Date: 17 October 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Skyclarys

International non-proprietary name: omaveloxolon
Pharmaceutical form: capsules
Dosage strength(s): 50 mg
Route(s) of administration: oral
Marketing authorisation holder: Biogen Switzerland AG
Marketing authorisation no.: 69610
Decision and decision date: approved on 24 September 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for omaveloxolon in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} paragraph no. 2 of the TPA. Orphan drug status was granted on 11 December 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

2.2.2 Approved indication

Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dosage of Skyclarys is 150 mg (3 capsules) taken orally once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 January 2024
Formal control completed	8 February 2024
Preliminary decision	30 April 2024
Response to preliminary decision	27 June 2024
Labelling corrections	3 September 2024
Response to labelling corrections	13 September 2024
Final decision	24 September 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority FDA. This SwissPAR relates to the publicly available assessment report for Skyclarys, application number 216718 (approval date: 28 February 2023) issued by the FDA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority FDA. The SwissPAR relating to quality aspects refers to the publicly available assessment report for Skyclarys, application number 216718 (approval date: 28 February 2023) issued by the FDA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority FDA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report for Skyclarys, application number 216718 (approval date: 28 February 2023) issued by the FDA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority FDA. The clinical aspects in this SwissPAR refer to the publicly available assessment report for Skyclarys, application number 216718 (approval date: 28 February 2023) issued by the FDA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Skyclarys was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected new or serious adverse reactions. See section «Undesirable effects» section for advice on the reporting of adverse reactions.

SKYCLARYS™

Composition

Active substances

Omaveloxolone.

Excipients

Pregelatinized starch, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate.
Hard capsule shell: Hypromellose, titanium dioxide (E171), FD&C Blue #1 (E133), ferric oxide yellow.
Printing Ink: shellac (E904), titanium dioxide (E171).
One hard capsule contains a maximum of 3.6 mg sodium.

Pharmaceutical form and active substance quantity per unit

Each hard capsule contains 50 mg omaveloxolone.
Opaque hard capsules having a light green body and blue cap, imprinted with «RTA 408» in white ink on the body and «50» in white ink on the cap.

Indications/Uses

SKYCLARYS is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

Dosage Administration

Recommended Testing Before Initiating SKYCLARYS and Monitoring to Assess Safety

Monitor ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating SKYCLARYS and during treatment (see section «Warnings and Precautions»).

Recommended Dosage

The recommended dosage of SKYCLARYS is 150 mg (3 capsules) taken orally once daily.

Special Dosage instructions

Recommendations for Concomitant Use with Strong or Moderate CYP3A4 Inhibitors and Inducers
The recommended dosage for concomitant use of SKYCLARYS with cytochrome P450 (CYP) 3A4 inhibitors and inducers are described in Table 1 *(*see also section *«Interactions»).*

Table 1: Recommended Dosage of SKYCLARYS with Concomitant Use of CYP3A4 Inhibitors and Inducers

Concomitant Drug Class	**Dosage**
Strong CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of SKYCLARYS to 50 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, coadministration with strong CYP3A4 inhibitors should be discontinued.
Moderate CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of SKYCLARYS to 100 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, further reduce the dosage of SKYCLARYS to 50 mg once daily.
Strong or moderate CYP3A4 inducer	Recommended to avoid concomitant use.

Recommended Dosage for patients with Hepatic Impairment

Omaveloxolone plasma exposure is increased in patients with moderate or severe hepatic impairment (Child-Pugh Class B and C) (see section «Pharmacokinetics»). Avoid treatment with SKYCLARYS in patients with severe hepatic impairment, including those who develop severe hepatic impairment. If hepatic function improves to moderate impairment, mild impairment, or normal function, initiation of SKYCLARYS treatment at the approved recommended dosage may be considered.
For patients with moderate hepatic impairment, a reduced dosage is recommended with close monitoring for adverse reactions.
For patients with mild hepatic impairment (Child-Pugh Class A), no dose adjustment is required.
The recommended dosage for patients with hepatic impairment are described in Table 2.

Table 2: Recommended Dosage in Patients with Hepatic Impairment

Impairment Classification (Child-Pugh)	**Dosage**
Severe (Child-Pugh class C)	Avoid use
moderate (Child-Pugh class B)	• 100 mg once daily with close monitoring for adverse reactions • Consider lowering to 50 mg once daily if adverse reactions emerge

Impairment Classification (Child-Pugh)	Dosage
Mild (Child-Pugh class A)	150 mg once daily

Patients with renal impairment

The effects of renal impairment on the pharmacokinetics of omaveloxolone are unknown.

Elderly patients

No clinical data in patients over the age of ≥ 65 years are currently available. Population pharmacokinetic analyses indicate that no dose adjustments based on age are necessary.

Children and adolescents

Skyclarys is not approved for the treatment of pediatric patients below 16 years of age. No clinical data are available in the patient population.

Missed Doses

If a dose of SKYCLARYS 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.

How to administer

- Administer SKYCLARYS on an empty stomach at least one hour before eating (see section «Pharmacokinetics»).
- Swallow SKYCLARYS capsules whole. Do not open, crush, or chew.

For patients who are unable to swallow whole capsules, Skyclarys capsules may be opened, and the entire contents sprinkled onto 2 tablespoons of apple puree. Patients should consume all the medicine/food mixture immediately on an empty stomach at least 1 hour before or 2 hours after eating. It should not be stored for future use.

Contraindications

Hypersensitivity to the active substance or to any of the excipients described in the composition.

Warnings and precautions

Elevation of Aminotransferases

Treatment with SKYCLARYS can cause an elevation in hepatic transaminases (ALT and AST). In Study 1 (see section «Properties/Effects»), the incidence of elevations of ALT or AST above 5 times and 3 times the upper limit of normal (ULN) was 16% and 31%, respectively, in patients treated with SKYCLARYS. 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 ULN, or greater than 3 times the ULN 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 (see sections «Undesirable Effects» and «Dosage/Administration»).

Elevation of B-Type Natriuretic Peptide

Treatment with SKYCLARYS can cause an increase in BNP, a marker of cardiac function. In Study 1, a total of 14% of patients treated with SKYCLARYS had an increase from baseline in BNP and a BNP above the ULN (100 pg/mL), compared to 4% of patients who received placebo. The incidence of elevation of BNP above 200 pg/mL was 4% in patients treated with SKYCLARYS. Cardiomyopathy and cardiac failure are common in patients with Friedreich’s ataxia. Patients were excluded from Study 1 if they had BNP levels > 200 pg/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 (see section «Undesirable Effects»). 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, such as sudden weight gain (3 pounds or more of weight gain in one day, or 5 pounds or more of weight gain in a week), peripheral edema, palpitations, and shortness of breath.
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.

Lipid Abnormalities

Treatment with SKYCLARYS can cause changes in cholesterol. In Study 1, 29% of patients treated with SKYCLARYS reported elevated cholesterol above ULN 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. A total of 16% of patients treated with SKYCLARYS had an increase in low-density lipoprotein cholesterol (LDL-C) from baseline, compared to 8% of patients who received placebo. The mean increase in LDL-C for all SKYCLARYS-treated patients was 23.5 mg/dL at 48 weeks. A total of 6% of patients treated with SKYCLARYS had decreases in high-density lipoprotein cholesterol (HDL-C) from baseline compared to 4% of patients who received placebo. The mean decrease in HDL-C for all SKYCLARYS-treated patients was 5.3 mg/dL at 48 weeks.
Assess lipid parameters prior to initiation of SKYCLARYS and monitor periodically during treatment. Manage lipid abnormalities according to clinical guidelines.

Hormonal contraceptives

SKYCLARYS may decrease the efficacy of hormonal contraceptives (see section «Interactions»). Counsel females being treated with SKYCLARYS not to rely on such contraceptives alone. During the treatment with SKYCLARYS and for 28 days after discontinuation of SKYCLARYS, additional non-hormonal contraceptives should be used (see section “Interactions” and “Pregnancy, Lactation”).

Natrium content

This medicinal product contains sodium, but less than 1 mmol (23 mg) per 3 hard capsules (=daily dose), i.e. it is essentially ‘sodium-free’.

Interactions

Effect of Other Drugs on SKYCLARYS

CYP3A4 inhibitors

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. Some examples of strong and moderate CYP3A4 inhibitors are clarithromycin, itraconazole, ketoconazole, ciprofloxacin, cyclosporine, fluconazole, and fluvoxamine. Avoid concomitant use of SKYCLARYS with moderate or strong CYP3A4 inhibitors. If use cannot be avoided, dosage modifications are recommended (see section «Dosage/Administration»).
As grapefruit and grapefruit juice are inhibitors of CYP3A4, patients should be warned to avoid these while taking Skyclarys (see section «Warnings and Precautions»).

Omaveloxolone C_{max} increased 3-fold and AUC 4-fold following concomitant use with itraconazole (strong CYP3A inhibitor).

Omaveloxolone C_{max} and AUC increased approximately 1.25-fold following concomitant use with verapamil (moderate CYP3A4 and P-gp inhibitor).
No clinically significant differences in the pharmacokinetics of omaveloxolone are expected following concomitant use with weak CYP3A4 inhibitors.

CYP3A4 inducers

Omaveloxolone is a CYP3A4 substrate. Concomitant use of SKYCLARYS with moderate or strong CYP3A4 inducers may significantly decrease exposure of omaveloxolone, which may reduce the effectiveness of SKYCLARYS. Some examples of strong or moderate CYP3A4 inducers are carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's wort, and efavirenz. Avoid concomitant use of SKYCLARYS with moderate or strong CYP3A4 inducers.
The effect of concomitant use with moderate and strong CYP3A4 inducers is unknown; however, a significant reduction in omaveloxolone exposure is likely following concomitant use based on its metabolic pathway.

CYP2C8 inhibitors

No clinically significant differences in the pharmacokinetics of omaveloxolone are expected following concomitant use with strong CYP2C8 inhibitors.

Effect of SKYCLARYS on other drugs

CYP3A4 and CYP2C8 substrates

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 decreased the AUC of midazolam (CYP3A4 substrate) by approximately 45%, AUC of repaglinide (CYP2C8 substrate) by approximately 35%.

BCRP and OATP1B1 substrates

Omaveloxolone decreased the AUC of rosuvastatin (BCRP and OATP1B1 substrate) by approximately 30%.

P-gp and OCT1 substrates

There were no clinically significant differences in the pharmacokinetics of digoxin (P-gp substrate) or metformin [(organic cation transporter (OCT)1 substrate] when coadministered with omaveloxolone.

Hormonal contraceptives

Omaveloxolone is a weak CYP3A4 inducer. Concomitant use of omaveloxolon together with homonal contraceptives may reduce their efficacy. This applies to combined hormonal contraceptives (e.g., oral preparations, patches, vaginal ring), and gestagen only pills alike (see sections “Warnings and Precautions” and «Pregnancy, Lactation»).

In vitro studies
Omaveloxolone inhibited the renal transporter OAT1.
Omaveloxolone is not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6.
Omaveloxolone is not an inducer of CYP1A2 and CYP2B6.
Omaveloxolone is not an inhibitor of BCRP, BSEP, OAT3, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2-K.

Pregnancy, Lactation

Pregnancy

There are no data from the use of omaveloxolone in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical Data”).
Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 28 days following discontinuation of treatment (see sections “Warnings and precautions” and “Interactions”).

Lactation

There are no data on the presence of omaveloxolone in human milk. Omaveloxolone is present in the milk of lactating rats and resulted in treatment-related effects in offspring (see section “Preclinical Data”). A risk to the newborn infant cannot be excluded. Skyclarys should not be used during breast-feeding.

Fertility

There are no data on the effects of Skyclarys on human fertility. Animal data did not indicate impairment of parent male or female fertility (see section “Preclinical Data”).

Effects on ability to drive and use machines

Omaveloxolone may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of omaveloxolone (see section “Undesirable Effects”).

Undesirable effects

Summary of safety profile

The most frequently occurring adverse reactions observed with Skyclarys are ALT increased and headache (37.3% each); weight decreased (34.0%); nausea (33.3%); AST increased and fatigue (21.6% each); diarrhoea (19.6%); oropharyngeal pain (17.6%); vomiting (15.7%), back pain, muscle spasms, and influenza (13.7% each); and decreased appetite (11.8%).

Tabulated list of adverse reactions

The adverse reactions observed in the randomized, double-blind, placebo-controlled trial in 51 patients treated with Skyclarys 150 mg/day for 48 weeks (median exposure 0.92 patient years) are listed in Table 3 by system organ class and frequency.
Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or unknown frequency (cannot be estimated for the available data basis).
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Selected adverse reactions are further described in following Table 3.

Table 3: Adverse Reactions

System Organ Class	Preferred Term	Frequency Category
Infections and infestations	Influenza	Very common
	Urinary tract infection	Common
Metabolism and nutrition disorders	Decreased appetite	Very common
	Hypertriglyceridemia	Common
	Very low density lipoprotein increased	Common
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Very common
Gastrointestinal disorders	Nausea	Very common
	Diarrhoea	Very common
	Vomiting	Very common
	Abdominal upper pain	Common
	Abdominal pain	Common

System Organ Class	Preferred Term	Frequency Category
Hepatobiliary disorders	ALT increased	Very common
	AST increased	Very common
	GGT increased	Common
Musculoskeletal and connective tissue disorders	Back pain	Very common
	Muscle spasms	Very common
Reproductive system and breast disorders	Dysmenorrhoea	Common
General disorders and administration site conditions	Fatigue	Very common
Investigations	BNP increased[a]	Common
	Weight decreased[b]	Very common

[a] Based on laboratory evaluations with values > 200 pg/mL.

[b] Based on weight measured in the clinic with on-treatment weight loss ≥ 5%.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; GGT=gamma glutamyltransferase.

Description of selected adverse reactions

Gastrointestinal disorders

Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, nausea occurred in 33.3% of patients, diarrhoea in 19.6% of patients, vomiting in 15.7% of patients, abdominal upper pain in 9.8% of patients, and abdominal pain in 7.8% of patients. All events were assessed as either mild or moderate in severity, and 75.8% of the events occurred within the first 12 weeks of therapy.

Aminotransferase elevations

Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, adverse reactions of aminotransferase elevations included: ALT increased in 37.3% of patients, AST increased in 21.6% of patients, and gamma glutamyltransferase (GGT) increased in 5.9% of patients. Treatment interruptions due to aminotransferase elevations occurred in 11.8% of all Skyclarys-treated patients. One patient (2%) was discontinued for aminotransferase elevation per protocol.

In patients treated with Skyclarys, the incidence of on-treatment elevations of ALT or AST ≥ 3 × the ULN was 29.4%, with 15.7% experiencing elevations ≥ 5 × the ULN. Elevations of ≥ 3 × the ULN were generally transient and reversible, with 80% of these patients experiencing maximal levels within the first 12 weeks of treatment. None of these patients had ALT or AST levels ≥ 3 × the ULN at the withdrawal visit. Mean values generally decreased towards baseline with continued treatment or after interruption in therapy. No patient had concomitant elevation of total bilirubin > 1.5 × the ULN.

Elevation of BNP

In the randomized, double-blind, placebo-controlled study, increases in laboratory evaluations of BNP were observed in patients treated with Skyclarys. Mean BNP values were elevated at Week 4, and remained elevated through Week 48, with peak mean elevations at Week 24. Mean BNP values remained below the ULN (< 100 pg/mL). A total of 13.7% of patients treated with Skyclarys had an increase from baseline in BNP and a BNP above the ULN (100 pg/mL), compared to 3.8% of patients who received placebo; 3.9% of patients had BNP values that exceeded 200 pg/mL while on treatment. There were no discontinuations due to BNP elevation.

Lipid abnormalities

Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, hypertriglyceridaemia was reported in 3.9% of patients, very low-density lipoprotein increased was reported in 3.9% of patients, and hypercholesterolaemia was reported in 2.0% of patients. At Week 48 in the Skyclarys treatment group, mean LDL increased by approximately 25 mg/dL and mean HDL decreased by approximately 5 mg/dL. After withdrawal of Skyclarys, mean LDL and HDL levels returned to baseline.

Weight decreased

In the randomized, double-blind, placebo-controlled study, weight decrease was reported for 2.0% of patients treated with Skyclarys and 1.9% of patients treated with placebo. No serious adverse reactions or discontinuations due to decreased appetite or weight decrease were reported in either treatment group.

Decrease in body weight was observed after Week 24. The mean weight decrease relative to baseline was 1.35 kg (SD 3.585 kg) in the Skyclarys group and the mean weight increase relative to baseline was 1.17 kg (SD 4.108 kg) in the placebo group after 48 weeks of treatment. Among all patients with baseline BMI < 25 kg/m^2 across both treatment groups (Skyclarys, n=37; placebo, n=37), weight loss of at least 5% from baseline was observed in 32.4% of Skyclarys-treated patients versus 2.7% of placebo-treated patients. *Paediatric population*

Based on evaluation of Skyclarys in randomized, placebo-controlled trials, the safety profile of Skyclarys in paediatric patients aged 16 to less than 18 years (n=24) was consistent with the safety profile in adult patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific antidote for Skyclarys. For patients who experience overdose, closely monitor and provide appropriate supportive treatment.

Properties/Effects

ATC code

N07.

Mechanism of action

The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown. 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.

Pharmacodynamics

Potential to prolong the QT interval

The effect of omaveloxolone on the QTc interval has not been adequately characterized.

Clinical efficacy

The efficacy of SKYCLARYS was evaluated in a 48-week, randomized, double-blind, placebo-controlled study in patients 16 to 40 years of age with Friedreich's Ataxia (Study 1; NCT02255435). A total of 103 patients were randomized (1:1) to receive SKYCLARYS 150 mg once daily (n=51) or placebo (n=52). N=24 of the randomized patients were adolescents.
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%. Patients were excluded from Study 1 if they had BNP levels > 200 pg/mL prior to 10 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. Additionally, patients were excluded from Study 1 if they had a history of clinically significant liver disease (eg, fibrosis, cirrhosis, hepatitis) or clinically relevant deviations in laboratory tests at screening including ALT and/or AST > 1.5-fold ULN, bilirubin > 1.2-fold ULN, alkaline phosphatase > 2-fold ULN, or albumin < lower limit of normal (LLN). In Study 1, 53% of enrolled patients were male,

97% were White, and the mean age was 24 years at study entry. Patients with or without pes cavus were included in Study 1. 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. Treatment with SKYCLARYS resulted in statistically significant lower mFARS scores (less impairment) relative to placebo (see Table 4) at Week 48.

Table 4: Primary Analysis in Full Analysis Population: mFARS Least Squares (LS) Mean Change from Baseline at Week 48

	Mean (SD) Baseline mFARS, Total Score	**LS Mean Change from Baseline at Week 48**	**Treatment difference SKYCLARYS vs. Placebo (95% CI)**	**p-value**
SKYCLARYS (n = 40)	40,95 (10,39)	-1.56	-2,41 (-4,32; -0,51)	0,0138
Placebo (n = 42)	38,78 (11,03)	0,85		

SD = Standard Deviation; LS = Least Squares; CI = Confidence Interval

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 (95% CI: -3.71, -0.16, 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.

Pharmacokinetics

Absorption

The median time to achieve peak plasma concentration was 7 to 14 hours. The total plasma omaveloxolone exposure based on area under the concentration-time curve (AUC) increased in a dose-dependent and dose proportional manner over a dose range of 50 mg (0.33 times the

recommended dosage) to 150 mg, but maximum omaveloxolone plasma concentration (C_{max}) increased in a less than dose proportional manner over the dose range in healthy fasted subjects.

Effect of food

Omaveloxolone C_{max} and $AUC_{0\text{-}inf}$ increased by approximately 350% and 15%, respectively, with a high-fat meal (800-1000 calories, approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively) compared to fasted conditions (see section «Dosage/Administration»).

Distribution

The mean volume of distribution of omaveloxolone is 7361 L (105 L/kg for a 70 kg person). Protein binding of omaveloxolone is 97%.

Metabolism

Omaveloxolone is primarily metabolized by CYP3A with minor metabolism by CYP2C8 and CYP2J2.

Elimination

The mean (range) terminal half-life of omaveloxolone is 57 hours (32 to 90 hours). The mean plasma clearance of omaveloxolone is 109 L/hr.
Following administration of a single oral dose of radiolabeled omaveloxolone 150 mg to healthy subjects, approximately 92% of the dose was recovered in feces (approximately 91% within 96 hours after administration) and 0.1% in urine.

Kinetics in specific patient groups

Effect of age, sex, and body weight on omaveloxolone pharmacokinetics

There were no clinically significant differences in the pharmacokinetics of omaveloxolone based on age (16 to 71 years of age), sex, race, or body weight (41 to 128 kg).

Patients with renal impairment

The effect of renal impairment on the pharmacokinetics of omaveloxolone is unknown.

Hepatic impairment

There were no clinically significant differences in the pharmacokinetics of omaveloxolone in subjects with mild hepatic impairment (Child-Pugh Class A). In subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C), omaveloxolone clearance was reduced, resulting in higher plasma exposure of omaveloxolone. The omaveloxolone AUC increased up to 1.65-fold and Cmax increased up to 1.83-fold in subjects with moderate hepatic impairment. The omaveloxolone AUC increased up to 2.17-fold in subjects with severe hepatic impairment; however, this change was variable (see section «Dosage/Administration»).

Preclinical data

Genotoxicity

Omaveloxolone was negative in a bacterial reverse mutation (Ames) assay, and positive in a chromosomal aberration assay in human peripheral blood lymphocytes but negative in in vitro (rat micronucleus and comet) assays.

Carcinogenicity

Carcinogenicity studies have not been conducted with omaveloxolone.

Reproductive toxicity

Oral administration of omaveloxolone (0, 1, 3, or 10 mg/kg/day) to pregnant rats throughout organogenesis resulted in no adverse effects on embryofetal development; however, in a dose rangefinding study, oral administration of omaveloxolone at doses up to 30 mg/kg/day to pregnant rats throughout organogenesis produced increases in post-implantation loss and resorptions, resulting in a decrease in viable fetuses, and reduced fetal weight at the highest dose tested. At the highest dose tested in the pivotal study (10 mg/kg/day), plasma exposure (AUC) was approximately 5 times that in humans at the recommended human dose (RHD) of 150 mg/day.
Oral administration of omaveloxolone (0, 3, 10, or 30 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in increased embryofetal mortality and skeletal variations and reduced fetal weight at the highest dose tested, which was associated with maternal toxicity. At the no-effect dose for adverse effects on embryofetal development (10 mg/kg/day), plasma exposure was less than that in humans at the recommended dose of 150 mg/day.
Oral administration of omaveloxolone (0, 1, 3, or 10 mg/kg/day) to rats throughout pregnancy and lactation resulted in an increase in stillbirths and impaired neurobehavioral function (increased locomotor activity and learning and memory deficits) in offspring at all doses, reduced body weight in offspring at all but the lowest dose tested, and delayed sexual maturation (males), increased postnatal mortality, and impaired reproductive performance in offspring at the highest dose tested. A no-effect dose for adverse effects on pre- and postnatal development was not identified. Plasma exposure (AUC) at the lowest dose tested was less than that in humans at the recommended dose of 150 mg / day.

Impairment of Fertility

Oral administration of omaveloxolone (0, 1, 3, and 10 mg/kg/day) to male and females rats prior to and during mating and continuing in females to gestation day 7 produced an increase in pre-and post-implantation loss and resorptions, resulting in a decrease in viable embryos at the highest dose tested. The no-effect dose (3 mg/kg/day) for adverse effects on fertility and reproductive function was associated with plasma exposures (AUC) approximately 2 times that in humans at the recommended human dose of 150 mg/day.

Other information

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Do not store above 25°C.
Keep out of the reach of children.

Authorisation number

69610 (Swissmedic)

Packs

Packs containing 90 and 270 (3 x 90) hard capsules (B).
SKYCLARYS is supplied in high density polyethylene bottles (HDPE), with a foil induction seal and child-resistant closure.

Marketing authorisation holder

Biogen Switzerland AG, 6340 Baar

Date of revision of the text

April 2024