Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for BOSENTAN ACTAVIS 62.5 mg and 125 mg film-coated tablets

This is a summary of the risk management plan (RMP) for BOSENTAN ACTAVIS 62.5 mg and 125 mg film-coated tablets (hereinafter referred to as Bosentan). The RMP details important risks of Bosentan, how these risks can be minimised, and how more information will be obtained about Bosentan's risks and uncertainties (missing information).

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

Important new concerns or changes to the current ones will be included in updates of Bosentan's RMP.

I. The Medicine and What It is used for

Bosentan is authorised for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III, and to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see SmPC for the full indication). It contains Bosentan as the active substance and it is given orally.

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

Important risks of Bosentan, together with measures to minimise such risks and the proposed studies for learning more about Bosentan'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 Bosentan, these measures are supplemented with *additional risk minimisation 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 Bosentan is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Bosentan 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 Bosentan. 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 8: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Teratogenicity • Decrease in haemoglobin concentration • Decrease of sperm count
Important potential risks	• Pulmonary oedema associated with PVOD • Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals) • Testicular disorders and male infertility • Respiratory tract infection in children
Missing information	• Use of bosentan with the addition of sildenafil in children • Use in children with renal function impairment

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 9: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures

	SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.2. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures Patient Alert Card
Important identified risk: Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4, 4.5, 4.6 and 5.3. PL section 2. Prescription only medicine. Additional risk minimisation measures Patient Alert 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 Bosentan.

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

There are no studies required for Bosentan.