SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR JERAYGO® (APROCITENTAN)

Version Number of RMP Summary:	1.0
Document Date:	17 November 2025
Based on the EU RMP version:	0.7, dated 19 April 2024
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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 JERAYGO 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 JERAYGO in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Idorsia Pharmaceuticals Ltd. is fully responsible for the accuracy and correctness of the content of the published summary RMP of JERAYGO.

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Summary of the risk management plan

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

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

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

I. The medicine and what it is used for

JERAYGO is authorised for the treatment of resistant hypertension (see SmPC for the full indication). It contains aprocitentan as the active substance and it is given as film-coated tablets for oral use.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of JERAYGO, together with measures to minimise such 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 JERAYGO, these measures are supplemented with one ***additional risk minimisation measure*** *(Patient Card)* mentioned under the relevant important risks of teratogenicity and severe liver injury (see below).

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

II.A List of important risks and missing information

Important risks of JERAYGO 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 JERAYGO. 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.

List of important risks and missing information	
Important identified risks	Teratogenicity
Important potential risks	Heart failure due to fluid retention in predisposed patients Severe liver injury Male infertility
Missing information	Long-term cardiovascular safety under controlled clinical setting

II.B Summary of important risks

Important potential risk: teratogenicity	
Evidence for linking the risk to the medicine	Evidence of teratogenicity with ERAs is limited to animal data. ERAs have shown teratogenic effects in rats and/or rabbits, mainly craniofacial and cardiovascular malformations, in offspring of animals during pregnancy [Ruest 2009]. There is limited post-marketing experience in humans [Hitzerd 2019, Kamp 2021]. Based on the limited post-marketing experience in humans, there is no indication of human teratogenicity.
Risk factors and risk groups	Women of childbearing potential who are not using a reliable method of contraception.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4.5, 4.6, and 5.3 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card

Important potential risk: Heart failure due to fluid retention in predisposed patients	
Evidence for linking the risk to the medicine	Aprocitentan is developed for the treatment of RHT in a population with high CV morbidity and mortality. In study 301, there was a small and slightly higher incidence of treatment-emergent heart failure leading to hospitalisation in the aprocitentan groups vs placebo during the double-blind periods; however, when the incidence of heart failure leading to hospitalisation was calculated taking into account the entire duration of exposure to aprocitentan (48 weeks), the incidence was consistent with that reported in published articles in the RHT population [Bhatt 2014, Bhandari 2016, Muntner 2014] and in a real-world study. Furthermore, all subjects randomised in the study had multiple risk factors (heart failure, CKD, diabetes, CHD, older age and obesity) at baseline. Of note, 19.6% of study 301 patients had a medical history of heart failure.
Risk factors and risk groups	Patients with underlying heart disease are considered at higher risk of aggravation of heart failure. Other important risk factors commonly observed in the RHT population which may predispose to fluid retention include CKD and diabetes. Risk groups mainly include the elderly and obese patients.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Severe liver injury	
Evidence for linking the risk to the medicine	Class labelling related to increased liver enzymes/hepatotoxicity is in place for all marketed ERAs, i.e., bosentan, ambrisentan, and macitentan, all approved for PAH. This was due to the safety profile of the first approved ERA, bosentan, which caused dose-dependent liver toxicity [Denton 2008, Rubin 2002]. Other approved ERAs, such as ambrisentan and macitentan, do not appear to confer the same risk of hepatotoxicity as bosentan, based on meta-analyses of clinical trials [Pan 2017, Wei 2016] and the accumulating post-marketing experience. Of note, darusentan, the first ERA developed (but not commercialised) for the treatment of RHT, was also not associated with an increased risk of abnormal aminotransferase levels [Bakris 2010, Black 2007, Weber 2009]. In the aprocitentan programme, there was no evidence of drug-induced hepatotoxicity based on the absence of an imbalance between treatment groups, the presence of underlying risk factors / alternative causes in most cases and/or non-suggestive chronology of the events. There were no cases meeting the Hy's rule. Marked elevation of transaminases was neither dose-dependent nor different from placebo in the double-blind periods of Phase 2 and Phase 3 studies.
Risk factors and risk groups	Subjects with pre-existing severe liver disease.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Male infertility	
Evidence for linking the risk to the medicine	*Nonclinical data* There were no effects on fertility in male rats after treatment for 10 weeks prior to pairing with untreated female rats at dose levels up to 26 (67)-fold the human exposure at MRHD, based on total (free) concentrations. In one out of two 26-week repeated dose toxicity study in rats, there were histological changes such as dilation of seminiferous tubules accompanied by minimal to slight tubular degeneration at dose levels corresponding to 21 (54)-fold the human exposure at MRHD based on total (free) concentrations. In dogs, similar effects were observed at exposure corresponding to 26 (88)-fold the human exposure at MRHD based on total (free) concentrations. *Clinical data* There is no evidence of male infertility based on post-marketing experience with other ERAs.
Risk factors and risk groups	Fertile male subjects
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 and 5.3 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None

Missing information: Long-term cardiovascular safety under controlled clinical setting	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 5.1 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section 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

The following studies are conditions of the marketing authorisation:

PASS ID-080A401 (study 401)

Purpose of the study: Phase 4 study in adult patients with RHT, which aims to further characterise the long-term safety profile of aprocitentan when used in clinical practice.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for JERAYGO.

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