Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Skyclarys®
Common Name: omaveloxolone
PDL Category: Central Nervous System Agents

Pharmacology/Usage: Skyclarys® contains omaveloxolone; the precise mechanism by which it exerts its therapeutic effect in patients with Friedreich's ataxia is not known. Omaveloxolone have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress.

Indication: For the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risks associated with the use of Skyclarys® in pregnant women. The safety and efficacy of use in the pediatric population less than 16 years of age have not been established.

Dosage Form: Capsules: 50mg.

Recommended Dosage: Before starting treatment, obtain ALT, AST, bilirubin, B-type natriuretic peptide (BNP), and lipid parameters prior to starting Skyclarys® and during treatment.

The recommended dosage of Skyclarys® is 150mg (3 capsules) taken PO QD. Administer on an empty stomach at least one hour before eating. Swallow capsules whole. Do not crush or chew. For patients who are unable to swallow whole capsules, the capsules may be opened and the entire contents of both halves of the capsule sprinkled onto 2 tablespoons (30ml) of applesauce. Stir the mixture and swallow all the drug/applesauce mixture immediately. Do not mix the contents of the capsules with milk or orange juice. If a dose is missed, take the next dose at its scheduled time the following day. A double dose should not be taken to make up for a missed dose.

Dose adjustments are not required with mild hepatic impairment. With moderate hepatic impairment, decrease the dose to 100mg QD, with close monitoring for adverse reactions. Consider lowering the dose to 50mg QD if adverse reactions emerge. Avoid use of Skyclarys® with severe hepatic impairment.

Clinical studies of Skyclarys® in Friedreich's ataxia did not include patients aged 65 and over. No data are available to determine whether they respond differently than younger adult patients.

Drug Interactions: Omaveloxolone is a CYP3A4 substrate. Concomitant use of Skyclarys® with moderate or strong CYP3A4 inhibitors is expected to result in clinically significant increased exposure of omaveloxolone, which may increase the risk of adverse reactions. Avoid concomitant use of Skyclarys® with moderate or strong CYP3A4 inhibitors. If use cannot be avoided, dosage modifications are recommended.

Concomitant use of Skyclarys® with moderate or strong CYP3A4 inducers may significantly decrease exposure of omaveloxolone, which may reduce the effectiveness of Skyclarys®. Avoid concomitant use of Skyclarys® with moderate or strong CYP3A4 inducers.

Omaveloxolone is a weak inducer of CYP3A4 and CYP2C8. Concomitant use with Skyclarys® can reduce the exposure of CYP3A4 and CYP2C8 substrates which may reduce the activity of these substrates. Refer to the

prescribing information of substrates of CYP3A4 and CYP2C8 for dosing instructions if used concomitantly with Skyclarys® and monitor for lack of efficacy of the concomitant treatment.

Omaveloxolone is a weak CYP3A4 inducer. Concomitant use with Skyclarys® may reduce the efficacy of hormonal contraceptives. Advise patients to avoid concomitant use with combined hormonal contraceptives (e.g., pill, patch, ring), implants, and progestin only pills.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Skyclarys®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included elevated liver enzymes (35%), headache (12%), nausea (20%), abdominal pain (23%), fatigue (10%), diarrhea (10%), musculoskeletal pain (5%), oropharyngeal pain (12%), influenza (10%), vomiting (4%), muscle spasms (8%), back pain (5%), decreased appetite (8%), and rash (6%).

Treatment with Skyclarys® can cause an elevation in hepatic transaminases (ALT and AST). There were no cases of concomitant elevation of transaminases and total bilirubin observed in Study 1. Maximum increases in ALT and AST occurred within 12 weeks after starting Skyclarys®. Increases in serum aminotransferases were generally asymptomatic and reversible following discontinuation of Skyclarys®. Patients with clinically significant liver disease were excluded from Study 1. Monitor ALT, AST, and total bilirubin prior to initiation of Skyclarys®, every month for the first 3 months of treatment, and periodically thereafter. If transaminases increase to levels greater than 5 times the upper limit of normal, or greater than 3 times the upper limit of normal with evidence of liver dysfunction (e.g., elevated bilirubin), immediately discontinue Skyclarys® and repeat liver function tests as soon as possible. If transaminase levels stabilize or resolve, Skyclarys® may be reinitiated with an appropriate increased frequency of monitoring of liver function.

Treatment with Skyclarys® can cause an increase in B-type natriuretic peptide (BNP), a marker of cardiac function. Cardiomyopathy and cardiac failure are common in patients with Friedreich's ataxia. Patients were excluded from Study 1 if they had BNP levels >200pg/ml prior to study entry, or a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia. Whether the elevations in BNP in study 1 are related to Skyclarys® or cardiac disease associated with Friedreich's ataxia is unclear. Elevations in BNP may indicate cardiac failure and should prompt an evaluation of cardiac function. Check BNP prior to initiation of Skyclarys®. Monitor patients for the signs and symptoms of fluid overload. If signs and symptoms of fluid overload develop, worsen, or require hospitalization, evaluate BNP and cardiac function, and manage appropriately. Management of fluid overload and heart failure may require discontinuation of Skyclarys®.

Treatment with Skyclarys® can cause changes in cholesterol. In Study 1, 29% of patients treated with Skyclarys® reported elevated cholesterol above the upper limit of normal at one or more time points. Mean increases were observed within 2 weeks of initiation of Skyclarys® and returned to baseline within 4 weeks of discontinuing treatment. Assess lipid parameters prior to initiation of Skyclarys® and monitor periodically during treatment. Manage lipid abnormalities per clinical guidelines.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Reata Pharmaceuticals, Inc.

Analysis: The efficacy of Skyclarys® was assessed in a 48-week, randomized, double-blind, placebo-controlled study that included patients 16 to 40 years of age with Friedreich's ataxia (Study 1). Patients were randomized to either Skyclarys® 150mg QD (N=51) or placebo (N=52) and patients had to have a stable modified Friedreich's Ataxia Rating Scale (mFARS) score between 20 and 80, be able to complete maximal exercise testing, and have a left ventricular ejection fraction of at least 40%. In this study, 53% enrolled were male, while 97% were white and the mean age of subjects was 24 years at study entry. Patients with or without pes cavus were included, and pes cavus was defined as having a loss of lateral support and was determined if light from a flashlight could be seen under the patient's arch when barefoot and weight bearing.

The prespecified primary analysis was the change from baseline in the mFARS score compared to placebo at week 48 in the full analysis population of patients without pes cavus (N=82). The mFARS is a clinical assessment tool to assess patient function, which consists of 4 domains to evaluate bulbar function, upper limb coordination, lower limb coordination, and upright stability. The mFARS has a maximum score of 99, with a lower score on the mFARS signifying lesser physical impairment. Results suggested that treatment with Skyclarys® resulted in a statistically significant lower mFARS scores (less impairment) relative to placebo. Results are presented in the table below, which was adapted from the prescribing information.

	Mean baseline mFARS total score	LS Mean change from baseline at week 48	Treatment difference Skyclarys®- placebo	p-value
Skyclarys® (N=40)	40.95	-1.56	-2.41	0.0138
Placebo (N=42)	38.78	0.85		

The all randomized population (N=103), which included all patients regardless of pes cavus status, demonstrated similar results to the full analysis population of lower mFARS scores in patients treated with Skyclarys® compared to placebo, with a nominally significant least squares mean difference between treatment groups of -1.94 (p=0.0331).

In a post hoc, propensity matched analysis, lower mFARS scores were observed in patients treated with Skyclarys® after 3 years relative to a matched set of untreated patients from a natural history study. These exploratory analyses should be interpreted cautiously given the limitations of data collected outside of a controlled study, which may be subject to confounding.

Place in Therapy: Skyclarys® is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. Prior to and during treatment, obtain ALT, AST, bilirubin, BNP, and lipid parameters. The safety and efficacy of Skyclarys® were assessed in a 48 week, randomized, double-blind, placebo-controlled study that included patients 16 to 40 years of age with Friedreich's ataxia. Treatment with Skyclarys® resulted in statistically significant lower mFARS scores (less impairment) as compared to placebo at week 48 in the population of patients without pes cavus (N=82). Similar results were obtained in the all randomized population, which included all patients regardless of pes cavus status, with a nominally significant least squares mean difference between treatment groups. The clinical significance of a 2.41 points difference on a 99 point rating scale, despite being statistically significant, is unclear. It is the first and only FDA-approved prescription medicine for this indication.

It is recommended that Skyclarys® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Skyclarys [package insert]. Plano, TX: Reata Pharmaceuticals; 2024.