropriately.

Interactions

Effects of Other Drugs on Ranolazine

Strong CYP3A Inhibitors

Do not use Ranolazine with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.

Moderate CYP3A Inhibitors

Limit the dose of Ranolazine to 500mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products.

P-gp Inhibitors

Concomitant use of Ranolazine and P-gp inhibitors, such as cyclosporine, may result in increases in Ranolazine concentrations. Titrate Ranolazine based on clinical response in patients concomitantly treated with predominant P-gp inhibitors such as cyclosporine.

CYP3A Inducers

Do not use Ranolazine with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort.

Effects of Ranolazine on Other Drugs

Drugs Metabolized by CYP3A

Limit the dose of simvastatin in patients on any dose of Ranolazine to 20 mg once daily, when Ranolazine is co-administered. Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may be required as Ranolazine may increase plasma concentrations of these drugs.

Drugs Transported by P-gp

Concomitant use of Ranolazine and digoxin results in increased exposure to digoxin. The dose of digoxin may have to be adjusted

Drugs Metabolized by CYP2D6

The exposure to CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics, may be increased during co-administration with Ranolazine, and lower doses of these drugs may be required.

Drugs Transported by OCT2

In subjects with type 2 diabetes mellitus, concomitant use of Ranolazine tablets 1000 mg twice daily and metformin is known to result in increased plasma levels of metformin. When Ranolazine tablets 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 Ranolazine tablets 500mg twice daily.

Pregnancy and Breastfeeding

Pregnancy Category C

There is no available data on Angiwell-XR(Ranolazine) use in pregnant women to inform any drug-associated risks.

There is no data available on the presence of Ranolazine in human milk, the effects on the breastfed infant, or the effects on milk production.

Adverse Reactions

Most common adverse reactions are dizziness, headache, constipation,nausea.

Nervous System Disorders

Tremor, paresthesia, abnormal coordination, and other serious neurologic adverse events have been reported to occur, sometimes concurrently, in patients taking Ranolazine. The onset of events are often known to be 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 are known in diabetic patients on antidiabetic medication.

Psychiatric Disorders

Hallucination.

Renal and Urinary Disorders

Dysuria, urinary retention.

Skin and Subcutaneous Tissue Disorders

Angioedema, pruritus, rash.

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 Ranolazine fatal outcomes have been reported. High intravenous exposure is known to result 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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other cardiac preparations, ATC code: C01EB18

Mechanism of Action

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

The QT prolongation effect of Ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential.

Pharmacokinetics Properties

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, C_{max} and AUC_{0-T} increase slightly more than proportionally to dose, 2.2 and 2.4-fold, respectively. With twice-daily dosing, the trough; peak ratio of the Ranolazine plasma concentration is 0.3 to 0.6. The pharmacokinetics of Ranolazine is unaffected by age, gender, or food.

Absorption and Distribution

After oral administration of Ranolazine, peak plasma concentrations of Ranolazine are reached between 2 and 5 hours. The bioavailability of Ranolazine from Ranolazine tablets are 76%. Because Ranolazine is a substrate of P-gp, inhibitors of P-gp may increase the absorption of Ranolazine.

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

Metabolism and Excretion

Ranolazine is metabolized mainly by CYP3A and, to a lesser extent, by CYP2D6. 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.

PHARMACEUTICAL INFORMATION

Shelf Life

2 years.

Special Precautions for Storage

- To be sold on the prescription of a registered medical practitioner only.
- Do not store above 30ºC.
- Keep out of the reach of children.
- Protect from light and moisture.

ہدایات :

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

۳۰ ڈگری سینٹی گریڈ سے زیادہ درجۂ حرارت پر نہ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔ دوا کو روشنی اور نمی سے بچائیں۔

Nature and Contents of Container

Angiwell–XR (Ranolazine) 500 mg tablets are supplied in the blister pack of 14's (7's x 2).

Angiwell–XR (Ranolazine) 1000 mg tablets are supplied in the blister pack of 14's (7's x 2).

MANUFACTURED BY

ASPIN

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