Name of the Drug Product	Doptelet
Drug Substance	Avatronbopag
Version	1.0
Market Authorization Holder	Swedish Orphan Biovitrum AG
Date	29.11.2021

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 Doptelet is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the Product Information 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 Doptelet in Switzerland is the Product Information (see www.swissmedic.ch) approved and authorized by Swissmedic. Swedish Orphan Biovitrum AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Doptelet.

SUMMARY OF THE RISK MANAGEMENT PLAN FOR DOPTELET®

This is a summary of the risk management plan (RMP) for Doptelet 20 mg film coated tablets. The RMP details important risks of Doptelet, how these risks can be minimised and how more information will be obtained about Doptelet's risks and uncertainties (missing information).

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

This summary of the RMP for Doptelet should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

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

I The Medicine and What it is Used for

Doptelet is authorised for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. Doptelet is also authorised for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). It contains avatrombopag as the active substance and it is given by oral administration.

Further information about the evaluation of Doptelet's benefits can be found in the EPAR for Doptelet, including in its plain-language summary, available on the European Medicines Agency (EMA) website under the medicine's webpage: https://www.ema.eurpa.eu/en/medicines/human/EPAR/doptelet.

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Doptelet, together with measures to minimise such risks and the proposed studies for learning more about Doptelet'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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report (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 Doptelet is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Doptelet 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 Doptelet. 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

List of Important Risks and Missing Information	
Important identified risks	• Blood clots and complications related to blood clots (Thrombotic/thromboembolic events) • Bone Marrow Fibrosis Related to Long-Term and Repeat Use
Important potential risks	• Hepatic worsening function in patients with Child-Pugh class C • Haematological malignancies
Missing information	• Use in splenectomy patients with chronic liver disease • Use in patients receiving interferon products • Safety in patients undergoing highly invasive procedures • Use in patients with MELD scores > 24

II.B Summary of Important Risks

Summary of Important Identified and Potential Risks

Important Identified Risks	
Thrombotic / Thromboembolic Events	
Evidence for linking the risk to the medicine	As a class, TPO receptor agonists stimulate the production of endogenous platelets, and thus may increase the risk of occurrence of thrombotic / thromboembolic events. In addition, patients with chronic liver disease (CLD) and immune thrombocytopenia (ITP) are also known to be at increased risk for occurrence of these events. In the clinical development program, 7.0% (9/128) of patients with chronic ITP who were treated with avatrombopag experienced a thromboembolic event. With the exception of cerebrovascular accident which was reported in 1.6% (2/128) patients, there was no clustering of a specific thromboembolic event type, the time to onset varied from greater than 26 weeks to less than 4 weeks after beginning treatment, there was no relationship to drug dose, and the events typically occurred at a platelet count below the upper limit of normal (450,000/μL). In patients with CLD, 0.4% (1/274) experienced a thromboembolic event.
Risk factor and risk groups	Avatrombopag was not studied in patients with prior thromboembolic events. Patients with chronic liver disease or chronic immune thrombocytopenia are at increased risk for thrombotic / thromboembolic events as a comorbidity. Additional risk factors include a history of deep vein thrombosis, pulmonary embolism, superficial vein thrombosis, stroke/other neurological disorders associated with paralysis, immobilization >3 days, increasing age, pregnancy and puerperium (<8 weeks from delivery), cancer, cancer therapy, contraceptives, obesity, smoking, acute myocardial infarction and heart failure, fractures, oestrogen intake, surgery/trauma, or genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS: Further characterisation of the safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia See section II.C of this summary for an overview of the post-authorisation development plan
Bone Marrow Fibrosis Related to Long-Term and Repeat Use	

Evidence for linking the risk to the medicine	With long-term use, thrombopoietin receptor agonists (TPO-RAs) may increase the risk of development or progression of reticulin fibres/fibrosis within the bone marrow. The clinical importance of this observation is unknown. The pathophysiology remains incompletely understood, however increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Cytokines appear to be necessary for fibrosis to occur. Avatrombopag, a TPO-RA, requires chronic dosing for use in patients with ITP and may pose a risk for the development of or progression of reticulin fibres/fibrosis within the bone marrow. In the clinical development programme, 1 of 128 (<1%) ITP patients was treated initially with eltrombopag for 56 days, followed by avatrombopag treatment for 161 days. Thirty-one days after avatrombopag therapy was discontinued, a bone marrow biopsy showed a bone marrow reticulin fibrosis of 2+ with focal areas of 3+. This patient also had a pre-treatment elevated bone marrow reticulin fibrosis (1+). For patients with CLD who undergo multiple procedures, avatrombopag may also be prescribed before each procedure is performed, but experience with repeat use is limited.
Risk factors and risk groups	No specific risk factor has been identified in clinical trials. Risk groups include patients on long-term treatment with TPO-R agonists, those undergoing multiple procedures, or patients with myeloproliferative disease or other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, or endocrine disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4, and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS: Further characterisation of the safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia See section II.C of this summary for an overview of the post-authorisation development plan
Important Potential Risks	
Hepatic worsening function in patients with Child-Pugh Class C	
Evidence for linking the risk to the medicine	Across the clinical development programme, a total of four fatal adverse events were reported, with three deaths occurring in the avatrombopag treatment group and one death in the placebo treatment group. All reported deaths in the avatrombopag group occurred in patients who had Child-Pugh class C liver disease, whereas no deaths in patients with Child-Pugh class C were reported in the placebo arm. It is possible that the fatal outcomes of hepatic coma and multi-organ failure (acute liver failure, acute kidney injury and respiratory failure) are associated with the natural progression of the underlying disease.
Risk factors and risk groups	Patients with Child-Pugh class C who receive treatment with avatrombopag; patients with bacterial infections/sepsis, GI bleeding, alcohol intake, drug toxicity, surgery. Hepatocellular carcinoma, or viral hepatitis.
Risk minimisation measures	Routine risk minimisation measures:

	• SmPC section 4.2 and 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS study: Hepatic safety of avatrombopag in patients with Child Pugh class C liver disease or MELD scores > 24 See section II.C of this summary for an overview of the post-authorisation development plan.
Haematological malignancies	
Evidence for linking the risk to the medicine	Given that some haematopoietic cancers express the thrombopoietin (TPO) receptors, it is theorized that administration of TPO-RAs, due to their mechanism of action, may further potentiate the risk of haematological malignancy in ITP patients. However, epidemiologic studies also suggest a possible association between ITP and haematological malignancy (Landgren, 2006; Söderberg, 2006).
Risk factors and risk groups	Risk groups include patients on long-term treatment with TPO-R agonists, those undergoing multiple procedures who receive repeat dosing with a TPO-R agonist, or patients with myeloproliferative disease or other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, or endocrine disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS: Further characterisation of the safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information	
Use in Splenectomy Patients with Chronic Liver Disease	
Risk minimisation measures	No risk minimisation measures.
Use in Patients Receiving Interferon Products	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Safety in Patients Undergoing Highly Invasive Procedures	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Additional risk minimisation measures: None

Use in Patients with MELD Scores > 24	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4, 5.1 and 5.2 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS study: Hepatic safety of avatrombopag in patients with Child Pugh class C liver disease or MELD scores > 24 See section II.C of this summary for an overview of the post-authorisation development plan.

PL = Package Leaflet, SmPC = Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are currently no studies which are conditions of the marketing authorisation or specific obligations of Doptelet®.

II.C.2 Other Studies in Post-authorisation Development Plan

II.C.2.1 Chronic liver disease

Study short name: Hepatic safety of avatrombopag in patients with Child Pugh class C liver disease or MELD scores > 24.

Purpose of the study: The primary objective of this study is to assess any potential for hepatic worsening function in Child Pugh class C liver disease patients, and to collect further safety information on patients with MELD scores > 24 who receive treatment with avatrombopag. A secondary objective is to assess 'other safety data' based on findings from the avatrombopag clinical development programme.

II.C.2.2 Primary chronic immune thrombocytopenia

Study short name: Further characterisation of the safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia.

Purpose of the study: Due to the low number of patients enroled in the clinical development programme, coupled with the limited safety from long-term exposure to avatrombopag, there is uncertainly with regards to the frequency in occurrence of various adverse events in the target population. Therefore, the primary objective of this study is to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia