▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
SKYCLARYS™ (omaveloxolone) CAPSULES

1 NAME OF THE MEDICINE

omaveloxolone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg omaveloxolone.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule.

Opaque size 0 hard hydroxypropyl methylcellulose (HPMC) capsule with “RTA 408” printed on the light green body in white ink and “50” printed on the blue cap in white ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Omaveloxolone should be initiated and supervised by a specialist medical practitioner (usually a Neurologist) experienced in the management of patients with Friedreich’s ataxia.

Dosage

The recommended dose is 150 mg omaveloxolone (3 capsules of 50 mg each) taken orally once daily.

Medicine lost through emesis should not be replaced with an additional dose.

If a dose is missed, the next dose should be taken as usual the following day.

A double dose should not be taken to make up for a missed dose.

Dose modifications for concomitant therapy

The recommended dosages for concomitant use of omaveloxolone with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors or inducers are described in Table 1 (see sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Table 1 Recommended dosage modifications of omaveloxolone with concomitant use of CYP3A4 inhibitors and inducers

Concomitant Drug Class	Dosage Recommendation
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	Concomitant use should be avoided.

Elderly

The safety and efficacy of omaveloxolone in patients aged 65 years and older have not been established. No dose adjustment is required based on age (see section 5.2 Pharmacokinetic properties).

Paediatrics

The safety and efficacy of SKYCLARYS in children and adolescents aged less than 16 years have not yet been established. No data are available.

Renal Impairment

The effect of moderate and severe renal impairment on the pharmacokinetics of omaveloxolone has not been studied (see section 5.2 Pharmacokinetic properties).

Hepatic Impairment

The recommended dosages for patients with hepatic impairment are described in Table 2.

Table 2 Recommended dose adjustments for patients with hepatic impairment

Impairment Classification (Child-Pugh)	Dosage
Severe (Child-Pugh Class C)	Use should be avoided.
Moderate (Child-Pugh Class B)	• 100 mg once daily with close monitoring for adverse reactions • If adverse reactions occur, a lower dose of 50 mg once daily should be considered.
Mild (Child-Pugh Class A)	150 mg once daily.

Method of Administration

This medicinal product is for oral use.

Omaveloxolone should be taken on an empty stomach at least 1 hour before or 2 hours after eating (see sections 4.5 Interactions with other medicines and other forms of interactions and 5.2 Pharmacokinetic properties).

SKYCLARYS capsules should be swallowed whole.

For patients who are unable to swallow whole capsules, SKYCLARYS capsules may be opened, and the entire contents sprinkled onto 2 tablespoons of apple sauce. 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 (see section 5.2 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Elevation of aminotransferases

Treatment with omaveloxolone in clinical trials with patients with Friedreich's ataxia has been associated with elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (see section 4.8 Adverse effects (Undersirable effects)). On-treatment aminotransferase elevations of ≥ 3 × the upper limit of normal (ULN) were reported in 29.4% of patients, with maximal values occurring in the majority of patients within the first 12 weeks of treatment. Initial increases were followed by a trend toward normalisation.

ALT, AST, and bilirubin should be monitored prior to initiation of omaveloxolone, monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated. If abnormal ALT or AST levels are present at 3 months after commencing treatment then monitoring of ALT, AST and bilirubin should continue monthly for an additional 3 months and then continue at a reduced frequency of 3 monthly thereafter if improvement is noted. ALT, AST and bilirubin levels should be monitored monthly for 3 months after introduction of a medicine which may increase the systemic exposure of omaveloxolone (e.g. CYP3A4 inhibitors). If ALT or AST increases to > 5 × the ULN, omaveloxolone should be immediately discontinued, and liver function tests should be repeated as soon as possible. If laboratory

abnormalities stabilise or resolve, omaveloxolone can be reinitiated. If ALT or AST increases to > 3 × the ULN and bilirubin increases to > 2 × the ULN, omaveloxolone should be immediately discontinued and liver function tests should be repeated. Testing should be continued as appropriate. When laboratory abnormalities stabilise or resolve, SKYCLARYS may be reinitiated with an appropriate frequency of monitoring liver function.

Drug interactions

Omaveloxolone is primarily metabolised by CYP3A4 (see section 5.2 Pharmacokinetic properties). Concomitant use of strong or moderate CYP3A4 inhibitors may significantly increase the systemic exposure of omaveloxolone (see section 4.5 Interactions with other medicines and other forms of interactions). If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, dose reduction of omaveloxolone with monitoring should be considered (see section 4.2 Dose and method of administration).

Concomitant use of omaveloxolone with strong or moderate CYP3A4 inducers may significantly decrease the exposure of omaveloxolone (see section 4.5 Interactions with other medicines and other forms of interactions), which may reduce the effectiveness of omaveloxolone. Patients treated with omaveloxolone should be warned to avoid concomitant use of CYP3A4 inducers while taking omaveloxolone. Alternative medicinal products should be considered if possible (see sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions).

Lipid abnormalities

Treatment with omaveloxolone has been associated with increases in low-density lipoprotein (LDL) cholesterol and decreases in high-density lipoprotein (HDL) cholesterol. Lipid parameters should be assessed prior to initiation of omaveloxolone and should be monitored periodically during treatment. Lipid abnormalities should be managed according to standard clinical guidelines.

Elevation of B-type natriuretic peptide (BNP)

Treatment with omaveloxolone has been associated with increases in BNP but without any concurrent increase in blood pressure or associated events of fluid overload or congestive heart failure. In Study 1, 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. The incidence of elevation of BNP above 200 pg/mL was 3.9% in patients treated with SKYCLARYS, compared to 0% of patients who received placebo. Whether the elevations in BNP in Study 1402 are related to SKYCLARYS or cardiac disease associated with Friedreich's ataxia is unclear.

In a study with a related compound in diabetic patients with chronic kidney disease (CKD), excess heart failure events due to fluid overload were observed among patients with stage IV CKD. Baseline BNP > 200 pg/mL and prior hospitalisation for congestive heart failure were identified as risk factors for heart failure among patients who had stage IV CKD but not in patients who had stage 3b CKD.

Cardiomyopathy and diabetes mellitus are common in patients with Friedreich's ataxia. BNP should be monitored prior to and periodically during treatment. Patients should be advised of the signs and symptoms of congestive heart failure associated with fluid overload, such as sudden weight gain (≥ 1.4 kg in 1 day or ≥ 2.3 kg in 1 week), peripheral oedema, and shortness of breath. If signs and symptoms of fluid overload and/or congestive cardiac failure develop, BNP (or NT-proBNP) should be monitored and managed according to standard clinical

guidance. Treatment with SKYCLARYS should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with SKYCLARYS should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalisation for fluid overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other aetiologies is strongly recommended.

Body weight decrease

Treatment with SKYCLARYS has been associated with mild decreases in body weight. Advise patients to monitor their weight regularly. Further evaluate the patient if unexplained or clinically significant body weight decrease occurs.

Use in the elderly

The safety and efficacy of omaveloxolone in patients aged 65 years and older have not been established. No data are available.

Paediatric use

The safety and efficacy of SKYCLARYS in children and adolescents aged less than 16 years have not yet been established. No data are available.

Effects on laboratory tests

No studies to assess drug effects on specific laboratory tests have been conducted with SKYCLARYS.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omaveloxolone is a substrate of CYP3A4. Co-administration of strong or moderate CYP3A4 inhibitors or CYP3A4 inducers will affect the pharmacokinetics of omaveloxolone.

Effect of other medicines on pharmacokinetics of omaveloxolone

Strong or moderate CYP3A4 inhibitors

In a clinical study, co-administration of SKYCLARYS with itraconazole, a strong CYP3A4 inhibitor, increased the area under the curve ($AUC_{0\text{-}inf}$) and maximal plasma concentration (C_{max}) by approximately 4-fold and 3-fold, respectively. In a clinical study with healthy subjects, co-administration of verapamil (120 mg once daily) increased the AUC and C_{max} by 1.24-fold and 1.28-fold, respectively. Verapamil is a known moderate CYP3A4 inhibitor and inhibitor of the P-gp transporter. If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, dosage reduction of SKYCLARYS should be considered with monitoring (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use). Some examples of strong and moderate CYP3A4 inhibitors are clarithromycin, itraconazole, ketoconazole, ciprofloxacin, cyclosporine, fluconazole, and fluvoxamine.

As grapefruit and grapefruit juice are inhibitors of CYP3A4, patients should be warned to avoid these while taking SKYCLARYS (see section 4.4 Special warnings and precautions for use).

Strong or moderate CYP3A4 inducers

Omaveloxolone is a CYP3A4 substrate. Concomitant use of SKYCLARYS with strong or moderate CYP3A4 inducers may significantly decrease the exposure of omaveloxolone, which may reduce the effectiveness of SKYCLARYS. Due to potential loss of efficacy, patients treated with SKYCLARYS should be warned to avoid use of strong or moderate CYP3A4 inducers while taking SKYCLARYS and alternatives should be considered if possible (see

Table 1 section 4.2 Dose and method of administration). Some examples of strong or moderate CYP3A4 inducers are carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's wort, and efavirenz.

Effect of omaveloxolone on other medicinal products

The following were evaluated in clinical studies with omaveloxolone 150 mg in healthy subjects:

CYP3A4 substrates

The AUC of midazolam, a CYP3A4 substrate, was reduced by approximately 45% when co-administered with omaveloxolone, indicating that omaveloxolone is a weak inducer of CYP3A4 and can reduce the exposure of CYP3A4 substrates. 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 (see section 4.6 Fertility, pregnancy and lactation).

CYP2C8 substrates

The AUC of repaglinide, a CYP2C8 substrate, was reduced by approximately 35% when co-administered with omaveloxolone, indicating that omaveloxolone is a weak inducer of CYP2C8 and can reduce the exposure of CYP2C8 substrates.

BCRP substrates

The AUC of rosuvastatin, a BCRP and OATP1B1 substrate, was reduced by approximately 30% when co-administered with omaveloxolone, indicating that omaveloxolone is a weak inducer of BCRP and can reduce the exposure of BCRP substrates.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Fertility and early embryonic development

Omaveloxolone, administered at oral doses of 1, 3, and 10 mg/kg/day to male rats for 28 days before mating and throughout the mating period and to female rats from 14 days before mating, throughout mating, and until gestation day 7 did not alter male or female fertility. No effects on fertility were observed in male rats up to 10 mg/kg/day (corresponding to approximately 7 times the clinical AUC in patients at the maximum human recommended dose [MHRD]). In female rats, there was an increase in pre- and post-implantation embryonic loss, resorptions, and a decrease in the number of implantation sites and viable embryos occurred at the dose corresponding to approximately 7 times the clinical AUC at the MHRD. No effects on pre- and post-implantation loss occurred at exposures approximately 2 times the clinical AUC.

Use in Pregnancy (Category C)

There are no data from the use of omaveloxolone in pregnant women.

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.

SKYCLARYS may decrease the efficacy of hormonal contraceptives (see section 4.5 Interactions with other medicines and other forms of interactions). Advise patients to avoid concomitant use with combined hormonal contraceptives (e.g., pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (e.g., non-hormonal intrauterine system) or additional non-hormonal contraceptive during concomitant use and for 28 days after discontinuation of SKYCLARYS.

Embryo-fetal development

In an embryo-fetal toxicity study in rats, no maternal toxicity or embryo-fetal abnormalities were detected in rats at an oral dose corresponding to approximately 6 times the clinical AUC in patients at the MHRD. However, at doses achieving exposure levels 19 times the clinical AUC, post-implantation loss, resorptions as well as decreases in number of viable fetuses, litter size, and fetal body weight were observed in rats. Embryo-fetal assessment in rabbits demonstrated maternal toxicity that was associated with early deliveries and interruptions of pregnancy as well as lower fetal body weights at a dose level corresponding to exposures 0.7-fold the clinical AUC (in the same study, no fetal malformations were observed at exposures approximately 1.3 times the clinical AUC). However, at the dose of 30 mg/kg/day (systemic exposures approximately 1.3 times the clinical AUC, a treatment-related increase in litter incidence of a variation (unilateral full rib) was observed.

Use in Lactation

There are no data on the presence of omaveloxolone in human milk. A risk to the newborn infant cannot be excluded. SKYCLARYS should not be used during breast-feeding.

Pre- and post-natal development

In a pre- and post-natal evaluation in rats, administration of omaveloxolone during the period of organogenesis through lactation at doses of 1, 3, and 10 mg/kg/day was associated with an increased percentage of litters with stillborn pups, reduced first generation pup survival, and decreased mean pup body weights at 10 mg/kg/day (corresponding to exposures approximately 6 times the clinical AUC in patients). Decreased reproductive function (reduced mean numbers of corpora lutea and implantation sites) were observed in F1 females and delayed sexual maturation was observed in F1 males at a dose level of approximately 6 times the clinical AUC. No adverse reactions were observed at a dose of 3 mg/kg/day (approximately 2 times the clinical AUC). Dose-dependent increases in omaveloxolone plasma concentrations were observed in pups, due to excretion of omaveloxolone in milk. Effects were directly linked to exposure to omaveloxolone.

4.7 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 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE 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 (32.4%); 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 randomised, 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: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse events with an incidence of ≥ 2% and excess in the omaveloxolone treatment group over the placebo group

System Organ Class Preferred Term	**Omaveloxolone 150 mg (n=51)**	**Placebo (n=52)**	**Frequency Category**
Gastrointestinal disorders			
Nausea	17 (33.3%)	7 (13.5%)	Very common
Diarrhoea	10 (19.6%)	5 (9.6%)	Very common
Vomiting	8 (15.7%)	6 (11.5%)	Very common
Abdominal pain upper	5 (9.8%)	1 (1.9%)	Common
Abdominal pain	4 (7.8%)	1 (1.9%)	Common
Nervous system disorders			
Headache	19 (37.3%)	13 (25.0%)	Very common
Musculoskeletal and connective tissue disorders			
Back pain	7 (13.7%)	4 (7.7%)	Very common
Muscle spasms	7 (13.7%)	3 (5.8%)	Very common
Hepatobiliary disorders			
ALT increased	19 (37.3%)	1 (1.9%)	Very common
AST increased	11 (21.6%)	1 (1.9%)	Very common
GGT increased	3 (5.9%)	0	Common
Investigations			
BNP increased[a]	2 (3.9%)	0	Common
Weight decreased[b]	12 (32.4.0%)[b]	10 (2.7%)[b]	Very Common

System Organ Class Preferred Term	**Omaveloxolone 150 mg** **(n=51)**	**Placebo** **(n=52)**	**Frequency Category**
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	9 (17.6%)	3 (5.8%)	Very common
General disorders and administration site conditions			
Fatigue	11 (21.6%)	7 (13.5%)	Very common
Infections and infestations			
Influenza	7 (13.7%)	2 (3.8%)	Very common
Urinary tract infection	4 (7.8%)	0	Common
Metabolism and nutrition disorders			
Decreased appetite	6 (11.8%)	2 (3.8%)	Very common
Hypertriglyceridemia	2 (3.9%)	0	Common
Very low density lipoprotein increased	2 (3.9%)	0	Common
Reproductive system and breast disorders			
Dysmenorrhoea	3 (5.9%)	0	Common

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

[b] Based on weight measured in the clinic with on-treatment weight loss $\geq$ 5%. (Omaveloxolone 15 mg n=37, placebo n=37)

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 randomised, 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 randomised, 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 randomised, 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, compared to 0% of patients who received placebo. There were no discontinuations due to BNP elevation.

Lipid abnormalities

Among patients treated with SKYCLARYS in the randomised, 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 randomised, 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 Body Mass Index (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 randomised, 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.

Post-marketing Experience

The following additional adverse reactions have been reported in post-marketing experience with omaveloxolone. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency:

Immune system disorders: hypersensitivity including urticaria and rash

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific information on overdose with SKYCLARYS.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX25

Mechanism of action

The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown. Omaveloxolone has 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. There is substantial evidence that Nrf2 levels and activity are suppressed in cells from patients with Friedreich's ataxia.

Pharmacodynamic effects

Omaveloxolone binds to Kelch-like ECH-associated protein 1 (Keap1), a protein that regulates the activity of Nrf2. Binding to Keap1 allows nuclear translocation of Nrf2 and transcription of its target genes. In fibroblasts isolated from patients with Friedreich's ataxia, omaveloxolone was shown to restore Nrf2 protein levels and increase Nrf2 activity. Omaveloxolone was also shown to rescue mitochondrial dysfunction and restore redox balance in these cells, as well as in neurons from mouse models of Friedreich's ataxia. Evidence of pharmacodynamic activity was observed in omaveloxolone-treated patients, with dose-dependent changes in the products of Nrf2 target genes, serum ferritin and GGT, across the dose range of 20 mg to 300 mg. Patients who received omaveloxolone 160 mg generally showed the largest increase from baseline for these serum markers.

Clinical trials

The efficacy and safety of SKYCLARYS were evaluated as a treatment for Friedreich's ataxia in two parts of a randomised, double-blind, placebo-controlled, study (Study 1402 MOXIe trial) and in an ongoing, open-label extension to Study 1402.

Study 1402 Part 2

Study 1402 Part 2 was a randomised, double-blind, placebo-controlled, multicentre study to evaluate the safety and efficacy of SKYCLARYS in patients with Friedreich's ataxia for 48 weeks of treatment. A total of 103 patients including 24 adolescents (no patients <16 years of age were included in study 1402 part 2) were randomised (1:1) to SKYCLARYS 150 mg/day (N=51) or placebo (N=52). Patients were excluded from Study 1402 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. Additionally, patients were excluded from Study 1402 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). Randomisation was stratified by pes cavus status. Pes cavus population 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 primary efficacy endpoint was change in the modified Friedreich's Ataxia Rating Scale (mFARS) score compared to placebo at Week 48 for patients without pes cavus (i.e. the full analysis set [FAS]; 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. In the FAS, 53.7% were male. The mean age was 23.9 years at study entry, and the mean age of Friedreich's ataxia onset was 15.5 years. Baseline mFARS and Friedreich's ataxia-Activities of Daily Living (FA-ADL) scores were 39.83 and 10.29 points, respectively. Mean GAA1 repeat length was 714.8. At study entry, 92.7% of patients were ambulatory, 37.8% had a history of cardiomyopathy, and 2.4% had a history of diabetes mellitus.

Treatment with SKYCLARYS significantly improved mFARS scores, with a least squares mean difference of 2.41 (standard error 0.955) relative to placebo (p=0.0138) (Table 4). All components of the mFARS assessment, including ability to swallow (bulbar), upper limb coordination, lower limb coordination, and upright stability, favoured SKYCLARYS over placebo.

Table 4 Study 1402 Part 2: mFARS Results (FAS)

	SKYCLARYS (n=40)	**Placebo (n=42)**
Total mFARS		
Baseline		
N	40	42
Mean (SD)	40.95 (10.394)	38.78 (11.025)
Week 48		
N	34	41
Mean (SD)	39.17 (10.019)	39.54 (11.568)
Week 48 Change from baseline		
LS Mean (SE)	-1.56 (0.689)	0.85 (0.640)
LS Mean Difference (SE)	-2.41 (0.955)	-
p-value vs. placebo	0.0138	

Abbreviations: FAS=Full Analysis Set; LS=least squares; mFARS=modified Friedreich's ataxia rating scale.

Note: mFARS scores can range from 0 to 99 points. Within each section of the mFARS, the minimum score is 0. The maximum score for each section is as follows: 11 points for Bulbar Function, 36 points for Upper Limb Coordination, 16 points for Lower Limb Coordination, and 36 points for Upright Stability.

In the All Randomised Population (n=103), which included all patients regardless of pes cavus status, SKYCLARYS improved mFARS scores relative to placebo, with a least squares mean difference of -1.94 (standard error 0.894) (nominal p=0.0331).

In exploratory subgroup analyses, point estimates for changes in mFARS consistently favoured SKYCLARYS relative to placebo across subgroups based on baseline age, ambulatory status, and GAA1 repeat length (Table 5).

Table 5 Study 1402 Part 2: Change in mFARS at Week 48 in subgroups (FAS)

Subgroup	Least Squares Mean Difference[a] (95% CI)	P-Value
Age		
≥ 16 years and < 18 years (n=20)	-4.21 (-8.48, 0.06)	0.0532
≥ 18 years (n=62)	-1.59 (-3.77. 0.58)	0.1486
GAA1 repeat length ≥ 675		
Yes (n=39)	-4.27 (-6.96, -1.58)	0.0024
No (n=28)	-1.95 (-5.209, 1.29)	0.2325
Ambulatory status		
Non-ambulatory (n=6)	-4.57 (-11.41, 2.27)	0.1864
Ambulatory (n=76)	-2.20 (-4.22, -0.18)	0.0336

Abbreviations: CI=confidence interval; FAS=Full Analysis Set; GAA1 repeat length=length of the trinucleotide repeats in the GAA1 allele composed of 1 guanine and 2 adenines; mFARS=modified Friedreich's ataxia rating scale.

[a] Least squares mean difference is SKYCLARYS – placebo.

Although Study 1402 was not powered to detect a difference in the key secondary endpoints, Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC), PGIC and CGIC scores at Week 48 were numerically improved in patients treated with SKYCLARYS relative to placebo in the primary analysis population (least squares [LS] mean difference in PGIC= -0.43, LS mean difference in CGIC= -0.13). None of these secondary endpoints met pre-determined levels for statistical significance. Additionally, treatment of patients with SKYCLARYS resulted in numerically improved FA-ADL scores relative to placebo, with an LS mean difference of -1.30 points (standard error=0.629).

In a post hoc, propensity-matched analysis of long term open-label treatment with SKYCLARYS, patients treated with SKYCLARYS had lower mFARS scores at 3 years, as compared to a matched natural history group. This exploratory analysis should be interpreted cautiously given the limitations of data collected outside of a controlled study, which may be subject to confounding.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omaveloxolone was absorbed after oral administration in healthy fasted subjects with peak plasma concentrations typically observed 7 to 14 hours post dose. Patients with Friedreich's ataxia demonstrated a 2.3-fold faster absorption of omaveloxolone than fasted healthy subjects.

Co-administration of a high-fat meal resulted in a small increase (1.15-fold) in area under the plasma concentration vs time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) but caused

a 4.5-fold increase in C_{max} compared to fasted conditions. It is recommended that SKYCLARYS be taken without food.

Omaveloxolone C_{max} and $AUC_{0\text{-}inf}$ were similar when capsule contents were sprinkled on apple sauce or when administered as intact capsules. The median time to achieve C_{max} (t_{max}) of omaveloxolone was shortened from approximately 10 hours to 6 hours when sprinkled on apple sauce (see section 4.2 Dose and method of administration).

The absolute or relative bioavailability of omaveloxolone has not been determined.

Distribution

Omaveloxolone is 97% bound to protein in human plasma. Omaveloxolone shows low membrane permeability. The average apparent volume of distribution is 7361 L (105 L/kg).

Metabolism

Following a single oral dose of [^{14}C]-omaveloxolone administered to healthy male subjects, omaveloxolone was found to be eliminated by metabolism via CYP3A4 to a series of 30 metabolites, of which 7 metabolites were quantified and identified. Metabolites M22 and M17 were major plasma metabolites that accounted for 18.6% and 10.9% of total plasma radioactivity, respectively. The other metabolites were minor, each accounting for less than 10% of total plasma radioactivity exposure. None of the metabolites has meaningful pharmacological activity.

Excretion

Following a single oral dose of radio-labelled omaveloxolone administered to healthy male subjects, approximately 92.5% of the dosed radioactivity was recovered within a 528-hour collection period: 92.4% via the faeces and 0.1% via the urine. The majority (90.7%) of the administered dose was recovered in the faeces within 96 hours after administration.

The average apparent plasma clearance of omaveloxolone is 109 L/hr and the average apparent plasma terminal half-life is 58 hours (32-94 hours).

Linearity/non-linearity

The total plasma omaveloxolone exposure (AUC) increased in a dose-dependent and dose proportional manner, but C_{max} increased in a less than dose proportional manner in healthy fasted subjects.

Pharmacokinetic/pharmacodynamic relationship(s)

<u>Effect of age, sex, and body weight on omaveloxolone pharmacokinetics</u>

Population pharmacokinetic analyses indicate that there is no clinically meaningful effect of age (16-71 years), sex, or body weight on the pharmacokinetics of omaveloxolone and no dose adjustments based on these factors are necessary.

Patients with renal impairment

Population pharmacokinetic analysis confirmed that estimated glomerular filtration rate values ≥ 63 mL/min/1.73 m^2 did not have a significant effect on the pharmacokinetics of omaveloxolone. The effect of moderate or severe renal impairment on the pharmacokinetics of omaveloxolone is unknown.

Patients with hepatic impairment

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. Subjects with moderate hepatic impairment exhibited up to a 65% increase in AUC and an 83% increase in C_{max} compared to subjects with normal hepatic function. In subjects with severe hepatic impairment, the AUC for omaveloxolone was increased by 117% as compared to subjects with normal hepatic function. However, the data in subjects with severe hepatic impairment are limited. In subjects with mild hepatic impairment (Child-Pugh Class A), there was no change in AUC and only a 29% increase in C_{max}. The recommended dosage for patients with hepatic impairment is described in section 4.2 Dose and method of administration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omaveloxolone was negative in the *in vitro* bacterial reverse mutation (Ames) test with or without metabolic activation. A potential clastogenic effect was observed with omaveloxolone in a chromosomal aberration assay (positive result) in human peripheral blood lymphocytes. The result was not confirmed (i.e. not observed) in two *in vivo* micronucleus tests in rat bone marrow which did not indicate clastogenic potential of omaveloxolone. Additionally, no genotoxic activity of omaveloxolone was seen in the *in vivo* rat liver (Comet assay).

Based on a panel of *in vitro* and *in vivo* mutagenicity tests, omaveloxolone is considered of low genotoxic potential.

Carcinogenicity

Omaveloxolone was not carcinogenic in a 6-month carcinogenicity study in rasH2 mice up to doses corresponding to approximately 14.6 and 54.5 times in males and females, respectively, the maximum human recommended dose (MHRD) and systemic exposure (AUC) in patients with Friedreich's ataxia.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents

pregelatinised maize starch

croscarmellose sodium

magnesium stearate

silicified microcystalline cellulose

Capsule shell

hypromellose

titanium dioxide

brilliant blue FCF

iron oxide yellow

opacode white A-8154NB (ID 2620) printing ink

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Capsules should be used within 30 days after first opening the container.

6.5 NATURE AND CONTENTS OF CONTAINER

High density polyethylene bottles with child-resistant, foil induction-sealed polypropylene closure.

Pack size of 90 capsules.

Pack size of 270 (3 packs of 90) capsules.*

*Not all pack sizes are marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material must be disposed of in accordance with local requirements.

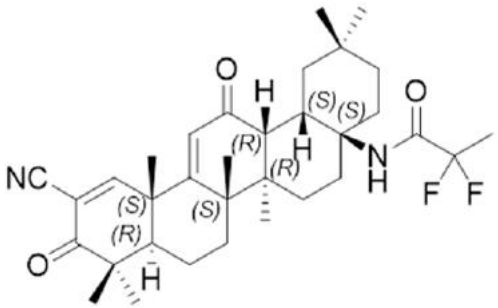
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name

N-(2-cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl)-2,2-difluoropropanamide

Chemical structure

$C_{33}H_{44}F_2N_2O_3$



CAS number

The CAS Registry Number is 1474034-05-3.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Biogen Australia Pty Ltd

ABN 30 095 760 115

Level 4, 2 Banfield Road

Macquarie Park NSW 2113

www.biogen.com.au

9 DATE OF FIRST APPROVAL

26 June 2025

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	New

SKYCLARYS™ is a registered trademark of Biogen MA Inc.