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.

The medicine and what it is used for

VOLIBRIS is authorised for treatment of pulmonary arterial hypertension (PAH) in adult patients (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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000839/human_med_001151.jsp&mid=WC0b01ac058001d124

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*.

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

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 - Decrease haemoglobin/haematocrit, anaemia, including anaemia requiring transfusion - Hepatotoxicity
Important potential risks	- Testicular tubular atrophy/Male infertility
Missing information	- None

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 **Additional risk minimisation measures** Pregnancy Prevention Program
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion	
Evidence for linking the risk to the medicine	Clinical Trial and Post-marketing data.
Risk factors and risk groups	Overall, anaemia is twice as prevalent in females as in males. This difference is significantly greater during the childbearing years. Anaemia of chronic disorders is more common in populations with a high incidence of chronic infectious disease (e.g., malaria, tuberculosis, acquired immunodeficiency syndrome Milman, 2011).
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.4, 4.8 and 5.1 of the EU SmPC PL Sections 2 and 4 **Additional risk minimisation measures** No additional risk minimisation measures.

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 (Naschitz, 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. (Henrion, 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 (Galiè, 2008a; Rubin, 2002; Barst, 2004; Barst, 2006; Oudiz, 2006; Galiè, 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 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 Section 4.2 - Posology and method of administration Section 4.3 - Contraindications Section 4.4 - Special warnings and precautions for use Section 4.8 – Undesirable effects Section 5.1 – Pharmacodynamic properties Section 5.2 – Pharmacokinetic properties PL Sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Package Size: The largest available packaging supply will be limited to a 30-day supply. Legal Status: Treatment must be initiated by a physician experienced in the treatment of PAH. **Additional risk minimisation measures** To minimize the potential risk of hepatotoxicity in patients prescribed ambrisentan through targeted education. • Educational material for prescribers, pharmacists and patients were developed and distributed • Controlled distribution system to ensure that prescribers and pharmacists have been provided with educational materials
Important potential risk:	
Testicular tubular atrophy/Male infertility	

Evidence for linking the risk to the medicine	Pre-clinical and clinical trial data
Risk factors and risk groups	Alterations in sperm count have been reported in men with severe chronic diseases such as PAH. No specific risk factors for reduction in sperm count have been identified.
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.6, 5.3 of the EU SmPC PL section 2 **Additional risk minimisation measures** No additional risk minimisation measures
Missing information: **None**	

C Post-authorisation development plan

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.

C.2 Other studies in post-authorisation development plan

There are no studies required for VOLIBRIS.