Johnson&Johnson

# Summary of the Risk Management Plan (RMP) for Tracleer® (Bosentan)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Tracleer® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Tracleer® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo-pro.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tracleer®.

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## 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 minimized, 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 (HCPs) 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 authorized for treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with World Health Organization functional class III and to reduce the number of new digital ulcers (DUs) in patients with systemic sclerosis and ongoing DU 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 Minimize or Further Characterize the Risks

Important risks of TRACLEER/STAYVEER, together with measures to minimize such risks and the studies for learning more about TRACLEER/STAYVEER's risks, are outlined below.

Measures to minimize 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 HCPs.
- Important advice on the medicine's packaging.
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In the case of TRACLEER/STAYVEER, these measures are supplemented with *additional risk minimization measures,* included under the relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

## 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 minimize 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 (eg, on the long-term use of the medicine).

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | • Hepatotoxicity<br>• Teratogenicity |
| Important potential risks | None |
| Missing information | None |

## II.B. Summary of Important Risks

| **Important Identified Risk: Hepatotoxicity** | |
|---|---|
| **Evidence for linking the risk to the medicine** | SmPC, Periodic Benefit-risk Evaluation Report/PSUR and the appended LSUR |
| **Risk factors and risk groups** | Rare cases of autoimmune hepatitis with a latency of a few months to years have been reported (see Sections 4.4 and 4.8 of SmPC). Liver dysfunction risk may be increased when medicinal products that are inhibitors of the bile salt export pump, eg, rifampicin, glibenclamide, and cyclosporine A (see Sections 4.4 and 4.5 of SmPC), are co-administered with bosentan, but limited data are available.<br><br>Bosentan is contraindicated in patients with moderate-to-severe hepatic impairment.<br><br>A causal relationship to bosentan or a superimposed contribution of the drug to the progression or worsening of severe liver |

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|---|---|
| | 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 minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.2, 4.3, 4.4, 4.5 and 4.8, patient information leaflet (PIL) Section 2 and 4, Legal status<br><br>**Additional risk minimization measures**<br>Patient Alert Card |
| **Important Identified Risk: Teratogenicity** | |
| **Evidence for linking the risk to the medicine** | SmPC, PBRER/PSUR<br><br>Co-administration of bosentan 125 mg bid for 7 days with a single dose of an oral contraceptive containing norethisterone 1 mg+ethinyl estradiol 35 µg decreased the area under the plasma concentration-time curve of norethisterone and ethinyl estradiol by 14% and 31%, respectively. Decreases in exposure were as much as 56% and 66%, respectively, in individual participants. Therefore, hormone-based contraceptives alone, including oral, injectable, transdermal, or implantable forms, are not considered reliable methods of contraception. |
| **Risk factors and risk groups** | All women of childbearing potential on bosentan therapy who are not using a reliable method of contraception. Bosentan may render hormonal contraceptives ineffective. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.3, 4.4, 4.5 and 4.6, PIL Section 2, Legal status<br><br>**Additional risk minimization measures**<br>Patient Alert Card |

## II.C. Postauthorization Development Plan

### II.C.1. Studies That are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligations of TRACLEER/STAYVEER.

### II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for TRACLEER/STAYVEER.