ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Dawnzera 80 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 80 mg donidalorsen (as donidalorsen sodium) in 0.8 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to yellow solution with a pH of approximately 7.4 and osmolality of approximately 290 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment is to be initiated under the supervision of a physician experienced in the diagnosis and management of patients with HAE.

Posology

The recommended starting dose in adult and adolescent patients aged 12 years and older is 80 mg donidalorsen by subcutaneous injection 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 Dawnzera.

Based on the clinical data, a gradual reduction in attack rate is seen as early as Week 1 after the initial dose of donidalorsen with an expected maximum effect after 1 month.

Consideration should be given to discontinuing treatment in patients with normal C1-INH HAE (nC1-INH) who have shown insufficient reduction in attacks after 4 months of treatment (see section 4.4 and 5.1).

Dawnzera is not intended for the treatment of acute HAE attacks (see section 4.4).

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.

Special populations

Elderly

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

Hepatic impairment

No dose adjustment of donidalorsen is required for patients with mild hepatic impairment (see section 5.2).
Dawnzera has not been studied in patients with moderate or severe impairment. Donidalorsen should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Renal impairment

No dose adjustment of donidalorsen is required for patients with mild renal impairment.
Dawnzera has not been studied in patients with moderate or severe impairment or end stage renal disease. Donidalorsen should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Paediatric population

The safety and efficacy of donidalorsen in children aged < 12 years have not yet been established. No data are available.
See sections 4.8 and 5.1.

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 Dawnzera (see section 5.1).

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

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

Method of administration

Dawnzera is intended for subcutaneous use only.

Dawnzera is to be administered as a subcutaneous injection in the abdomen, upper thigh region, or for caregivers only, the back of the upper arm. Rotation of the injection site is recommended. Dawnzera must not be injected into areas where the skin is tender, bruised, red, hard, infected or discoloured.

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

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis have been observed (see section 4.8). 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.

General

Dawnzera is not intended for treatment of acute HAE attacks. In case of a breakthrough HAE attack, individualised treatment should be initiated with an approved rescue medicinal product.

There are limited data available on the use of donidalorsen in HAE patients with HAE-nC1INH (see section 5.1). Patients with HAE nC1-INH having mutations that are not associated with the kallikrein-kinin system (KKS) pathway are not expected to respond to Dawnzera.

It is recommended to perform genetic testing, if available, according to current HAE guidelines and to discontinue the treatment if clinical response is not observed (see sections 4.2 and 5.1).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug-drug interaction studies have been performed with donidalorsen. *In vitro* studies show that donidalorsen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound active substances, and is not a substrate or inhibitor/inducer of cytochrome P450 (CYP) enzymes. 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

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of donidalorsen in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of donidalorsen during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of donidalorsen/metabolites in milk (see section 5.3).
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from donidalorsen therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of this medicinal product on human fertility are available. Donidalorsen had no effect on fertility and early embryonic development toxicity in murine models (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) in patients treated with 80 mg donidalorsen every 4 weeks were injection site reactions (24.4 %).

Tabulated list of adverse reactions

Adverse reactions associated with donidalorsen obtained from clinical trials 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 donidalorsen

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

[a] Injection site reactions include also: erythema, discolouration, pain, pruritus, induration, haematoma, bruising, exfoliation, hypersensitivity and swelling.
[b] 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 and 4.4).

Injection site reactions

During double-blinded, 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 discoloration led to permanent discontinuation of treatment.

Paediatric population

The safety of donidalorsen was evaluated in a double-blind placebo-controlled clinical trial in a subset of 7 adolescent patients aged 12 to 17 years. The safety profile in these adolescent patients was similar to the profile observed in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no available information to identify potential signs and symptoms of overdose. If symptoms should occur, symptomatic treatment is recommended. There is no antidote available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 results in the release of bradykinin, a potent vasodilator causing inflammation and swelling in HAE.

Pharmacodynamic effects

In Trial 1, a 24-week multicenter, randomised, double blind, placebo-controlled trial 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. The mean percentage change from baseline to

Week 24 in trough plasma PKK concentrations indicated reductions of 73 % and 47 % following treatment with donidalorsen 80 mg every 4 weeks and every 8 weeks, respectively, compared with 2 % in the placebo group.

Clinical efficacy and safety

The efficacy of Dawnzera for the prevention of angioedema attacks in patients was studied in Trial 1.

Trial 1- "OASIS-HAE"

Trial 1 included 90 (48 female and 42 male) 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 investigational medicinal product (IMP). Paediatric patients were 7 adolescents aged 12 years and older; furthermore, the trial included 2 elderly patients (≥ 65 years). 3 patients had a body weight of < 50 kg at baseline, of which 2 were adolescents (see also section 5.2). 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 Dawnzera 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 medicinal products prior to entering the trial; however, all patients were allowed to use rescue medicinal products for treatment of any breakthrough HAE attacks.

Overall, 93 % of patients had HAE 1 and 7 % had HAE 2. A history of laryngeal angioedema attacks was reported in 52 % of patients, and 18 % of patients were on prophylactic therapy prior to enrolment. The mean HAE attack rate during the prospective run-in period (baseline attack rate) was 3.33 (SD 2.086) attacks/4 weeks and an attack rate of > 2 attacks/4 weeks was observed in 69 % of patients overall.

Donidalorsen 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. A sustained response to donidalorsen with mean decreases from baseline in the HAE attack rate was observed throughout the treatment period in the Dawnzera treatment groups.

Table 3: Results of primary and secondary efficacy endpoints (full analysis set)

Endpoint statistics	**Placebo (N=22)**	**Dawnzera 80 mg q4wks (N=45)**	**Dawnzera 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	1.15 (0.72, 1.83)	0.12 (0.04, 0.35)	0.68 (0.37, 1.23)

Endpoint statistics	Placebo (N=22)	Dawnzera 80 mg q4wks (N=45)	Dawnzera 80 mg q8wks (N=23)
from second dose (Week 4)			
% Reduction (95 % CI) relative to placebo starting from second dose (Week 4)		−89 (−97, −66)	−41 (−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 = not statistically significant; 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 Dawnzera 80 mg q4wks group and the placebo group.
† Moderate: mild to moderate limitation in activity, some assistance needed; severe: marked limitation in activity, assistance required.
‡ Statistically significant.

For 4 adolescent patients (aged 12 to 17 years) in the q4wks group, a 97.1 % decrease (95 % CI: -106.26 %, -88.01 %) from baseline (run-in period) in the time-normalized HAE attack rate (per 4 weeks) from Week 0 to Week 24 was observed.

Additional pre-defined trial secondary endpoints included the proportion of responders to IMP 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 in the Dawnzera treatment group was 93 %, 82 %, 62 %, and 53 %, respectively, in the 80 mg q4wks group, and 83 %, 65 %, 48 %, and 35 %, respectively, in the 80 mg q8wks 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 Dawnzera treatment group 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 Dawnzera 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 Dawnzera treatment group was −24.8 and −19.9 for the 80 mg q4wks group (p <0.001) 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 Dawnzera in an open-label extension trial (Trial 2) of up to 3 years. Of these, 83 patients were previously treated with Dawnzera 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).

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

After 52 weeks of Dawnzera 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 Dawnzera, 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.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. ADA did not affect maximum plasma concentrations, but increased trough plasma concentrations. No evidence of ADA impact on pharmacodynamics, efficacy or safety was observed, however, the available data are limited to make definitive conclusions.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of trials with Dawnzera in one or more subsets of the paediatric population in the treatment of hereditary angioedema for the routine prevention of recurrent attacks of hereditary angioedema. See section 4.2.

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 (area under the plasma concentration time curve [AUC]) increased in a dose dependent manner following 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 4. No accumulation of donidalorsen C_{max} and AUC was observed in plasma after repeated dosing every 4 weeks.

Table 4: Summary of simulated pharmacokinetic parameters from population pharmacokinetic analysis following dosing of donidalorsen 80 mg q4wks or 80 mg q8wks in patients with HAE at steady state

Pharmacokinetic parameters (geometric mean)	**Donidalorsen**	
	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)	5 240	5 210

$AUC_{\tau,ss}$ = 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 1 840 L, respectively. Donidalorsen is highly bound to human plasma proteins (>98 % bound) *in vitro*.

Biotransformation

Donidalorsen is metabolised by endo- and exonucleases to short oligonucleotide fragments of varying sizes within the liver.

Elimination

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 (12 to 74 years), sex, 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). Regarding body weight, donidalorsen AUC predicted values for the 30-40 kg body weight range were > 17 500 ng·h/mL, > 10 000 ng·h/mL for 40-50 kg and around 10 000 ng·h/mL for 50-60 kg. The corresponding values for patients with body weights > 60 kg were < 7 500 ng·h/mL. Donidalorsen 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Carcinogenicity

In a 6 month carcinogenicity study in transgenic (Tg.rasH2) mice, subcutaneous administration of donidalorsen (5, 10, 20, or 60 mg/kg) or a rodent specific surrogate (10 mg/kg) once every 2 weeks did not result in an increase in malignant tumors, indicating a lack of human carcinogenic risk.

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.

Pregnancy, lactation and fertility

Subcutaneous administration of donidalorsen (0, 5, 10, or 20 mg/kg/week) or a rodent active inhibitor of PKK (5 mg/kg/week) to mice every other day throughout pregnancy and weekly throughout lactation produced no adverse effects on pre- and postnatal development.

In the mouse pre- and postnatal development study, the concentrations of donidalorsen in breast milk from lactating mice increased in a dose dependent manner at doses ≥ 10 mg/kg/week, but these concentrations of donidalorsen in breast milk were > 3 000 fold lower than the observed tissue concentrations. Even though donidalorsen was detected in the maternal mouse milk, systemic exposure in pups was not expected due to the lack of oral absorption of donidalorsen.

In animal studies, administration of donidalorsen or a pharmacologically active rodent specific surrogate in a combined fertility and embryofetal development toxicity study in mice did not result in effects on male and female fertility or embryofetal development.

Subcutaneous administration of donidalorsen (0, 1, 4, or 10 mg/kg/week) or a rodent active inhibitor of prekallikrein (PKK) (4 mg/kg/week) 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 fertility, pregnancy, or embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate (E 339)
Disodium hydrogen phosphate (E 339)
Sodium chloride
Water for injections
Hydrochloric acid (E 507) (for pH adjustment)
Sodium hydroxide (E 524) (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

3 years.

Dawnzera may be stored in the original carton at room temperature (up to 30 °C) for a single period of up to 6 weeks, but not beyond the expiry date.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Keep the pre-filled pen in the outer carton in order to protect from light.

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 size of one pre-filled pen.
Pack size of three pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to initiation, patients and/or caregivers must be trained on proper preparation and administration of Dawnzera (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 solution must not be injected if it appears frozen. The pre-filled pen must not be used if cloudiness, particulate matter, or discolouration is observed prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2001/001
EU/1/25/2001/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Tjoapack Netherlands B.V
Nieuwe Donk 9
4879 AC Etten-Leur
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dawnzera 80 mg solution for injection in pre-filled pen
donidalorsen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 80 mg of donidalorsen (as donidalorsen sodium) in 0.8 mL solution

3. LIST OF EXCIPIENTS

Sodium dihydrogen phosphate (E 339), disodium hydrogen phosphate (E 339), sodium chloride, water for injections, hydrochloric acid (E 507), sodium hydroxide (E 524). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
3 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous use.

Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored at room temperature (up to 30 °C) for a single period of up to 6 weeks.
Discard date: _____

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2001/001 (pack with one pen)
EU/1/25/2001/002 (pack with three pens)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dawnzera

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dawnzera 80 mg injection
donidalorsen
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Dawnzera 80 mg solution for injection in pre-filled pen
donidalorsen

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dawnzera is and what it is used for

Dawnzera is a type of medicine called an antisense oligonucleotide inhibitor that contains the active substance donidalorsen. It is used in patients 12 years and older with hereditary angioedema (HAE).to prevent angioedema attacks.

HAE is an inherited condition where the blood does not have enough of a protein called 'C1 inhibitor' or where the C1 inhibitor does not work properly. This leads to too much 'plasma kallikrein', which in turn produces higher levels of a substance called bradykinin in your bloodstream. High levels of bradykinin causes blood vessels to widen and leak fluid into the surrounding tissue leading to the swelling attacks seen in HAE. Symptoms may include stomach pains and swelling of the hands and feet, face, eyelids, lips or tongue, voice-box (larynx), which may make breathing difficult, genitals stomach and intestines

The active substance in Dawnzera, donidalorsen, blocks the activity of plasma kallikrein, which helps to reduce the amount of bradykinin in the bloodstream and prevents symptoms of HAE.

2. What you need to know before you use Dawnzera

Do not use Dawnzera

If you are allergic to donidalorsen or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Dawnzera.

Dawnzera can cause serious allergic reactions (see section 4). If you have a severe allergic reaction to Dawnzera seek emergency medical assistance **immediately**. Symptoms may include:
- rash
- difficulties in breathing
- tight chest
- wheezing
- swelling around the mouth
- fast heart beat

Dawnzera is not meant to be used during an acute HAE attack. If you experience a breakthrough HAE attack, you should use your regular rescue medicine to treat it.

Children and adolescents

Dawnzera is not recommended for use in children under 12 years. It has not been studied in this age group.

Other medicines and Dawnzera

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Dawnzera is not known to affect other medicines or be affected by other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

There is limited information on the safety of Dawnzera during pregnancy and breast-feeding. As a precautionary measure, it is preferable to avoid the use of donidalorsen during pregnancy.

This medicine may pass into breast milk and it is not known if this medicine can affect your baby. Your doctor will discuss with you whether to stop treatment with this medicine while you are breast-feeding, or to stop breast-feeding.

Your doctor will discuss with you the risks and benefits of using this medicine.

Driving and using machines

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

Dawnzera contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per pre-filled pen, that is to say essentially ‘sodium-free’.

3. How to use Dawnzera

Always use use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dawnzera is a solution provided in a single-use pre-filled pen for injection.

How much Dawnzera to use

The recommended dose is one pre-filled pen once a month. If you have not had an attack for a long period, your doctor may change the dose to one pen every 2 months.

How to inject Dawnzera

Your treatment will be started and managed under the supervision of a doctor experienced in the care of patients with HAE. You or a caregiver can inject this medicine after appropriate training. A doctor, pharmacist or nurse should show you how to prepare and inject Dawnzera properly before you use it for the first time. Do not inject yourself or someone else until you have been trained to inject the medicine.

If you inject Dawnzera yourself or if your caregiver injects it, you or your caregiver must carefully read and follow the detailed instructions in the "Instructions for use".

- Dawnzera should be injected under the skin (subcutaneous injection).
- **Do not** inject
  - within 5 cm of the belly button (navel).
  - into skin that is tender, bruised, red, hard, infected or discoloured.
  - into scars or damaged skin.
- Insert the needle into the fatty tissue in the tummy (abdomen), the front of the thigh or the back of the upper arm.
- Injections in the back of the upper arm must only be given by caregivers.
- Inject the medicine in a different place each time.
- Use each pre-filled pen of Dawnzera only once.

If you use more Dawnzera than you should

Tell your doctor, pharmacist or nurse if you use too much Dawnzera.

If you forget to use Dawnzera

Do not use a double dose to make up for a forgotten dose.

Use the missed dose as soon as you remember. Thereafter resume dosing at the prescribed dosing frequency (once monthly or once every 2 months) from the date of the most recently administered dose.

If you stop using Dawnzera

It is important that you keep injecting Dawnzera as instructed by your doctor, even if you feel better.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This medicine may cause a severe allergic reaction (with a **common** frequency: may affect up to 1 in 10 people). If you have a severe allergic reaction, **tell your doctor, pharmacist or nurse immediately.** Symptoms include:

- rash
- difficulties in breathing
- tight chest
- wheezing
- swelling around your mouth
- fast heart beat

Tell your doctor, pharmacist or nurse if you notice any of the following side effects.

Very common (may affect more than 1 in 10 people)
- Reactions where the injection is given. Symptoms may include redness, change in skin colour, pain, itching, hardening, haematoma (bleeding under the skin at the site of the injection), bruising, scaling of the skin, allergic reaction or swelling.
- Blood tests showing liver changes.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dawnzera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Keep the pre-filled pen in the outer carton in order to protect from light.

The pre-filled pen may be stored at room temperature (up to 30 °C) for a single period of up to 6 weeks, but not beyond the expiry date.

If you store Dawnzera at room temperature, write the discard date on the original carton. The discard date is maximally 6 weeks after you take the medicine out of the refrigerator, and should be noted in the space indicated on the original carton for storage at room temperature up to 30 °C.

Do not use this medicine if you notice the following:
- clear cap is missing or not attached.
- expiry date (EXP) or discard date has passed.
- medicine looks frozen, cloudy, discoloured, or has particles.
- pre-filled pen appears damaged.

Do not throw away any medicines via household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Dawnzera contains

- The active substance is donidalorsen. Each pre-filled pen contains 80 mg donidalorsen (as donidalorsen sodium) in 0.8 mL solution.
- The other ingredients are sodium dihydrogen phosphate (E 339), disodium hydrogen phosphate (E 339), sodium chloride, water for injections, hydrochloric acid (E 507) (for pH adjustment), sodium hydroxide (E 524) (for pH adjustment) – see section 2 “Dawnzera contains sodium”.

What Dawnzera looks like and contents of the pack

Dawnzera is a clear, colourless to yellow solution for injection in a pre-filled pen.

Dawnzera is available as:
- a single pack containing one pre-filled pen in a carton
- a single pack containing three pre-filled pens in a carton

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT Amsterdam
Netherlands

Manufacturer

Tjoapack Netherlands B.V
Nieuwe Donk 9
4879 AC Etten-Leur
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

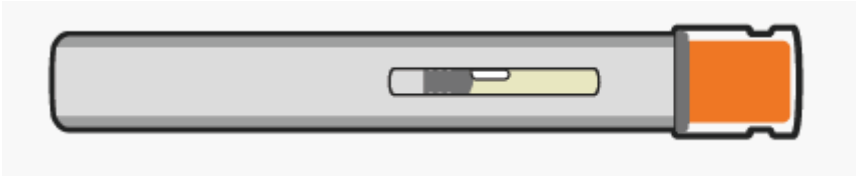
<--->

INSTRUCTIONS FOR USE

Dawnzera 80 mg solution for injection in pre-filled pen

This Instructions for Use contains information on how to inject **Dawnzera** using the pre-filled pen.

Read this 'Instructions for Use' before you start using your Dawnzera pre-filled pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Your healthcare provider should show you or your caregiver how to use the **Dawnzera** pre-filled pen the right way. If you or your caregiver have any questions, talk to your healthcare provider.



Important information:

- **Dawnzera** is injected under the skin (subcutaneous use) only.
- Each pre-filled pen contains 1 single-dose and can only be used 1 time.
- **Do not** remove the clear cap until you are ready to inject **Dawnzera** (See Step 5).
- **Do not** share your pre-filled pen with anyone.
- **Do not** use the pre-filled pen if it appears damaged.

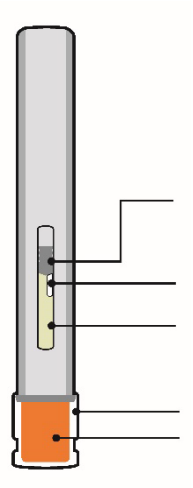
Storage information:

- Store the pre-filled pen in the refrigerator between 2 °C - 8 °C in the original carton.
- If needed, the pre-filled pen can be stored at room temperature up to 30 °C in the original carton for up to 6 weeks.
- If you store Dawnzera at room temperature, write the discard date on the original carton. The discard date is maximally 6 weeks after you take the medicine out of the refrigerator, and should be noted in the space indicated on the original carton for storage at room temperature up to 30 °C.
- If you do not use the pre-filled pen kept at room temperature within 6 weeks, throw it away.
- Keep the pre-filled pen in the carton until ready to use.
- **Do not** store the pre-filled pen with the clear cap removed.

Keep Dawnzera out of the sight and reach of children.

Dawnzera overview

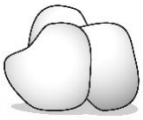
Single-dose pre-filled pen



Other supplies (not included)

Alcohol wipe

Sharps container



Cotton ball or gauze

Small bandage

Preparing to inject Dawnzera

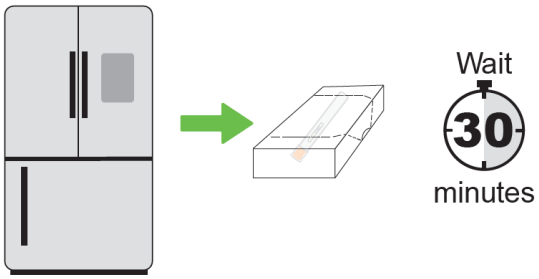
Step 1 Remove from the refrigerator

a) Remove the pre-filled pen from the refrigerator.

b) Keep the pre-filled pen in the original carton and let the pre-filled pen come to room temperature for 30 minutes before injecting.

c) When one pre-filled pen from a pack with 3 pens is removed from refrigeration, **return the remaining pre-filled pens to the refrigerator** for future use until needed.

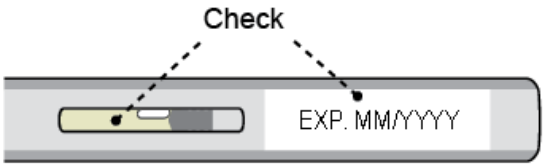
Do not try to speed up the warming process using other heat sources, such as a microwave or hot water.



Step 2 Inspect the medicine

a) Check the expiry date (EXP) on the pen and also the discard date on the original carton if the medicine was stored at room temperature up to 30 °C.

b) Check the medicine through the viewing window. The **Dawnzera** medicine should be clear and colourless to yellow. There should be no particles. It is normal to see air bubbles in the solution.



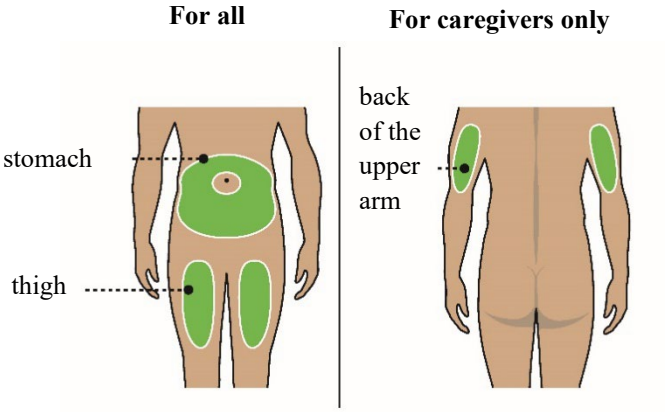
Do not use the pre-filled pen if the:

- clear cap is missing or not attached.
- expiry date (EXP) or discard date has passed**.**
- medicine looks frozen, cloudy, discoloured, or has particles.
- pre-filled pen appears damaged.

Step 3 Choose the injection site

a) Choose an injection site on the stomach or the front of the thigh.

b) Only caregivers may choose the back of upper arm.



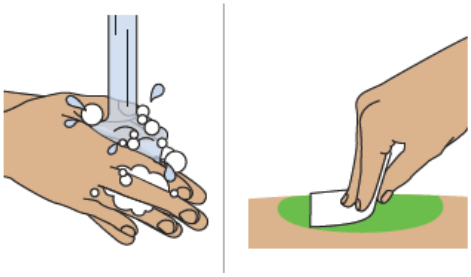
Do not inject:

- within 5 cm of the belly button (navel).
- into skin that is tender, bruised, red, hard, infected or discoloured.
- into scars or damaged skin.
- into the site of the previous injection

Step 4 Wash hands and clean the injection site

a) Wash your hands with soap and water.

b) Clean the injection site with an alcohol wipe in a circular motion. Let the skin air dry.



Do not touch the cleaned skin before injecting.

Injecting Dawnzera

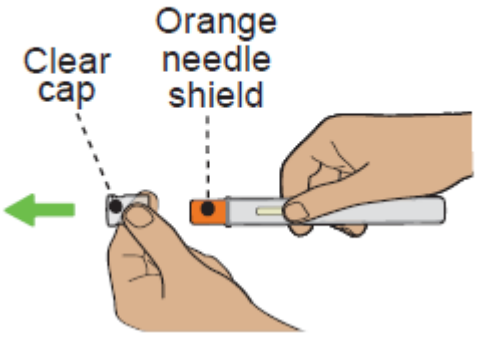
Step 5 Remove and throw away the clear cap

a) Hold the pre-filled pen by the middle with the clear cap facing away from you.

b) Remove the clear cap by pulling it straight off. **Do not** twist it off. The needle is inside the orange needle shield.

c) Throw away the clear cap in the trash or sharps container.

Do not remove the clear cap until right before you inject.
Do not recap the pre-filled pen.
Do not push the orange needle shield against the hand or finger.



Step 6 Begin injection

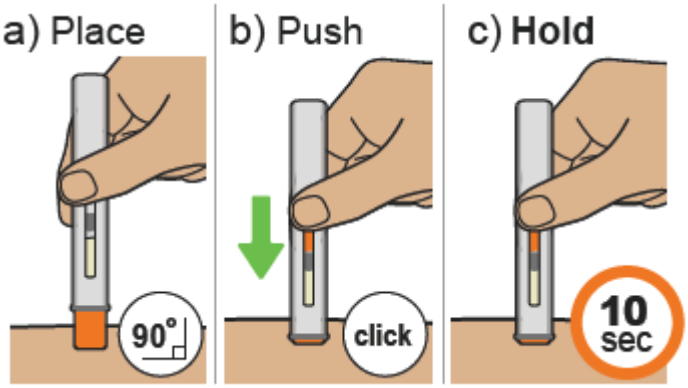
a) Hold the pre-filled pen in 1 hand. Place the orange needle shield at a 90-degree angle against your skin. Make sure you can see the viewing window.

b) Push firmly and hold the pre-filled pen straight against the skin. You will hear a click as the injection starts.

You may hear a second click. This is normal. The procedure is not finished.

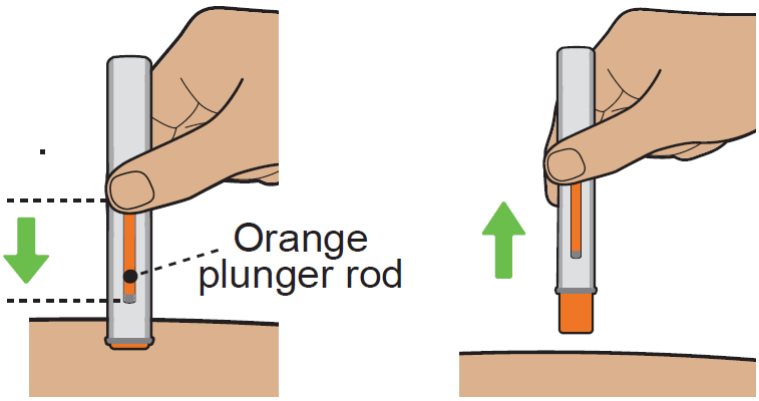
c) Hold the pre-filled pen against the skin for 10 seconds to make sure the full dose has been given.

Do not move, turn, or change the angle of the pre-filled pen during the injection.



Step 7 Finish injection

a) Check that the orange plunger rod has moved down to fill the entire viewing window. If the orange plunger rod does not fill the viewing window, you may not have received the full dose.
If this happens or if you have other concerns, contact your healthcare provider.



b) Remove the pre-filled pen by lifting it straight up. After removal from the skin, the orange needle shield locks into place and covers the needle.

c) There may be a small amount of blood or liquid where you injected. This is normal.

If needed, press a cotton ball or gauze on the area and apply a small bandage.

Do not reuse the pre-filled pen.

Throwing away Dawnzera

Step 8 Throw away pre-filled pen

a) Put the used pre-filled pen in a sharps container right away after use.

Do not throw away the pre-filled pen in your household trash.
Do not recycle your used sharps disposal container.
Do not reuse the pre-filled pen or clear cap.

If you do not have a sharps container, you may use a household container that is:
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labelled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps disposal container.
There may be local laws about how you should throw away used pre-filled pens.

Do not throw away your used sharps disposal container in your household trash unless your local guidelines permit this. **Do not** recycle your used sharps disposal container.