Swiss Summary of the Risk Management Plan (RMP) for

VOLIBRIS

(Ambrisentan)

RMP Summary:	Version 1
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License holder:	GlaxoSmithKline AG, Baar

Based on EU RMP v10.0 (approved 25 July 2025)

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 minimize them.

The RMP summary of Volibris 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 Volibris in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

GlaxoSmithKline AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Volibris.

Part VI: Summary of the risk management plan

Summary of risk management plan for VOLIBRIS (ambrisentan)

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

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

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

I. The medicine and what it is used for

VOLIBRIS is authorised for treatment of pulmonary arterial hypertension (PAH) in adult and pediatric patients aged 8 and over (see SmPC for the full indication). It contains ambrisentan as the active substance and it is given by oral route.

Further information about the evaluation of VOLIBRIS's benefits can be found in VOLIBRIS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/volibris-epar-medicine-overview_en.pdf

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

Important risks of VOLIBRIS, together with measures to minimise such risks and the proposed studies for learning more about VOLIBRIS 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 VOLIBRIS, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of VOLIBRIS 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 VOLIBRIS. 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).

List of important risks and missing information	
Important identified risks	Teratogenicity Hepatotoxicity
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: **Teratogenicity**	
Evidence for linking the risk to the medicine	Preclinical toxicology studies
Risk factors and risk groups	Pregnant women and women of child-bearing potential
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card

Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical trials and post-marketing data
Risk factors and risk groups	One of the challenges of analyzing reports of liver related events in patients with PAH is that this patient population has an underlying risk of liver disease. One of the most common causes of elevated liver enzymes in pulmonary hypertension patients is liver congestion associated with severe pulmonary hypertension or right heart failure. In addition to congestive hepatopathy, since the liver typically receives 20% of cardiac output, circulatory failure, which can occur in PAH patients with decompensated heart failure, can be associated with ischemic hepatitis, especially if the cardiac index <1.5 liters/min/m2 (**Error! Reference source not found.**, 2000). Hypoxic hepatitis is associated with PaO2 < 45 mmHg (which may also occur in severe or end stage PAH patients) and results in a high (62%) in-hospital mortality. Hypoxic hepatitis is rare and has similar findings to ischemic hepatitis: abrupt, marked ALT & AST elevations (10-20 fold normal) which resolve rapidly, with centrilobular necrosis on liver biopsy. (**Error! Reference source not found.**, 2012). Additionally, hepatitis in PAH patients may be associated with underlying diseases (e.g., autoimmune hepatitis, HIV co-infected viral hepatitis, connective tissue disease associated hepatitis and existing liver disease resulting in portopulmonary hypertension). A review of placebo data in ambrisentan, bosentan and sitaxentan clinical studies in PAH patients indicated that elevated aminotransferase levels of greater than three times the upper limit of normal (ULN) occurred in placebo patients at an incidence of between 1.5 and 6% over a 12 to 24 week period (**Error! Reference source not found.**, 2008a; **Error! Reference source not found.**, 2002; **Error! Reference source not found.**, 2004; **Error! Reference source not found.**, 2006; **Error! Reference source not found.**, 2006; **Error! Reference source not found.**, 2008b). The background rate of liver dysfunction in PAH patients makes it challenging to disentangle a possible causal association with ambrisentan from the underlying predisposition of PAH patients to experience liver events. It is not clear whether a history of transaminase elevations prior to initiation of ambrisentan constitutes a risk factor for hepatotoxicity with ambrisentan. At the time of submission for marketing authorisation the assessment of liver safety also included a cohort of patients who have discontinued other ERAs due to elevations in hepatic transaminases previously. Over a period of exposure (mean 52.9 weeks, maximum exposure 76 weeks) none of the 36 patients enrolled had LFT abnormalities that required permanent discontinuation of ambrisentan. In this study the duration of exposure to ambrisentan is considerably longer than the median time to discontinuation of bosentan or sitaxentan (14 and 29 weeks respectively).

Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the EU SmPC PL Sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card

II.C Post-authorisation development plan

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 VOLIBRIS.

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

There are no studies required for VOLIBRIS.