Part VI: Summary of the risk management plan

This Summary of the risk management plan is applicable to Macitentan Devatis 10 mg, filmomhulde tabletten.

Summary of risk management plan for *Macitentan Devatis 10 mg, filmomhulde tabletten* (Macitentan)

This is a summary of the risk management plan (RMP) for *Macitentan Devatis 10 mg, filmomhulde tabletten.* The RMP details important risks of *Macitentan Devatis 10 mg, filmomhulde tabletten*, how these risks can be minimised, and how more information will be obtained about *Macitentan Devatis 10 mg, filmomhulde tabletten*'s risks and uncertainties (missing information).

Macitentan Devatis 10 mg, filmomhulde tabletten's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Macitentan Devatis 10 mg, filmomhulde tabletten* should be used.

Important new concerns or changes to the current ones will be included in updates of *Macitentan Devatis 10 mg, filmomhulde tabletten*'s RMP.

I. The medicine and what it is used for

Macitentan Devatis 10 mg, filmomhulde tabletten is authorised for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III (see SmPC for the full indication). It contains macitentan 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 Macitentan Devatis 10 mg, filmomhulde tabletten, together with measures to minimise such risks and the proposed studies for learning more about *Macitentan Devatis 10 mg, filmomhulde tabletten* '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 Macitentan Devatis 10 mg, filmomhulde tabletten, 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, 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 *Macitentan Devatis 10 mg, filmomhulde tabletten* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Macitentan Devatis 10 mg, filmomhulde tabletten* 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 *Macitentan Devatis 10 mg, filmomhulde tabletten*. 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
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.**Important identified risk: Hepatotoxicity**	
Evidence for linking the risk to the medicine	Macitentan, like other medicines of the same chemical class, may affect the liver. The mechanism of this adverse effect is unclear. Interruption or stopping treatment may be necessary.
Risk factors and risk groups	Unknown in patients with alanine aminotransferase/aspartate aminotransferase >3x upper limit of normal at baseline or patients with moderate or severe liver impairment, as they were excluded from clinical trials with macitentan. Based on postmarketing data, there were no new safety concerns noted in patients with moderate or severe hepatic impairment receiving macitentan.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Macitentan' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Macitentan' SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects' Instructions for liver function monitoring and actions to be taken in case of elevated hepatic enzymes are provided in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** Risk minimization tools (patient card)
Important identified risk: Teratogenicity	
Evidence for linking the risk to the medicine	According to results from animal studies, macitentan and medicines of the same chemical class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed.
Risk factors and risk groups	All women of childbearing potential on macitentan therapy who are not using a reliable method of contraception.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Macitentan' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Macitentan' SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Macitentan' Instructions for the use of Macitentan in women of childbearing potential and recommendation for monthly

	pregnancy tests during treatment are provided in SmPC section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** Risk minimization tools (patient 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 *Macitentan Devatis 10 mg, filmomhulde tabletten*.

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

There are no studies required for *Macitentan Devatis 10 mg, filmomhulde tabletten*.