Summary of risk management plan for Tracleer®/ STAYVEER® (bosentan)

This is a summary of the risk management plan (RMP) for Tracleer/STAYVEER. The RMP details important risks of Tracleer/STAYVEER, how these risks can be minimised, and how more information will be obtained about Tracleer/STAYVEER's risks and uncertainties (missing information).

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

This summary of the RMP for Tracleer/STAYVEER 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 Tracleer/STAYVEER's RMP.

I The medicine and what it is used for

Tracleer/STAYVEER 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 twice a day.

Further information about the evaluation of Tracleer/STAYVEER's benefits can be found in Tracleer/STAYVEER's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/tracleer
https://www.ema.europa.eu/en/medicines/human/EPAR/stayveer

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

Important risks of Tracleer/STAYVEER, together with measures to minimise such risks and the proposed studies for learning more about Tracleer/STAYVEER'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 Tracleer/STAYVEER, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks in Section II.B 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 Tracleer/STAYVEER is not yet available, it is listed under 'missing information' in Section II.A below.

II.A List of important risks and missing information

Important risks of Tracleer/STAYVEER 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 Tracleer/STAYVEER. 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

List of important risks and missing information	
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

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Bosentan, like other medicines of the same chemical class, may affect the liver. The mechanism of this adverse event is unclear. Interruption or stopping treatment may be necessary.
Risk factors and risk groups	Liver dysfunction risk may be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP), e.g., rifampicin, glibenclamide and cyclosporine A (see sections 4.3 and 4.5 of SmPC), are co-administered with bosentan, but limited data are available. Bosentan is contraindicated in patients with moderate to severe hepatic impairment. A causal relationship to bosentan or a superimposed contribution of the drug to the progression or worsening of severe liver complications in some patients with pre existing liver disease or progressive hepatic co morbidity in PAH or connective tissue disease is difficult to establish/assess due to the complexity of the cases and presence of multiple confounding factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, 4.3, 4.4, 4.5 and 4.8, patient information leaflet (PIL) section 2 and 4, Legal status Additional risk minimisation measures: Controlled distribution system, Healthcare Professional and Patient education material (SmPC, Patient information leaflet and Patient Alert Card)

Important identified risk: Teratogenicity	
Evidence for linking the risk to the medicine	According to results from animal studies, bosentan 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 bosentan, no translation of this risk to humans has been observed.
Risk factors and risk groups	All women of childbearing potential on bosentan therapy who are not using a reliable method of contraception.
Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.3, 4.4, 4.5 and 4.6, PIL section 2, Legal status Additional risk minimisation measures: Controlled distribution system, Healthcare Professional and Patient education material (SmPC, Patient information leaflet and Patient Alert Card)
Important identified risk: Decrease in haemoglobin concentration	
Evidence for linking the risk to the medicine	In clinical trials, bosentan therapy is associated with a decrease in haemoglobin concentration, thought to be due to fluid shift.
Risk factors and risk groups	General risk factors for anaemia are, e.g., iron-deficiency, history of anaemia, concomitant use of platelet inhibitors, anticoagulants, steroids, pre-existing or concurrent bleeding.
Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.4 and 4.8, PIL section 2 and 4, Legal status Additional risk minimisation measures: Controlled distribution system, Healthcare Professional and Patient education material (SmPC and Patient information leaflet)

Important identified risk: Decrease of sperm count	
Evidence for linking the risk to the medicine	In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan (see SmPC). Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men.
Risk factors and risk groups	Male patients.
Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.6, PIL section 2, Legal status Additional risk minimisation measures: Controlled distribution system, Healthcare Professional education material (SmPC)
Important potential risk: Pulmonary oedema associated with PVOD	
Evidence for linking the risk to the medicine	Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema occur when bosentan is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary oedema in patients treated with bosentan who had a suspected diagnosis of pulmonary veno-occlusive disease.
Risk factors and risk groups	Patients with PVOD treated with bosentan.

Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.4, Legal status Additional risk minimisation measures: Controlled distribution system
Important potential risk: Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)	
Evidence for linking the risk to the medicine	Bosentan is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution.
Risk factors and risk groups	Co-administration with substances metabolised by isoenzymes CYP2C9 and CYP3A4, including hormonal contraceptives, sildenafil and antiretrovirals.
Risk minimisation measures	**Interaction with hormonal contraceptives:** Routine risk mimimisation measures: SmPC section 4.5 and 4.6, PIL section 2, Legal status Additional risk minimisation measures: Controlled distribution system, Healthcare Professional and Patient education material (SmPC, Patient information leaflet and Patient Alert Card) **Interaction with sildenafil:** Routine risk mimimisation measures: SmPC section 4.5, PIL section 2, Legal status Additional risk minimisation measures: Controlled distribution system **Drug interaction with antiretrovirals:** Routine risk mimimisation measures: SmPC section 4.4 and 4.5, PIL section 2, Legal status

	Additional risk minimisation measures: Controlled distribution system
Important potential risk: Testicular disorders and male infertility	
Evidence for linking the risk to the medicine	Development of testicular tubular atrophy and impaired fertility has been linked with with chronic administration of endothelin receptor antagonists in preclinical studies.
Risk factors and risk groups	Male patients.
Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.6, PIL section 2, Legal status Additional risk minimisation measures: None.
Important potential risk: Respiratory tract infection in children	
Evidence for linking the risk to the medicine	Cumulative data from both clinical trials and post-marketing experience showed a higher reporting rate of respiratory infections in paediatric patients compared with adult/elderly patients. The mechanism of this adverse event is unclear.
Risk factors and risk groups	Infants and children with congenital heart disease (CHD).
Risk minimisation measures	Routine risk mimimisation measures: SmPC section 4.8, Legal status Additional risk minimisation measures: None.

Missing information: Use of bosentan with the addition of sildenafil in children	
Risk minimisation measures	Routine risk mimimisation measures: Legal status Additional risk minimisation measures: None.
Missing information: Use in children with renal function impairment	
Risk minimisation measures	Routine risk mimimisation measures: Legal status Additional risk minimisation measures: None.

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 Tracleer/STAYVEER.

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

There are no studies required for Tracleer/STAYVEER.