Part VI: Summary of the risk management plan

Summary of risk management plan for Bosentan 62.5 mg and 125 mg Cipla film-coated tablet

This is a summary of the risk management plan (RMP) for bosentan Cipla 62.5 mg film-coated tablet and bosentan Cipla 125 mg film-coated tablet. The RMP details important risks of bosentan 125 mg film-coated tablet, how these risks can be minimised, and how more information will be obtained about bosentan Cipla 125 mg film-coated tablet risks and uncertainties (missing information).

The summary of product characteristics (SmPC) and package leaflet (PL) of bosentan Cipla 62.5 mg film-coated tablet and bosentan Cipla 125 mg film-coated tablet give essential information to healthcare professionals and patients on how this product should be used.

Important new concerns or changes to the current ones will be included in updates of bosentan Cipla film-coated tablet RMP.

I. The medicine and what it is used for

Bosentan Cipla film-coated tablet is indicated for the treatment of Pulmonary Arterial Hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. It is also indicated 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 by oral route.

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

Important risks of Bosentan Cipla film-coated tablet, 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 Cipla film-coated tablet is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of bosentan Cipla film-coated tablet are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Cipla film-coated tablets. 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).

Summary of safety concerns	
Important identified risks	• Hepatotoxicity • Teratogenicity • Decrease in haemoglobin concentration • Decrease of sperm count
Important potential risks	• Pulmonary oedema associated with PVOD (Pulmonary veno-occlusive disease) • Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)

Summary of safety concerns	
	• 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

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

Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.2, 4.3 4.4, 4.5 and 4.8 – PL sections 2 and 4 – Treatment with Bosentan Cipla should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis. – Legal status: 'Prescription Only Medicine' Additional risk minimisation measures: As an additional risk minimisation measure, a Patient Alert Card will be distributed to patients receiving bosentan which will help to facilitate patient's awareness regarding the risk of hepatotoxicity and the need for regular blood tests for liver function.

Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.3, 4.4 and 4.6 – PL sections 2 – Treatment with Bosentan Cipla should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis. – Legal status: 'Prescription Only Medicine' Additional risk minimisation measures: As an additional risk minimisation measure, a Patient Alert Card

	will be distributed to patients receiving bosentan which will help to facilitate patient's awareness regarding the need to avoid pregnancy and to ensure that effective contraceptive measures are used.

Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)	
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.3, 4.4 and 4.5 – PL sections 2 – Treatment with Bosentan Cipla should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis. – Legal status: 'Prescription Only Medicine' Additional risk minimisation measures: As an additional risk minimisation measure, a Patient Alert Card will be distributed to patients receiving bosentan which will help to facilitate patient's awareness regarding Interactions with hormonal contraceptives to ensure effective contraceptive measures are used.

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 Cipla film-coated tablet.

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

There are no studies required for bosentan Cipla film-coated tablet.