AstraZeneca	AZ Swiss Marketing Company

ORPATHYS®

100 mg, film-coated tablets

Summary of the Risk Management Plan (RMP) for ORPATHYS® (Savolitinib)

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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 Orpathys 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 Orpathys in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedicinfo-pro.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Orpathys.

This is a summary of the risk management plan (RMP) for savolitinib. The RMP details important risks of savolitinib, how these risks can be minimised, and how more information will be obtained about savolitinib's risks and uncertainties (missing information).
The Prescribing Information (PI) and its package leaflet (PL) give essential information to healthcare professionals and patients on how savolitinib should be used.
Important new concerns or changes to the current ones will be included in updates of savolitinib RMP.

1. THE MEDICINE AND WHAT IT IS USED FOR

Savolitinib is authorised in combination with osimertinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have mesenchymal-epithelial transition (MET) overexpression or amplification, and who had disease progression on or after osimertinib. It contains savolitinib as the active substance and is given as three 100 mg tablets taken orally twice a day.

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of savolitinib, together with measures to minimise such risks and the proposed studies for learning more about the risks of savolitinib, 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 PI and PL 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 (eg, 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 Periodic Benefit Risk Evaluation Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

2.1 List of Important Risks and Missing Information

Important risks of savolitinib 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 savolitinib. 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 (eg, on the long-term use of the medicine).

Table 1 List of Important Risks and Missing Information

Important identified risks	• Hepatotoxicity • Hypersensitivity/allergic reactions
Important potential risks	• Interstitial lung disease/pneumonitis
Missing Information	None

2.2 Summary of Important Risks

Summaries of the safety concerns for savolitinib are provided in Table 2 (hepatotoxicity), Table 3 (hypersensitivity/allergic reactions), and Table 4 (interstitial lung disease/pneumonitis).

Table 2 Important Identified Risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Hepatotoxicity is considered a potential class effect of MET inhibitors, and dose-responsive minimal-to-mild hepatocellular hypertrophy was observed in non-clinical repeat-dose toxicology studies. In the savolitinib clinical development programme, a high frequency of low-grade enzyme elevations (reported as specific adverse events [AEs] or observed as elevations in laboratory parameters) and less commonly higher-grade enzyme elevations and/or hepatic AEs (including serious/severe drug-induced liver injury) have been reported.
Risk factors and risk groups	No specific risk factors for the development of hepatotoxicity in savolitinib-treated patients have been identified; however, common risk factors for hepatotoxicity include the concomitant use of hepatotoxic medication, chronic alcohol consumption and/or substance abuse, and pre-existing liver conditions (eg, hepatitis and liver metastases). Elderly and/or female patients may also have an increased susceptibility to liver injury due to differences in drug metabolism and hormonal influences, and obesity and metabolic syndrome may also contribute to liver vulnerability through mechanisms such as insulin resistance and lipid accumulation.
Risk minimisation measures	**Routine risk minimisation measures:** • PI Sections *Dosage/Administration*, *Warnings and precautions* and *Undesirable effects* • PL Sections *When is caution required when taking ORPATHYS?* and *Possible side effects* • Prescription-only medicine **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table 3 Important Identified Risk: Hypersensitivity/Allergic Reactions

Evidence for linking the risk to the medicine	Hypersensitivity/allergic reactions were confirmed as identified risks for savolitinib based on detailed reviews of individual case data obtained in the early clinical development programme.
Risk factors and risk groups	Other than a history of hypersensitivity reaction to savolitinib or its excipients, there are no other known risk factors. General risk factors for drug-induced hypersensitivity reactions include age (with older adults exhibiting increased susceptibility due to age-related changes in drug metabolism and immune function), female gender (associated with a higher incidence of hypersensitivity reactions, potentially due to hormonal influences on immune responses), concurrent illnesses (eg, viral infection), and polypharmacy. A history of previous hypersensitivity reactions to related drugs is also a critical risk factor, and genetic predispositions, particularly specific human leukocyte antigen alleles, play a crucial role in determining individual susceptibility to drug hypersensitivity.

Table 3 Important Identified Risk: Hypersensitivity/Allergic Reactions

Evidence for linking the risk to the medicine	Hypersensitivity/allergic reactions were confirmed as identified risks for savolitinib based on detailed reviews of individual case data obtained in the early clinical development programme.
Risk minimisation measures	**Routine risk minimisation measures:** • PI Section *Dosage/Administration*, *Warnings and precautions* and *Undesirable effects* • PL Section *When is caution required when taking ORPATHYS?* and *Possible side effects* • Prescription-only medicine **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table 4 Important Potential Risk: Interstitial Lung Disease/Pneumonitis

Evidence for linking the risk to the medicine	Based on data from other MET inhibitors and the limited reporting of AEs of interstitial lung disease (ILD)/pneumonitis in the savolitinib clinical development programme, there is a theoretical concern that savolitinib may be associated with the development of such events.
Risk factors and risk groups	There are no known risk factors for the development of ILD/pneumonitis in savolitinib-treated patients; however, ILD is listed as an adverse drug reaction in the osimertinib prescribing information, which is of relevance to savolitinib when given as part of the indicated combination treatment regimen. More broadly, major risk factors for the development of ILD/pneumonitis in cancer patients include smoking, a prior personal or family history of ILD/pneumonitis, poor performance status (≥ 2), advanced stage of underlying cancer, and pre-existing lung disease (such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and bronchiectasis). Other risk factors for ILD/pneumonitis also include older age, prior chemotherapy or previous radiation therapy to the lungs, Asian ethnicity, underlying health conditions (such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, bronchiectasis, sarcoidosis, autoimmune diseases, connective tissue disorders, parenchymal lung disease, or pulmonary infection) and long-term exposure to specific environmental or occupational toxins/pollutants (eg, mould, silica dust, asbestos fibres, grain dust, etc).
Risk minimisation measures	**Routine risk minimisation measures:** • PI Section *Warnings and precautions* and *Undesirable effects*[a] • Prescription-only medicine **Additional risk minimisation measures:** • No additional risk minimisation measures.

[a] Of note, whilst ILD is listed in Section *Undesirable effects* of the savolitinib PI, causality is attributed to osimertinib (administered as part of the indicated combination treatment regimen), and no causal relationship with savolitinib has been established.

3. POST-AUTHORISATION DEVELOPMENT PLAN

3.1 Studies Which are Conditions of the Marketing Authorisation

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

3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for savolitinib.