PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VELSIPITY (Etrasimod)

Marketing Authorization Number 69377

Film-coated tablet, 2 mg

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LIST OF ABBREVIATIONS

EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
S1P receptor	Sphingosine 1-Phosphate (S1P) receptor
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (Europe)

OVERVIEW

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 for Velsipity 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 marketing authorization.

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

SUMMARY OF RISK MANAGEMENT PLAN FOR VELSIPITY (ETRASIMOD)

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

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

This summary of the RMP for Velsipity 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 Velsipity's RMP.

I. The Medicine and What It Is Used For

Velsipity is authorised for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent (see SmPC for the full indication). It contains Etrasimod as the active substance and it is given orally as a film-coated tablet.

Further information about the evaluation of Velsipity's benefits can be found in Velsipity's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Velsipity, together with measures to minimise such risks and the proposed studies for learning more about Velsipity'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 advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so 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 the case of Velsipity, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including 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 Velsipity is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Velsipity are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Velsipity. 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. List of Important Risks and Missing Information

Important identified risks	• Macular oedema • Embryofoetal toxicity
Important potential risks	• Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion
Missing information	• Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

II.B Summary of Important Risks and Missing Information

Table 2. Important Identified Risk: Macular Oedema

Evidence for linking the risk to the medicine	Macular oedema was observed in the Etrasimod clinical trials and has been reported for other S1P receptor modulators.
Risk factors and risk groups	It has been hypothesised that patients with pre-existing impaired blood-retinal barrier function, e.g., patients with a history of diabetes mellitus, uveitis, or underlying/coexisting retinal disease, may be at elevated risk of developing macular oedema.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.8 Undesirable effects • PL section 2 What you need to know before you take Velsipity • PL section 4 Possible side effects Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 3. Important Identified Risk: Embryofoetal Toxicity

Evidence for linking the risk to the medicine	This is inferred from non-clinical data. There are a limited amount of data from the use of Etrasimod in pregnant women.
Risk factors and risk groups	Other than women of childbearing potential who are not using effective contraception, no specific risk factors or risk groups for embryofoetal toxicity subsequent to Etrasimod exposure are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide • Pregnancy-Specific Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 See II.C of this summary for an overview of the post-authorisation development plan.

Table 4. Important Potential Risk: Symptomatic Bradycardia (Including Conduction Disorders)

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of S1P receptor modulators and clinical study data.
Risk factors and risk groups	Patients with pre-existing cardiac conditions (e.g., patients with resting heart rate < 50 bpm, second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 Posology and method of administration • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity • PL section 3 How to take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 5. Important Potential Risk: Serious Opportunistic Infections

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of Etrasimod and clinical study data. The only serious opportunistic infection in an Etrasimod-treated patient reported from the clinical studies was a case of herpes simplex meningitis, which rapidly resolved with antiviral treatment.
Risk factors and risk groups	Patients with underlying immunodeficiency due to a comorbidity or recent or concomitant treatment with immunosuppressive drugs might be at elevated risk for opportunistic infections subsequent to treatment initiation with Etrasimod.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 6. Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of Etrasimod and clinical study data. Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with other S1P receptor modulators. In the Etrasimod clinical trials, the overall incidence of malignancies was consistent with the frequency expected in the general population.
Risk factors and risk groups	Ulcerative colitis is discussed as a risk factor for colorectal cancer and other malignancies. However, no risk factors specific to patients treated with Etrasimod are known for this potential risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 7. Important Potential Risk: Serious Liver Injury

Evidence for linking the risk to the medicine	Serious liver injury is classified as an important potential risk in view of reports of such events in patients treated with other S1P receptor modulators.
Risk factors and risk groups	No specific risk factors are known for this potential risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 8. Important Potential Risk: Neurological Events of PRES or Convulsion

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of Etrasimod and publicly available information on other S1P receptor modulators.
Risk factors and risk groups	No risk factors or risk groups specific to Etrasimod are known. The cases of convulsion or PRES during treatment with other S1P receptor modulators were generally reported from patients participating in multiple sclerosis trials.

Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 9. Missing Information: Safety in Elderly Patients ≥65 Years of Age, Particularly with Regard to Infections, Cardiovascular Events, and Eye Affections

Risk minimisation measures	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties • PL: not applicable Additional risk minimisation measures: • None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Velsipity.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: An Open-Label Extension Study of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis (ELEVATE UC OLE; APD334-303)

Purpose of the study: The primary objective is to assess the safety of long-term administration of Etrasimod in subjects with moderately to severely active UC. The secondary objective is to assess the long-term efficacy of Etrasimod in subjects with moderately to severely active UC. Safety concerns addressed:

- Macular oedema
- Symptomatic bradycardia (including conduction disorders)
- Serious opportunistic infections
- Malignancy

- Serious liver injury
- Neurological events of PRES or convulsion
- Embryofoetal toxicity
- Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

Study short name: An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (C5041046).

Purpose of the study: This study will be an active safety surveillance study to assess safety events of interest that may be associated with Etrasimod in the post-approval setting in the EU.

The primary objective is to estimate the incidence rates of safety events of interest among patients with UC who initiate Etrasimod during routine clinical care in the EU. The following are the primary safety events of interest:

- Macular oedema
- Symptomatic bradycardia (including conduction disorders)
- Serious opportunistic infections
- Malignancy
- Serious liver injury
- Neurological events of PRES or convulsion
- Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections
- Follow-up for the primary safety events of interest will be long-term (8 years).