Public Summary of the Risk Management Plan (RMP)

Dawnzera™ (donidalorsen)

Based on Part VI of EU RMP Version 1.1

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Dawnzera is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/ Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Dawnzera in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Otsuka Pharmaceuticals (Switzerland) GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Dawnzera.

1 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1.1 VI.1: Summary of the Risk Management Plan for Dawnzera (donidalorsen)

This is a summary of the risk management plan (RMP) for Dawnzera. The RMP details risks of Dawnzera, how these risks can be minimised, and how more information will be obtained about Dawnzera's risks and uncertainties (missing information).

Dawnzera's summary of product characteristics (SmPC) and package leaflet gives essential information to healthcare professionals and patients on how Dawnzera should be used.

This summary of the RMP for Dawnzera should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dawnzera's RMP.

1.1.1 I: The Medicine and What it is Used for

Dawnzera is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older. It contains donidalorsen as the active substance and it is administered as subcutaneous injection.

Further information about the evaluation of Dawnzera's benefits can be found in Dawnzera's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage */* [link to product's EPAR summary landing page on the EMA webpage.]*/*

1.1.2 II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Dawnzera, together with measures to minimise such risks and the proposed studies for learning more about Dawnzera's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important instructions on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including a Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Dawnzera is not yet available, it is listed under 'missing information' as described below.

1.1.2.1 II.A: List of Important Risks and Missing Information

Important risks of Dawnzera are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Important identified risks are concerns for which there is sufficient proof of a link with the use of Dawnzera. Important potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 1.1.2.1-1 II.A-1: List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	• Hepatotoxicity • Renal toxicity • Bleeding/thrombocytopenia
Missing Information	• Use in pregnancy • Use during breastfeeding • Long-term use

1.1.2.2 II.B: Summary of Important Risks

Table 1.1.2.2-1 II.B-1: Hepatotoxicity

Evidence for linking the risk to the medicine	Across the clinical programme of donidalorsen, 26 cases with 56 events related to increased hepatic enzymes were observed. Most of these cases were confounded by pre-existing medical conditions and concomitant conditions such as diabetes mellitus, thalassaemia beta, hypertransaminasaemia, hypothyroidism, polycystic ovarian syndrome, Lyme disease, hepatic steatosis, obesity, hypercholesterolaemia, and infections. The majority of these patients also reported polypharmacy

Table 1.1.2.2-1 II.B-1: Hepatotoxicity	
	(paracetamol, antibiotics, and statins), which is an additional risk factor for elevated liver enzymes. However, the Applicant decided to include hepatotoxicity as an important potential risk, until further data is available.
Risk factors and risk groups	Alcohol consumption, underlying comorbidities such as type 2 diabetes, Metabolic Dysfunction-Associated Steatohepatitis (MASH), hepatitis, autoimmune diseases, exposure to hepatotoxins or hepatotoxic materials/drugs, malnutrition, and herbal supplements not approved by healthcare provider
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activity	Study ISIS 721744-CS7

Table 1.1.2.2-2 II.B-2: Renal Toxicity	
Evidence for linking the risk to the medicine	Donidalorsen has not been associated with renal toxicity based on completed chronic renal toxicology studies in non-human primates. Donidalorsen was not associated with renal toxicity during clinical trials including completed and ongoing open-label extension studies.
Risk factors and risk groups	Risk factors that may predispose individuals to renal toxicity include underlying cardiac and renal comorbidities, dehydration, diabetes mellitus, infections, and co-administration of nephrotoxic medications.
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activity	Study ISIS 721744-CS7

Table 1.1.2.2-3 II.B-3: Bleeding/Thrombocytopenia	
Evidence for linking the risk to the medicine	Donidalorsen has not been associated with thrombocytopenia or interference with coagulation based on completed chronic toxicology studies in non-human primates. No patient met the predefined stopping rule regarding platelet counts, or discontinued treatment due to a thrombocytopenia TEAE, and no patient with platelet count < LLN experienced a concurrent serious or severe bleeding event.
Risk factors and risk groups	Patients with baseline thrombocytopenia (platelet count $<100 \times 10^9$/L) and pre-existing coagulation abnormalities could be at an increased risk of experiencing adverse events.
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activity	Study ISIS 721744-CS7

Table 1.1.2.2-4 II.B-4: Use in Pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 PL Section 2 Prescription only medicine

Table 1.1.2.2-5 II.B-5: Use during Breastfeeding	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 PL Section 2 Prescription only medicine

Table 1.1.2.2-6 II.B-2: Long-Term Use	
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine **Additional risk minimisation measures**: None
Additional Pharmacovigilance Activities	Study ISIS 721744-CS7

1.1.2.3 II.C: Post-authorisation Development Plan

1.1.2.3.1 II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of donidalorsen.

1.1.2.3.2 II.C.2 Other Studies in Post-authorisation Development Plan

Protocol Number: ISIS 721744-CS7 (EudraCT No: 2022-000757-93)

An Open-Label, Long Term Safety and Efficacy Study of Donidalorsen in the Prophylactic Treatment of Hereditary Angioedema (HAE)

Primary objective: To evaluate the safety of long-term dosing with donidalorsen in patients with HAE.

Secondary objective: To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the quality of life (QoL) of patients with HAE.

Exploratory Objective: Further characterize the effects of donidalorsen on HAE attacks, additional Patient Reported Outcomes (PROs) and biomarkers.

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