▼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 www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ZIRDAWNY® (DONIDALORSEN) SOLUTION FOR INJECTION IN PRE-FILLED PEN

1 NAME OF THE MEDICINE

Donidalorsen sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 80 mg donidalorsen (equivalent to 84 mg donidalorsen sodium) in 0.8 mL of solution. Each mL contains 100 mg donidalorsen, equivalent to 105 mg donidalorsen sodium.

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

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZIRDAWNY is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment is to be initiated under the supervision of a physician experienced in the management of patients with HAE. Product is for single use in one patient only. Discard any residue.

Dosage

The recommended starting dose in adult and adolescent patients is 80 mg donidalorsen by subcutaneous injection. Doses should be administered once monthly.

A dosing interval of 80 mg once every 2 months may be considered if the patient is well controlled (e.g., attack free) for at least 3 months while receiving ZIRDAWNY.

Missed dose

If a dose is missed, the patient or caregiver should be instructed to administer the dose as soon as possible. Thereafter, dosing should be resumed at the prescribed dosing frequency (once monthly or once every 2 months) from the date of the most recently administered dose.

Changing from other HAE prophylactic medicinal products

The following treatment schedules (Table 1) are recommended for patients that are changing their HAE prophylactic therapy from berotralstat, a C1 esterase inhibitor, or lanadelumab to ZIRDAWNY (see Section 5.1 Pharmacodynamic properties).

Table 1: Treatment schedule for patients changing from other prophylactic therapy to ZIRDAWNY.

Other Prophylactic Therapy:	**Recommended treatment schedule when changing to ZIRDAWNY:**
Berotralstat	Continue taking the current dose of berotralstat for 14 days after initiating treatment with ZIRDAWNY.
C1 esterase inhibitor	Continue taking the current dose of C1 esterase inhibitor for 14 days after initiating treatment with ZIRDAWNY.
Lanadelumab	Administer last dose of lanadelumab 14 days prior to initiating treatment with ZIRDAWNY.

Method of administration

ZIRDAWNY is only intended for subcutaneous use.

After proper training on correct subcutaneous injection technique, a patient or caregiver may inject ZIRDAWNY if their physician determines it is appropriate. Comprehensive instructions for administration using the pre-filled pen are provided in the package insert.

Prior to initiation, patients and/or caregivers have to be trained on proper preparation and administration of ZIRDAWNY (see Instructions for Use).

- The single-dose pre-filled pen should be removed from the refrigerator 30 minutes prior to the injection to reach room temperature. Other warming methods must not be used.
- The pre-filled pen must be inspected visually before use. The solution should appear clear and colourless to yellow. The pre-filled pen must not be used if cloudiness, particulate matter, or discolouration is observed prior to administration.
- ZIRDAWNY is to be administered as a subcutaneous injection in the abdomen, upper thigh region, or, for caregivers only, the back of the upper arm.
- ZIRDAWNY must not be injected into areas where the skin is tender, bruised, red, or hard.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis have been observed (see Section 4.8 Adverse effects (undesirable effects)). In case of a severe hypersensitivity reaction, administration of donidalorsen must be stopped immediately and appropriate treatment must be initiated.

Patients must be advised on the signs and symptoms of hypersensitivity reactions and instructed to promptly seek medical attention and to discontinue use of donidalorsen if serious hypersensitivity reactions occur.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

Use in hepatic impairment

No dose adjustment of ZIRDAWNY is required for patients with mild hepatic impairment (see Section 5.2 Pharmacokinetic properties).

ZIRDAWNY has not been studied in patients with moderate or severe hepatic impairment.

Use in renal impairment

No dose adjustment of ZIRDAWNY is required for patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2).

ZIRDAWNY has not been studied in patients with moderate or severe renal impairment or end stage renal disease.

Use in the elderly

No dose adjustment is required for patients above 65 years of age (see Section 5.2 Pharmacokinetic properties).

Paediatric use

The dosage is the same in adults and adolescents.

The safety and efficacy of ZIRDAWNY in children aged < 12 years have not yet been established. No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical drug-drug interaction studies have been performed with donidalorsen. *In vitro* studies show that donidalorsen is not a substrate or inhibitor of common drug transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP), or, cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). It does not induce the expression of CYP1A2, CYP2B6 and CYP3A4 *in vitro*. Donidalorsen exhibits high human plasma protein binding. An *in vitro* study showed that no interactions with respect to protein binding were seen with warfarin and ibuprofen, which both bind extensively to plasma proteins. Donidalorsen is not expected to cause or be affected

by drug-drug interactions mediated through drug transporters, plasma protein binding, or CYP enzymes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical data on the effect of this medicinal product on human fertility are available.

Subcutaneous administration of donidalorsen (up to 10 mg/kg/week; equivalent to up to 2.3 times the clinical dose on a body surface area) or a pharmacologically active rodent-specific oligonucleotide surrogate to male and female mice weekly, prior to and during mating, and continuing every other day in females throughout the period of organogenesis, resulted in no adverse effects on functional fertility, pregnancy, or embryofetal development.

Use in pregnancy – Pregnancy Category B1

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ZIRDAWNY in pregnant women.

Subcutaneous administration of donidalorsen (up to 20 mg/kg/week; equivalent to up to 4.5 times the clinical dose on a body surface area basis) or a pharmacologically active rodent-specific oligonucleotide surrogate to mice every other day throughout pregnancy and weekly throughout lactation produced no adverse effects on pre- and postnatal development.

As a precautionary measure, it is preferable to avoid the use of ZIRDAWNY during pregnancy.

Use in lactation

Available data in animals have shown excretion of donidalorsen/metabolites in milk. Donidalorsen was quantifiable in the milk of lactating mice; however, levels were low relative to maternal liver levels and minimal systemic exposure in breast-fed pups was expected due to poor oral absorption of oligonucleotides.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ZIRDAWNY therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ZIRDAWNY has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) in patients treated with ZIRDAWNY were injection site reactions (24.4%).

No deaths or serious adverse drug reactions occurred during clinical trials.

Tabulated list of adverse reactions

Adverse reactions associated with ZIRDAWNY obtained from clinical studies are tabulated below.

All ADRs are listed by system organ class and frequency; 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions to ZIRDAWNY

System organ class	**Adverse drug reaction**	**Frequency**
Immune system disorders	**Hypersensitivity (including anaphylaxis)**	**Common**
General disorders and administration site conditions	Injection site reactions*	Very common
Investigations	Hepatic enzyme increased #	Very common

* Injection site reactions such as: discolouration, erythema, pain, pruritus, induration, haematoma, bruising, exfoliation, hypersensitivity and swelling

Mainly mild, and mostly in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Description of selected adverse reactions

Hypersensitivity including anaphylaxis

In clinical trials, a serious hypersensitivity reaction of anaphylaxis was reported in one patient. Symptoms included generalised rash, dyspnoea, chest pain and peri-oral swelling (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Injection site reactions

During double-blind, placebo-controlled trials, injection site reactions were observed. All injection site reactions were non serious, mild to moderate in severity, and generally resolved over time. In some patients, the injection site reactions such as injection site erythema, injection site pruritus, and injection site discolouration persisted for 2 or more days. In one patient who received higher than labelled doses in accordance with the protocol, injection site discolouration led to permanent discontinuation of treatment.

Treatment-emergent adverse events

Table 3: Treatment-Emergent Adverse Events in > 5% of Patients in Any Treatment Group in Trial 1 - *"OASIS-HAE"*

System Organ Class Adverse Event (MedDRA Preferred Term)	Trial 1 - "OASIS-HAE"		
	Placebo (N = 22)	Donidalorsen 80 mg Every 4 Weeks (N = 45)	Donidalorsen 80 mg Every 8 Weeks (N = 23)
Patients with any TEAEs, n (%)	**18 (81.8)**	**33 (73.3)**	**14 (60.9)**
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	4 (18.2)	5 (11.1)	3 (13.0)
Upper respiratory tract infection	1 (4.5)	4 (8.9)	2 (8.7)
Urinary tract infection	0	4 (8.9)	2 (8.7)
Influenza	2 (9.1)	2 (4.4)	4 (17.4)
COVID-19	2 (9.1)	1 (2.2)	0
Gastroenteritis	2 (9.1)	1 (2.2)	1 (4.3)
Oral herpes	0	0	2 (8.7)
Sinusitis	2 (9.1)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Injection site erythema	0	6 (13.3)	1 (4.3)
Injection site discolouration	0	3 (6.7)	1 (4.3)
Injection site pruritus	0	3 (6.7)	0
Injection site pain	0	3 (6.7)	0
NERVOUS SYSTEM DISORDERS			
Headache	4 (18.2)	6 (13.3)	2 (8.7)
GASTROINTESTINAL DISORDERS			
Abdominal discomfort	0	3 (6.7)	0
Abdominal pain	2 (9.1)	1 (2.2)	0
Dyspepsia	2 (9.1)	0	0
Vomiting	1 (4.5)	0	2 (8.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Limb injury	4 (18.2)	0	1 (4.3)

Treatment-emergent adverse event (TEAE) is defined as any AE starting or worsening in severity on or after the first dose of the study drug.
At each level of summation (Overall, SOC, PT), patients reporting more than one TEAE are counted only once for the total incidence and for each treatment.
Abbreviations: AE = adverse event; PT = preferred term; SOC = System organ class.

Paediatric population

The safety of ZIRDAWNY has been established in adolescent patients aged 12 to 17 years in a double-blind placebo-controlled clinical trial that included a total of 7 adolescent patients supplemented by 4 ZIRDAWNY naïve adolescent patients from an open label trial. The safety profile in these adolescents was similar to the profile observed in adults.

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 clinical experience with overdose of this medicinal product. In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate. Symptoms of overdose are expected to be limited to constitutional symptoms and injection site reactions.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC09.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Donidalorsen is a 2'-O-methoxyethyl–modified antisense oligonucleotide (ASO) conjugated to a triantennary N-acetylgalactosamine ($GalNAc_3$) moiety that causes ribonuclease H1 (RNase H1) mediated degradation of prekallikrein (PKK) mRNA through selective binding to PKK mRNA, which results in reduced production of PKK protein. PKK is a pro-enzyme for plasma kallikrein, which drives the release of bradykinin, a vasodilator responsible for the swelling and pain in HAE. In patients with HAE, C1 inhibitor (C1-INH) deficiency or dysfunction leads to excessive plasma kallikrein activity and bradykinin generation, resulting in angioedema attacks. Donidalorsen lowers PKK and plasma kallikrein concentrations, preventing excessive bradykinin production in patients with HAE.

Pharmacodynamic effects

In Trial 1 in adult and paediatric patients (≥12 years) with HAE 1 or HAE 2 (see clinical efficacy and safety below), a decrease in plasma PKK concentrations was observed at the first assessment (Week 4) following treatment with ZIRDAWNY 80 mg. The mean percentage change from baseline to Week 24 in trough plasma PKK concentrations indicated reductions of 73% and 47% following treatment with ZIRDAWNY 80 mg every 4 weeks and every 8 weeks, respectively, compared with a slight increase (2%) observed in the placebo group.

Clinical trials

The efficacy of ZIRDAWNY for the prevention of angioedema attacks in patients with HAE due to C1-INH deficiency type 1 (HAE 1) or HAE due to C1-INH deficiency type 2 (HAE 2) was demonstrated in a 24-week multicenter, randomised, double blind, placebo-controlled trial (Trial 1) and a 16 week multicenter, randomised, double blind, placebo-controlled trial (Trial 3).

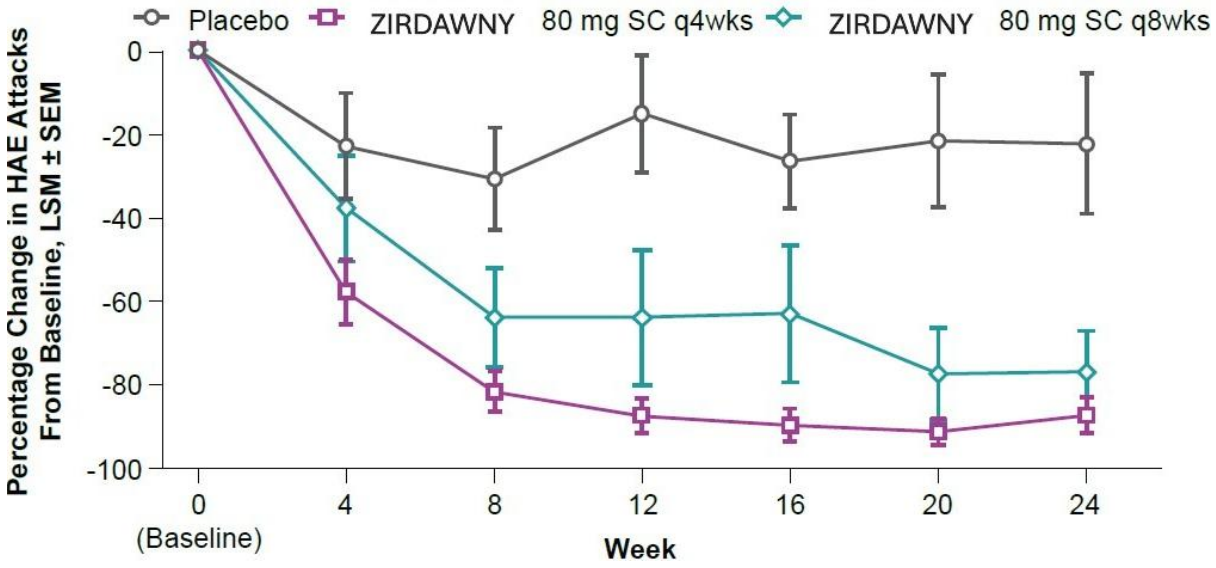
Trial 1- "OASIS-HAE"

Trial 1 included 90 adult and paediatric patients (≥12 years) with at least 2 investigator-confirmed attacks during the 8-week run in period, who received at least 1 dose of study treatment. Patients were randomised in a 2:1 ratio to 1 of 2 groups to receive study treatment either once every 4 weeks (q4wks group) or once every 8 weeks (q8wks group). Within each group, patients were randomised in a 3:1 ratio to receive ZIRDAWNY 80 mg or a matching volume of placebo. The 2 placebo treated groups were combined for analysis. Patients were required to discontinue other prophylactic HAE medications prior to entering the trial; however, all patients were allowed to use rescue medications such as C1 esterase inhibitors or icatibant, for treatment of any breakthrough HAE attacks.

Overall, 93% of patients had HAE 1. A history of laryngeal angioedema attacks was reported in 52% of patients, and 18% of patients were on prior prophylactic therapy. The median HAE attack rate during the prospective run-in period (baseline attack rate) was 2.85 attacks/4 weeks and an attack rate of >2 attacks/4 weeks was observed in 69% of patients overall.

ZIRDAWNY administered every 4 or 8 weeks produced statistically significant reductions in the HAE attack rate (number of investigator-confirmed HAE attacks per 4 weeks) compared to placebo, meeting the primary endpoint in this trial. A sustained response to ZIRDAWNY with mean decreases from baseline in the HAE attack rate was observed throughout the treatment period in the ZIRDAWNY treatment groups as shown in Figure 1. All secondary endpoint analyses for the q4wks group and all but 2 secondary endpoint analyses for the q8wks group were statistically or nominally significant compared with placebo as shown in Table 4 and discussed further below.

Figure 1: Percentage change (LSM ± SEM) from baseline in the rate of investigator-confirmed HAE attacks/4 weeks in trial 1



HAE = hereditary angioedema; LSM = least square mean; q4wks = every 4 weeks; q8wks = every 8 weeks; SC = subcutaneous; SEM = standard error of the mean.

Table 4: Results of primary and secondary efficacy endpoints (full analysis set)

Endpoint Statistics	**Placebo (N=22)**	**ZIRDAWNY 80 mg q4wks (N=45)**	**ZIRDAWNY 80 mg q8wks (N=23)**
HAE attack rate per 4 weeks from baseline to Week 24*			
LS mean (95% CI) attack rate	2.26 (1.66, 3.09)	0.44 (0.27, 0.73)	1.02 (0.65, 1.59)
% Reduction (95% CI) relative to placebo		−81 (−89, −65)	−55 (−74, −22)
Wald chi-square p-value		<0.001†	0.004†
HAE attack rate per 4 weeks from Week 4 to Week 24			
LS mean (95% CI) attack rate starting from second dose (Week 4)	2.25 (1.59, 3.18)	0.30 (0.15, 0.58)	0.90 (0.53, 1.52)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−87 (−94, −72)	−60 (−79, −25)
Wald chi-square p-value		<0.001†	0.004†
Moderate or severe HAE attack rate per 4 weeks from Week 4 to Week 24			
LS mean (95% CI) moderate or severe attack rate starting from second dose (Week 4)	1.15 (0.72, 1.83)	0.12 (0.04, 0.35)	0.68 (0.37, 1.23)
% Reduction (95% CI)		−89	−41

Endpoint Statistics	Placebo (N=22)	ZIRDAWNY 80 mg q4wks (N=45)	ZIRDAWNY 80 mg q8wks (N=23)
relative to placebo starting from second dose (Week 4)		(−97, −66)	(−72, 26)
Wald chi-square p-value		<0.001†	NS
HAE attacks per 4 weeks requiring acute therapy from Week 4 to Week 24			
LS mean (95% CI) HAE attacks requiring acute therapy starting from second dose (Week 4)	1.80 (1.23, 2.62)	0.15 (0.06, 0.39)	0.59 (0.31, 1.15)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−92 (−97, −77)	−67 (−85, −29)
Wald chi-square p-value		<0.001†	0.004‡

CI = confidence interval; HAE = hereditary angioedema; LS = least square; N = number of patients in the specific treatment group; NS = nonsignificant; q4wks = every 4 weeks; q8wks = every 8 weeks.

* Primary efficacy endpoint = comparison of the time normalised number of investigator-confirmed HAE attacks per 4 weeks from baseline to Week 24 between the ZIRDAWNY 80 mg q4wks group and the placebo group.

† Reached statistical significance (p value <0.05).

‡ Reached nominal significance (p value <0.05).

Additional pre-defined study secondary endpoints included the proportion of responders to study drug and percentage of patients who had well controlled angioedema activity. The proportion of patients with a ≥50%, ≥70%, ≥90%, and 100% (attack free) reduction from baseline in HAE attack rate from Week 4 to Week 24 was 93%, 82%, 62%, and 53%, respectively, in the ZIRDAWNY 80 mg q4wks treatment group, and 83%, 65%, 48%, and 35%, respectively, in the ZIRDAWNY 80 mg q8wks treatment group, compared to 27%, 18%, 9%, and 9%, respectively, in the placebo group. The number of patients who had well controlled disease at Week 24 in the ZIRDAWNY treatment groups based on the Angioedema Control Test (AECT) score ≥10 at Week 24 was 41 (91%) in the 80 mg q4wks group and 17 (74%) in the 80 mg q8wks group, compared to 9 (41%) in the placebo group.

Health-related Quality of Life

An improvement was observed for ZIRDAWNY treatment groups compared to placebo in the Angioedema Quality of Life Questionnaire (AE-QoL) total score. A reduction of 6 points is considered a clinically meaningful improvement. For the total AE-QoL score at Week 24, the least square mean change from baseline in the ZIRDAWNY treatment groups was −24.8 and −19.9 for the 80 mg q4wks group and 80 mg q8wks group, respectively, compared to −6.2 in the placebo group.

Trial 2 – "OASISplus"

A total of 147 adult and paediatric patients (≥12 years) with HAE 1 or HAE 2 received at least 1 dose of ZIRDAWNY in an open-label extension trial (Trial 2) of up to 3 years. Of these, 83 patients were previously treated with ZIRDAWNY or placebo in Trial 1 and were included in the rollover group. Non-rollover patients (n=64) were to continue to take their prior HAE prophylactic treatment (berotralstat, C1 esterase inhibitors, or lanadelumab) during the run-in period as per the respective recommended treatment schedules based on the half-life of the individual medicinal products (see Section 4.2 Dose and method of administration).

Open label extension rollover group (Trial 1 rollover patients, n = 83)

After 52 weeks of ZIRDAWNY treatment, patients showed a sustained 93% mean reduction in HAE attack rate compared to the baseline (0.22 vs. 3.42 attacks/4 weeks), with well-controlled disease by AECT increasing from 20.3% to 91.3% in the Q4W group and from 41.7% to 100.0% in the Q8W group, alongside improvements in AE-QoL scores at Week 24.

Non-rollover group (patients previously treated with other HAE long-term prophylactic medicinal products, n = 64)

During the switch from lanadelumab, berotralstat, or C1-esterase inhibitor to ZIRDAWNY, no increase in HAE attack rate was observed, with mean rates reduced by 66.1% (95% CI -79.69, -52.55) at Week 52, with overall disease control by AECT improving from 66.7% to 93.0% by Week 16, and AE-QoL scores showing meaningful reductions across all groups.

Trial 3 – Phase 2 trial including patients with HAE-nC1INH

The phase 2 Trial 3 had an open-label arm for patients with HAE-nC1INH. It included 3 adult patients who received donidalorsen 80 mg every 4 weeks for up to 16 weeks. None of these patients had an established mutation in factor XII, plasminogen or angiopoietin-1 gene and only one had a positive family history.

For the 3 HAE-nC1-INH patients, there was an overall 76% reduction in HAE attack rate during the treatment period. The reduction in mean HAE attack rate was from 4.23 attacks/4 weeks during the run-in period to 1.52 attacks/4 weeks from baseline to Week 16. One patient was attack free from Week 1 to end of treatment. Quality of life improved concurrently.

A reduction in investigator-confirmed monthly angioedema attack rate was observed in all three enrolled patients with HAE with normal functional and antigenic C1-inhibitor levels following monthly administration of 80 mg donidalorsen.

Cardiac electrophysiology

No clinically significant prolongation of QTc interval was observed at the recommended dosage of ZIRDAWNY 80 mg every 4 weeks or every 8 weeks.

Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the studies described below with the incidence of ADAs in other studies, including those of ZIRDAWNY or of other ASO products.

In Trial 1, with a treatment duration up to 24 weeks, the incidence rate of treatment emergent ADAs in adult and paediatric patients (≥12 years) with HAE was 20% (9 of 45 patients) in the ZIRDAWNY 80 mg q4wks group and 22% (5 of 23 patients) in the ZIRDAWNY 80 mg q8wks group. In Trial 2, an open label extension trial, patients that rolled over from Trial 1 continued treatment with ZIRDAWNY in the 80 mg q4wks or q8wks groups for up to 3 years (current median exposure duration of 227 days) and showed an incidence rate of treatment emergent ADAs of 36% (25 of 69 patients) in the ZIRDAWNY 80 mg q4wks group and 21% (3 of 14 patients) in the ZIRDAWNY 80 mg q8wks group. The incidence rate of treatment emergent ADAs was 42% (27 of 64 patients) for the non-rollover, ZIRDAWNY naïve patients who were previously treated with berotralstat, C1 esterase inhibitors, or lanadelumab before receiving ZIRDAWNY 80 mg every 4 weeks for a current median exposure duration of 253 days in Trial 2.

The presence of ADAs did not affect donidalorsen plasma C_{max}, but increased C_{trough} was observed. The development of ADAs was not found to affect the pharmacodynamics, safety, or efficacy of ZIRDAWNY in these patients.

Elderly patients

The safety and effectiveness of ZIRDAWNY for prophylaxis to prevent attacks of HAE were evaluated in a subgroup of patients 65 years and older. Use of ZIRDAWNY in this population is supported by evidence from Trials 1 and 3 that included 3 geriatric patients (≥65 years) supplemented by 2 ZIRDAWNY naïve geriatric patients from an open label trial (Trial 2) that were previously maintained on other HAE prophylactic therapies and not previously enrolled in Trial 1. The safety profile and reduction in HAE attack rate in these geriatric patients were similar to those observed in younger adult patients.

Paediatric population

The safety and effectiveness of ZIRDAWNY for prevention of attacks of HAE have been studied in paediatric patients 12 years and older. Use of ZIRDAWNY in this population is supported by evidence from Trial 1 that included adults and a total of 7 adolescent patients (12 to 17 years) supplemented by 4 ZIRDAWNY naïve adolescent patients from an open label trial (Trial 2) that were previously maintained on other HAE prophylactic therapies and not previously enrolled in Trial 1. The safety profile and reduction in HAE attack rate in these adolescents were similar to those observed in adults (see Section 4.8 Adverse effects (undesirable effects).

The safety and effectiveness of ZIRDAWNY in paediatric patients less than 12 years of age have not been established.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of donidalorsen were evaluated following subcutaneous administration of multiple doses every 4 weeks in healthy subjects and every 4 weeks or every 8 weeks in patients with HAE.

Donidalorsen exposure (maximum plasma concentration [C_{max}] and area under the plasma concentration time curve [AUC]) increased in a dose dependent manner following single subcutaneous doses ranging from 20 to 80 mg in healthy volunteers but was greater than dose proportional over the entire dose range.

Population estimates (Geometric Mean) of steady state maximum plasma concentration ($C_{max,ss}$), trough plasma concentration ($C_{trough,ss}$), and area under the plasma concentration time curve over the dosing interval ($AUC_{\tau,ss}$) are presented in Table 5. No accumulation of donidalorsen C_{max} and AUC was observed in plasma after repeated dosing every 4 weeks.

Table 5: Summary of Simulated Pharmacokinetic Parameters from Population Pharmacokinetic Analysis Following Dosing of ZIRDAWNY 80 mg q4wks or 80 mg q8wks in Patients with HAE at Steady State

Pharmacokinetic Parameters (Geometric Mean)	ZIRDAWNY	
	80 mg q4wks	80 mg q8wks
$C_{max,ss}$ (ng/mL)	417	416
$C_{trough,ss}$ (ng/mL)	0.755	0.255
$AUC_{\tau,ss}$ (ng·h/mL)	5240	5210

$AUC_{\tau,ss}$ = area under the plasma concentration time curve over the dosing interval at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{trough,ss}$ = trough plasma concentration at steady state; q4wks = every 4 weeks; q8wks = every 8 weeks.

Absorption

Following subcutaneous administration, donidalorsen is absorbed with the time to maximum plasma concentration of approximately 2.5 hours post dose, based on population estimates.

Distribution

Donidalorsen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing. The population estimate of apparent volume of distribution for the central (Vc/F) and peripheral (Vp/F) compartment were 69.8 L and 1840 L, respectively. Donidalorsen is highly bound to human plasma proteins (>98% bound) *in vitro*.

Metabolism

The oligonucleotide component of donidalorsen is expected to be metabolised primarily in the liver by endo- and exonuclease-mediated degradation to short oligonucleotide fragments of varying sizes. The linker that covalently connects the oligonucleotide to the GalNAc residues is cleaved by hydrolysis. Both the linker and the GalNAc components undergo further metabolism.

Excretion

The population estimate of the terminal elimination half-life of donidalorsen in a typical patient with HAE is approximately 1 month.

The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose in healthy subjects within 24 hours. Linker related metabolites are minimally released to circulation and subsequently rapidly excreted to urine or faeces.

Special populations

Population pharmacokinetics and pharmacodynamics analyses showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of donidalorsen based on age, body weight, sex, race, ethnicity, geographical region, disease status, mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2), or mild hepatic impairment (total bilirubin ≤1 × ULN and AST >1 × ULN, or total bilirubin >1 to 1.5 × ULN and any AST). ZIRDAWNY has not been studied in patients with moderate or severe renal impairment, end stage renal disease, or moderate or severe hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Donidalorsen was negative for genotoxicity in *in vitro* (bacterial reverse mutation, chromosomal aberration in Chinese hamster lung cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Carcinogenicity

In a 6-month carcinogenicity study, subcutaneous administration of donidalorsen in male (up to 20 mg/kg) or female (up to 60 mg/kg) transgenic (Tg.rasH2) mice once every 2 weeks did not result in an increase in malignant tumours. Based on plasma AUC exposure, the highest tested doses were approximately 7- and 20-fold exposure margins in male and female mice, respectively, over the maximum recommended human dose (MRHD). Further, no evidence of carcinogenicity was observed when both sexes of transgenic mice received a rodent-specific oligonucleotide once every 2 weeks subcutaneously for 6 months.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Monobasic sodium phosphate dihydrate

Dibasic sodium phosphate

Sodium chloride

Water for injections

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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 at 2°C to 8°C (Refrigerate. Do not freeze).

Keep the pre-filled pen in the outer carton in order to protect from light.

Do not expose to heat.

ZIRDAWNY may be stored in the original carton unrefrigerated for up to 6 weeks below 30°C. If not used within 6 weeks, it should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

0.8 mL sterile solution in a single-use Type I glass syringe with a stainless steel staked needle, rigid needle shield, and siliconised chlorobutyl elastomer plunger stopper. The filled primary container and a pen are assembled to a pre-filled pen, which is labelled and packaged in an opaque carton with a partition to secure the pre-filled pen and protect from light.

Pack sizes:

- 1 single-use pre-filled pen.
- 3 single-use pre-filled pens.

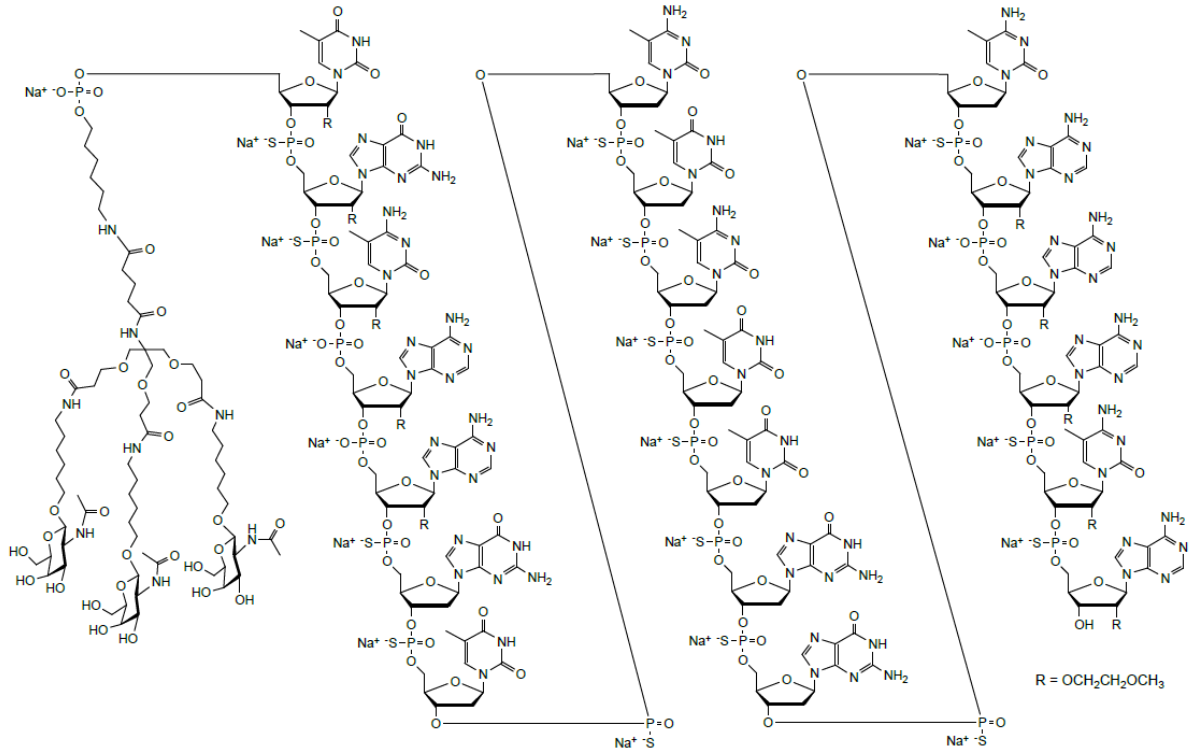
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular formula

$C_{296}H_{435}N_{83}O_{151}P_{20}S_{15}$ (free acid)

$C_{296}H_{415}N_{83}O_{151}P_{20}S_{15}Na_{20}$ (sodium salt)

Molecular weight

8672.66 Da (free acid)

9112.27 Da (sodium salt)

CAS number

2304692-48-4 (free acid)

2304701-45-7 (sodium salt)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – PRESCRIPTION ONLY MEDICINE

8 SPONSOR

Otsuka Australia Pharmaceutical Pty Ltd

Suite 2.03, Level 2

9 Help Street

Chatswood NSW 2067

www.otsuka.com.au

9 DATE OF FIRST APPROVAL

11 June 2026

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information