NEW DRUG APPROVAL

Brand Name	Aspruzyo Sprinkle™
Generic Name	ranolazine
Drug Manufacturer	Sun Pharmaceutical Industries, Inc.

New Drug Approval

FDA approval date: February 28, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form, New Drug Application (NDA): 216018

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Chronic angina is a prevalent manifestation of cardiovascular disease and is most commonly due to insufficient oxygen supply from fixed epicardial lesions in the coronary arteries. In addition to increasing the risk of cardiovascular death and recurrent myocardial infarction, chronic angina has a significant impact on functional capacity and quality of life. All patients with cardiovascular disease should be closely questioned to determine the functional and symptomatic limitations attributable to ischemic symptoms. The Canadian Cardiovascular Society Classification of Angina is the easiest metric to use; however, more sensitive measures such as the Seattle Angina Questionnaire offer a better overall assessment of angina symptoms and quality of life and can be used to compare the efficacy of different treatments. Treatment strategies that begin with either immediate revascularization or optimal medical therapy with antianginal agents significantly improve angina frequency and quality of life. Initial revascularization, especially with coronary artery bypass grafting, appears to offer more rapid relief of angina compared with percutaneous coronary intervention or medical therapy in the first months after initial revascularization. After a year of follow-up, though, much of the treatment differences are lost and all strategies (surgical/percutaneous revascularization or medical therapy) result in a significant improvement of angina symptoms.

Coronary heart disease impacts over 17 million adults in the United States. Of the 17 million Americans affected, 55% of those are male. It contributes to over 500,000 deaths each year in the U.S. At age 40 years, the lifetime risk of developing coronary disease is estimated at 49% for men and 32% for women. The incidence of coronary events increases with age, although the male predominance with these events gradually narrows with advancing age. coronary heart disease/ischemic heart disease is not unique to the U.S., it is the leading cause of death in adults from low, middle, and high-income countries.

Coronary heart disease can also cause significant debility. This debility can manifest in several ways, one of which is angina. Angina affects over 10 million people in the U.S., with over 500,000 new cases diagnosed each year.

Efficacy

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 ranolazine 750 mg, 1000 mg, or placebo, who also continued on daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg. Sublingual nitrates were used in this study as needed. In this trial, statistically significant ($p < 0.05$) increases in modified Bruce treadmill exercise duration and time to angina were observed for each ranolazine dose versus placebo, at both trough (12

hours after dosing) and peak (4 hours after dosing) plasma levels, with minimal effects on blood pressure and heart rate. The changes versus placebo in exercise parameters are presented in Table 1. Exercise treadmill results showed no increase in effect on exercise at the 1000 mg dose compared to the 750-mg dose.

Table 1. Exercise Treadmill Results (CARISA)

	Mean Difference from Placebo (sec)	
Study	**CARISA (N = 791)**	
Ranolazine Twice-daily Dose	**750 mg**	**1000 mg**
Exercise Duration Trough Peak	24[a] 34[b]	24 [a] 26 [a]
Time to Angina Trough Peak	30 [a] 38 [b]	26 [a] 38 [b]
Time to 1 mm ST-Segment Depression Trough Peak	20 41 b	21 35[b]

[a]p-value ≤ 0.05 [b]p-value ≤ 0.005

The effects of ranolazine on angina frequency and nitroglycerin use are shown in Table 2.

Table 2. Angina Frequency and Nitroglycerin Use (CARISA)

		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. Ranolazine has been evaluated in patients with chronic angina who remained symptomatic despite treatment with the maximum dose of an antianginal agent. In the ERICA (Efficacy of Ranolazine In Chronic Angina) trial, 565 patients were randomized to receive an initial dose of ranolazine 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with ranolazine 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine 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. Results are shown in Table 3. Statistically significant decreases in angina attack frequency (p = 0.028) and nitroglycerin use (p = 0.014) were observed with ranolazine compared to placebo. These treatment effects appeared consistent across age and use of long-acting nitrates.

Table 3: Angina Frequency and Nitroglycerin Use (ERICA)

		Placebo	Ranolazine[a]
Angina Frequency (attacks/week)	N	281	277
	Mean	4.3	3.3
	Median	2.4	2.2
Nitroglycerin Use (doses/week)	N	281	277
	Mean	3.6	2.7
	Median	1.7	1.3

[a]1000 mg twice daily

Gender: Effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In CARISA, 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 ERICA, 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 subgroup.

Lack of Benefit in Acute Coronary Syndrome: In a large (n = 6560) placebo-controlled trial (MERLIN-TIMI 36) in patients with acute coronary syndrome, there was no benefit shown on outcome measures. However, the study is somewhat reassuring regarding proarrhythmic risks, as ventricular arrhythmias were less common on ranolazine, and there was no difference between ranolazine and placebo in the risk of all-cause mortality (relative risk ranolazine: placebo 0.99 with an upper 95% confidence limit of 1.22).

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 may be dose related. In open-label, long-term treatment studies, a similar adverse reaction profile was observed.

Safety

ADVERSE EVENTS

Most common adverse reactions (> 4% and more common than with placebo) are dizziness, headache, constipation, nausea.

WARNINGS & PRECAUTIONS

- Moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin): Limit Aspruzyo Sprinkle™ to 500 mg twice daily.
- P-gp inhibitors (e.g., cyclosporine): Ranolazine exposure increased. Titrate Aspruzyo Sprinkle™ based on clinical response.
- CYP3A substrates: Limit simvastatin to 20 mg when used with Aspruzyo Sprinkle™. Doses of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may need to be reduced with Aspruzyo Sprinkle™.
- OCT2 substrates: Limit the dose of metformin to 1700 mg daily when used with Aspruzyo Sprinkle™ 1000 mg twice daily. Doses of other OCT2 substrates may require adjusted doses.
- Drugs transported by P-gp (e.g., digoxin), or drugs metabolized by CYP2D6 (e.g., tricyclic antidepressants) may need reduced doses when used with Aspruzyo Sprinkle™.

CONTRAINDICATIONS

- Strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir).
- CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort).
- Liver cirrhosis

Clinical Pharmacology

MECHANISMS 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 I_{kr} which prolongs the ventricular action potential.

Dose & Administration

ADULTS

500 mg orally twice daily and increase to 1000 mg orally twice daily.

PEDIATRICS

Safety and effectiveness have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment necessary.

HEPATIC IMPAIRMENT

No dosage adjustment necessary.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Extended-release granules: 500 and 1000 mg.