

## Regulatory Affairs

### Drug generic name

#### **Summary of the EU Safety Risk Management Plan**

Active substance(s) (INN or common name):	Eltrombopag
Product(s) concerned (brand name(s)):	Revolade®
Document status:	Final
Version number of the RMP Public Summary:	55.0
Date of final sign off of the RMP Public Summary	22-Feb-2024

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 "Revolade" 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 "Revolade" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see [www.swissmedic.ch](http://www.swissmedic.ch)) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Revolade".

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### ***Summary of the risk management plan for Revolade***

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

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

*This summary of the RMP for eltrombopag 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 eltrombopag's RMP.*

## **I. The medicine and what it is used for**

Revolade contains eltrombopag as the active substance and it is used for in the following indications:

- **Immune thrombocytopenia:**

Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Revolade is indicated for the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

- **HCV-associated thrombocytopenia:**

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

- **Severe aplastic anaemia:**

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

### **Dosing requirements**

- **Immune (primary) thrombocytopenia**

Adults and paediatric population aged 6 to 17 years: The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg once daily.

Paediatric population aged 1 to 5 years: The recommended starting dose of eltrombopag is 25 mg once daily.

- **Chronic hepatitis C (HCV) associated thrombocytopenia:**

The recommended starting dose of eltrombopag is 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment.

- **Severe aplastic anaemia:**

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Further information about the evaluation of eltrombopag's benefits can be found in eltrombopag's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

## **II. Risks associated with the medicine and activities to minimize or further characterize the risks**

Important risks of eltrombopag, together with measures to minimize such risks and the proposed studies for learning more about eltrombopag'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 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of eltrombopag, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, 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 eltrombopag is not yet available, it is listed under "missing information" below.

## II.A: List of important risks and missing information

Important risks of eltrombopag 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 eltrombopag. 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	<p><b>Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia</b></p> <ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Thromboembolic events</li> </ul> <p><b>HCV-associated thrombocytopenia</b></p> <ul style="list-style-type: none"> <li>• Hepatic decompensation</li> </ul>
Important potential risks	<p><b>Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia</b></p> <ul style="list-style-type: none"> <li>• Increased Bone Marrow Reticulin Formation</li> <li>• Haematological malignancies</li> </ul> <p><b>Severe aplastic anaemia</b></p> <ul style="list-style-type: none"> <li>• Cytogenetic abnormalities</li> </ul>
Missing information	<p><b>Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia</b></p> <ul style="list-style-type: none"> <li>• Patients with hepatic impairment</li> </ul> <p><b>Severe aplastic anaemia</b></p> <ul style="list-style-type: none"> <li>• Use in paediatric population</li> </ul>

## II B: Summary of important risks

### Table-1 Important identifies risks

Risk	What is known	Preventability
Liver laboratory abnormalities (hepatotoxicity)	Revolade can increase some blood markers indicating liver damage.	<p>Patients will have blood tests to check liver function before starting Revolade and at intervals while taking it. Patients may need to stop taking Revolade if the amount of these substances increases too much, or if physical signs of liver damage appear. Patients should tell their doctor immediately if they have any of these signs and symptoms of liver problems:</p> <ul style="list-style-type: none"> <li>• yellowing of the skin or the whites of the eyes (jaundice)</li> </ul>

		<ul style="list-style-type: none"> <li>unusually dark-coloured urine</li> <li>right upper stomach area pain.</li> </ul>
Liver abnormalities in patients with hepatitis C who are receiving antiviral medication (hepatic decompensation) (risk for HCV-associated thrombocytopenia)	Revolade can increase some blood markers indicating liver damage. When patients are given certain interferonbased antiviral treatments together with Revolade for the treatment of thrombocytopenia due to hepatitis C virus (HCV) infections some liver problems can get worse.	<p>Patients will have blood tests to check liver function before starting Revolade and at intervals while taking it. Patients may need to stop taking Revolade if the amount of these substances increases too much, or if physical signs of liver damage appear. Patients should tell their doctor immediately if they have any of these signs and symptoms of liver problems:</p> <ul style="list-style-type: none"> <li>yellowing of the skin or the whites of the eyes (jaundice)</li> <li>unusually dark-coloured urine</li> <li>right upper stomach area pain.</li> </ul>
High platelet counts and higher chance for blood clots (thromboembolic events {TEE})	If a patient has very high blood platelet counts, this may increase the risk of blood clotting, however, blood clots can occur with normal or even low platelet counts.	<p>A doctor can adjust the dose of Revolade to ensure that the platelet count does not become too high. Patients should tell their doctor immediately if they have any of these signs and symptoms of a blood clot:</p> <ul style="list-style-type: none"> <li>swelling, pain or tenderness in one leg (deep vein thrombosis)</li> <li>sudden shortness of breath especially when accompanied with sharp pain in the chest and/or rapid breathing (pulmonary embolism)</li> <li>abdominal pain, enlarged abdomen, blood in stool (portal vein thrombosis)</li> </ul>

**Table-2 Important potential risks**

<b>Risk</b>	<b>What is known</b>
Cytogenetic Abnormalities (risk for severe aplastic anaemia)	A known complication of SAA is the development of changes in the chromosome(s). These changes have been reported in 15-20 out of every 100 patients with SAA. The importance of these chromosomal changes depends on the type of changes and any abnormal results to the blood cells.
Bone marrow abnormalities (increased bone marrow reticulon formation)	People with thrombocytopenia may have problems with their bone marrow. Medicines like Revolade could make this problem worse. Signs of bone marrow changes may show up as abnormal results in blood tests. A doctor may also carry

	out tests to directly check a patient's bone marrow during treatment with Revolade.
Worsening of blood cell cancers cells (worsening haematological malignancies)	Revolade belongs to a group of medicines called thrombopoietin receptor agonists. For TPO-R agonists there is a concern that they may worsen already existing blood cell cancers. Ongoing studies have not shown increased growth of these cells when exposed to Revolade. Patients should tell their doctor if they have ever been diagnosed with a blood cell cancer.

**Table-3 Missing information**

<b>Risk</b>	<b>What is known</b>
Children	With the exception of paediatric ITP, there is limited experience with the use of Revolade in children
Patients with decreased liver function (hepatic impairment)	If the use of eltrombopag is considered necessary for adult and paediatric ITP patients with decreased liver function, the starting dose must be 25 mg once daily. No dose adjustment is needed for thrombocytopenic patients with chronic HCV and decreased liver function. Thrombocytopenic patients with chronic HCV should initiate eltrombopag at a dose of 25 mg once daily. Severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily.

## II C: Post-authorization development plan

### II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of eltrombopag.

### II.C.2. Other studies in post-authorization development plan

**Table-4 Other studies in the post-authorization development plan**

<b>Study short name</b>	<b>Rationale and study objectives</b>
Study RAD200936 (CETB115E2201): A phase II, open-label, non-controlled, intra-patient dose escalation study to characterize the pharmacokinetics after oral administration of	This study will evaluate eltrombopag treatment in paediatric patients who have either refractory/relapsed SAA or recurrent aplastic anemia after immunosuppressive therapy (IST) for SAA (Cohort A), or who have SAA, previously untreated with IST. This study will fulfill a requirement agreed upon in the Paediatric Investigational Plan for SAA (EMEA-000170-PIP03-13).

eltrombopag in paediatric patients with refractory, relapsed or treatment naïve severe aplastic anemia or recurrent aplastic anemia

Primary Objective: To characterize the PK of eltrombopag at steady state after oral administration in paediatric patients with SAA.

Secondary Objective: To determine the safety and tolerability of eltrombopag given orally in paediatric patients with SAA. To assess the efficacy defined as overall response (ORR).