Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Bosentan Zentiva (Bosentan)
This is a summary of the risk management plan (RMP) for Bosentan Zentiva. The RMP details important risks of Bosentan Zentiva, how these risks can be minimised, and how more information will be obtained about Bosentan Zentiva's risks and uncertainties (missing information).
Bosentan Zentiva's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Bosentan Zentiva should be used.

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

I. The medicine and what it is used for

Bosentan Zentiva is authorised for 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 (DU) 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 by oral route.

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

Important risks of Bosentan Zentiva, together with measures to minimise such risks and the proposed studies for learning more about Bosentan Zentiva'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 Zentiva, 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 Zentiva is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Bosentan Zentiva 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 Zentiva. 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	• Hepatotoxicity • Teratogenicity • Decrease in haemoglobin concentration • Decrease of sperm count
Important potential risks	• Pulmonary oedema associated with pulmonary veno-occlusive disease (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 addition of sildenafil in children • Use in children with renal function impairment

II.B Summary of important risks

Summary of important risk that have corresponding additional pharmacovigilance/risk minimisation activities are:

Important identified risk: Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8. SmPC section 4.4 where advice is given on monitoring the liver function. PL sections 2, 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 and 4.6. SmPC section 4.4 where advice is given on regular pregnancy testing. 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 Zentiva.

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

There are no studies required for Bosentan Zentiva.