EU Risk Management Plan

For

Eltrombopag Accord 12.5 mg film-coated tablets
Eltrombopag Accord 25 mg film-coated tablets
Eltrombopag Accord 50 mg film-coated tablets
Eltrombopag Accord 75 mg film-coated tablets
(Eltrombopag)

RMP version to be assessed as part of this application:

RMP Version number	1.2
Data lock point for this RMP	15-Jan-2025
Date of final sign off	22-Jan-2025

Rationale for submitting an RMP: This RMP has been updated as per Day 188 Joint CHMP and PRAC response assessment report of Eltrombopag Accord (EMEA/H/C/006459), dated 15-Jan-2025 and also in line with updated SmPC of Eltrombopag.

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part I, Part II, Part VI and Part VII (Annex 7 and 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

QPPV Name: Dr. Arletta Werynska

QPPV Signature: 

TABLE OF CONTENT

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LIST OF TABLES

Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Eltrombopag
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group:** Antihemorrhagics, other systemic hemostatics **ATC code**: B02BX05
Marketing Authorisation Holder	Accord Healthcare S.L.U, Spain
Medicinal products to which this RMP refers	04
Invented name(s) in the European Economic Area (EEA)	Eltrombopag Accord 12.5 mg film-coated tablets Eltrombopag Accord 25 mg film-coated tablets Eltrombopag Accord 50 mg film-coated tablets Eltrombopag Accord 75 mg film-coated tablets
Marketing authorisation procedure	EMEA/H/C/006459
Brief description of the product	Chemical class: Eltrombopag is a Thrombopoietin Receptor (TPO-R) Agonist.
	Summary of mode of action: Eltrombopag functions in a similar manner to endogenous thrombopoietin (TPO), inducing proliferation and differentiation of bone marrow progenitor cells.

[redacted]

	Important information about its composition: *Eltrombopag Accord 12.5 mg film-coated tablets* Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag. *Eltrombopag Accord 25 mg film-coated tablets* Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag. *Eltrombopag Accord 50 mg film-coated tablets* Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag. *Eltrombopag Accord 75 mg film-coated tablets* Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL
Indication(s) in the EEA	***Current*** Eltrombopag Accord is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Eltrombopag Accord 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). Eltrombopag Accord is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the

[redacted]

	main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.
Dosage in the EEA	***Current:*** **<u>Posology</u>** Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts. <u>*Immune (primary) thrombocytopenia*</u> The lowest dose of eltrombopag to achieve and maintain a platelet count ≥50 000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation. *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, 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. *Monitoring and dose adjustment* After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥50 000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

	<u>*Chronic hepatitis C (HCV) associated thrombocytopenia*</u> When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications. *Initial dose regimen* Eltrombopag should be initiated at a dose of 25 mg once daily. *Monitoring and dose adjustment* The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided. <u>Method of administration</u> Eltrombopag should be administered orally.
Pharmaceutical forms and strengths	***Current*** Film-coated tablet 12.5 mg, 25 mg, 50 mg & 75 mg
Is the product subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable

Part II: Module SIII - Clinical trial exposure

Not applicable

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been considered as per European Public Assessment Report (EPAR) - RMP of Revolade (Eltrombopag, version 54.1) published on EMA website on 16-May-2023. There is no change proposed by MAH in the safety concerns and they are in-line with Revolade EPAR as mentioned in Module SVIII of this RMP.

Hence this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not Applicable

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Hepatotoxicity • Thromboembolic events **HCV-associated thrombocytopenia** • Hepatic decompensation
Important potential risks	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia*** • Cytogenetic abnormalities
Missing information	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Patients with hepatic impairment **Severe aplastic anaemia*** • Use in paediatric population

*Severe aplastic anaemia is not currently included as an indication for Eltrombopag.

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concern listed in module SVIII.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for following risks concerning use of Eltrombopag:

- Hepatobiliary laboratory abnormalities
- Hepatic decompensation
- Thrombotic and thromboembolic events
- Worsening thrombocytopenia and bleeding
- Hematological malignancy
- Bone Marrow Reticulin / Bone Marrow Fibrosis

Purpose: For collection and reporting of safety information while use of Eltrombopag Accord.
Targeted follow-up questionnaires and data collection forms are appended in Annex 4 of this RMP.
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III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Eltrombopag Accord 12.5/25/50/75 mg film-coated tablets (Eltrombopag)

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

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

This summary of the RMP for Eltrombopag Accord 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 Accord's RMP.

I. The medicine and what it is used for

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

Eltrombopag Accord 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).

Eltrombopag Accord 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.

It contains eltrombopag as the active substance and it is given by oral route.

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

[redacted]

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

Important risks of Eltrombopag Accord, together with measures to minimise such risks and the proposed studies for learning more about Eltrombopag Accord'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, 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 Accord is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Eltrombopag Accord are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Accord. 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).

Important identified risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Hepatotoxicity • Thromboembolic events **HCV-associated thrombocytopenia** • Hepatic decompensation
Important potential risks	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia*** • Cytogenetic abnormalities
Missing information	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia, and severe aplastic anaemia*** • Patients with hepatic impairment **Severe aplastic anaemia*** • Use in paediatric population

* Severe aplastic anaemia is not currently included as an indication for Eltrombopag.

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

[redacted]

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 Eltrombopag Accord.

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

There are no studies required for Eltrombopag Accord.

Annex 4 – Specific adverse drug reaction follow-up forms

MAH proposed specific adverse reaction targeted questionnaires for potential/confirmed events of

- Hepatobiliary laboratory abnormalities
- Hepatic decompensation
- Thrombotic and thromboembolic events
- Worsening thrombocytopenia and bleeding
- Hematological malignancy
- Bone Marrow Reticulin / Bone Marrow Fibrosis

Targeted Follow-up Questionnaire for Hepatobiliary Laboratory Abnormalities

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s): ___/___/__ ___(DD/MMM/YYYY)
- Date when eltrombopag was started: ___/____/_____ (DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? ____ mg; Date: __/____/____ (DD/MMM/YYYY)

Current Liver Function Laboratory Tests

Please provide the following regarding the current liver function laboratory test for this event.

Tests	Lab Value	Date (DD/MMM/YYYY)	Reference range
Alanine Aminotransferase (ALT)			
Aspartate Aminotransferase (AST)			
Total Bilirubin			
Direct Bilirubin			
Alkaline Phosphatase (Alk Phos)			
Gamma glutamyltranspeptidase (GGT)			
International Normalized Ratio (INR)			

Was a liver biopsy performed? ☐ Yes ☐ No

If YES, what were the results?

You may attach anonymized copy of these reports, if available. ☐ **Check this box, if attached.**

Diagnostic imaging

Were any of the following diagnostic imaging tests of the hepatobiliary system performed?

Yes	No	
☐	☐	Liver Ultrasound
☐	☐	CAT Scan
☐	☐	MRI Scan

[redacted]

☐ ☐ Endoscopic/Magnetic Retrograde Cholangiopancreatography (ERCP) / (MRCP)

☐ ☐ Other

_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached.

Liver Function Laboratory Tests – Peak and Return to Baseline Values

Please provide the following information regarding the peak and return to baseline liver function laboratory tests, if available.

Tests	**Peak Value**	**Date of Peak** (DD/MMM/YYYY)	**Value at Return to baseline**	**Date of Return to baseline** (DD/MMM/YYYY)	**Reference range**
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					
Gamma glutamyltranspeptidase (GGT)					
International Normalized Ratio (INR)					

You may attach anonymized copy of these reports, if available. **☐ Check this box, if attached.**

Patient history

Does the patient have a history of drug allergies? Yes ☐ No ☐

Does the patient have a history of statin use? Yes ☐ No ☐

If YES, please provide treatment details?

Any concomitant medication(s)? Yes ☐ No ☐

If YES, please list the concomitant medication(s) if patient was taking any at the time of event?

Please list concurrent disease (s)

Targeted Follow-up Questionnaire for Hepatic Decompensation

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s): __/___/____ (DD/MMM/YYYY)
- Date when eltrombopag was started: __/___/____ (DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____ mg; Date: _/___/____(DD/MMM/YYYY)

Patient history

	YES	**NO**
Does the patient have right side heart failure?	☐	☐
Is there a history of prior liver disease (e.g., hepatitis A, B, C, fatty liver, hepatic failure, cirrhosis)?	☐	☐
Is there a history of Gilbert's Disease?	☐	☐
Is there a history of recent travel to a developing country?	☐	☐
Does the patient have autoimmune disease?	☐	☐

If yes, please specify:-

Does the patient have a history of any of the following?

☐ Active gall bladder disease ☐ Active pancreatitis ☐ Alcohol use ☐ NSAID use ☐ IV drug Use

☐ acetaminophen consumption in patients with chronic alcohol exposure – please state number of g/day taken:

If diabetic, has the patient taken any of the following?

☐ Rosiglitazone/ Metformin ☐ Sulfonylureas ☐ Metformin ☐ Insulin ☐ Alpha-glucosidase inhibitors
☐ Repaglinide ☐ Troglitazone ☐ None ☐ Other- please specify:_____

If yes, please give start and stop dates and dose:

Description of the Event

Is the patient symptomatic? ☐ Yes ☐ No

If yes, please indicate all that apply

☐ Right upper quadrant (RUQ) pain ☐ abdominal pain ☐ fever ☐ hepatic encephalopathy/confusion

☐ nausea ☐ jaundice ☐ anorexia ☐ variceal bleeding (please specify site):_____

☐ ascites

☐ Other (Please Specify):

_____

Please describe the results for the following or provide anonymized hard copy of results

1. Did the patient have any triggers for the hepatic decompensation (e.g., infection, medication)?

   ☐ Yes ☐ No

   If yes, please specify: _____

2. Were any diagnostic imaging tests performed e.g. CT or MRI scan abdomen/ liver, abdominal ultrasound of liver/ hepatobiliary tree? ☐ Yes ☐ No

   If yes, please describe results or provide anonymized hard copy of results:

3. Was an Endoscopic/Magnetic Retrograde Cholangiopancreatography (ERCP) / (MRCP) performed? ☐ Yes ☐ No

   If yes, please attach anonymized copy of report.

4. Was a liver biopsy performed?

   ☐ Yes ☐ No

   If yes, please describe results or provide anonymized copy of results:

5. Are liver enzymes (ALT/SGPT, AST/SGOT, Alkaline Phosphatase, LDH, GGT or bilirubin (total, direct, or indirect bilirubin) elevated?

   ☐ Yes ☐ No

   If yes, please provide anonymized copies of results, including baseline and normal ranges

   Liver Function Laboratory Tests – Peak and Return to Baseline Values

Tests	**Value at Peak**	**Date of Peak** (DD/MMM/YYYY)	**Value after Return to baseline**	**Date of Return to baseline** (DD/MMM/YYYY)	**Reference range**
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					
Gamma glutamyltranspeptidase (GGT)					
International Normalized Ratio (INR)					

You may attach anonymized copy of these reports, if available. ☐ **Check this box, if attached.**

Please specify if additional liver studies were obtained?

Please specify or attach anonymized copy of tests if serology for Hepatitis A, B, and C was done

Please specify or attach anonymized copy of tests Prothrombin time/International Normalized Ratio, Thrombin time, Partial thromboplastin time, Albumin, Total protein, if available?

Does the patient have a history of drug allergies? ☐ Yes ☐ No

Does the patient have a history of statin use? Yes ☐ No ☐

If YES, please provide treatment details?

Any concomitant medication(s)? Yes ☐ No ☐

Please list the concomitant medication(s) if patient was taking any at the time of event?

[redacted]

Has the patient had close contact with a person with active hepatitis? ☐ Yes ☐ No

Did the patient receive treatment for liver disease? ☐ Yes ☐ No

If yes, please describe:

Targeted Follow-up Questionnaire for Thrombotic and Thromboembolic Events

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- History of the event(s)

  _____

- Date of the event(s): _/___/____(DD/MMM/YYYY)
- Date when eltrombopag was started: __/___/____(DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____ mg; Date:__/___/____ (DD/MMM/YYYY)
- What is the platelet count most proximal to this event?

  Unit _____ Normal range _____ Date:__/___/____ (DD/MMM/YYYY)
- What was the platelet count after this event?_____
  Date:__/___/____(DD/MMM/YYYY)

Diagnostic tests

Were any of the following diagnostic tests performed? **Check all that apply. Please specify which test(s), providing dates and results. Please provide anonymized copy of these reports, if available.**

☐ CT scan_____

☐ ECG_____

☐ Phlebography_____

☐ Blood gas analysis_____

☐ Doppler\ ultrasound_____

☐ Echocardiography_____

☐ V\P scintigraphy_____

Other tests? Please specify

Please provide anonymized copy of these reports, if available.

[redacted]

Thrombophilic Laboratory Profile (You may attach anonymized copy of these reports, if available).

☐ Check this box (if attached)

Status	Normal	Abnormal	Not done
Lupus anticoagulants	☐	☐	☐
Antiphospholipid antibodies	☐	☐	☐
Anti-prothrombin antibodies	☐	☐	☐
Beta 2 glycoprotein antibodies	☐	☐	☐
Factor VIII	☐	☐	☐
Protein C	☐	☐	☐
Protein S	☐	☐	☐
Serum homocysteine	☐	☐	☐
Anti-thrombin III	☐	☐	☐
Factor V Leiden mutation	☐	☐	☐
☐ Heterozygous ☐ Homozygous ☐ Unknown			
Prothrombin mutation	☐	☐	☐
☐ Heterozygous ☐ Homozygous ☐ Unknown			
MTHFR-Polymorphism	☐	☐	☐
☐ Heterozygous ☐ Homozygous ☐ Unknown			

Patient History: Does the patient have a history of any of the following conditions? **Check all that apply. Please specify date of onset**

☐ Hypertension ☐ Diabetes Mellitus

☐ Hyperlipidemia ☐ Cardiovascular disease

☐ Thromboembolic event ☐ Family history of thromboembolism

☐ Varicose Vein(s)

Risk Factors

Was there trauma prior to the event? ☐ Yes ☐ No

Was the patient immobilized /hospitalized prior to this event (e.g. surgical procedures)?

☐ Yes ☐ No

If YES, was prophylactic anticoagulation administered? ☐ Yes ☐ No

If female, is the patient taking oral contraceptives? ☐ Yes ☐ No

If female, has the patient taken hormone replacement therapy? ☐ Yes ☐ No

Evidence of any autoimmune disease at any time other than ITP (e.g. IBD, SLE, RhA, etc.)?

☐ Yes ☐ No

If YES, please describe:

_____

Please list past or concomitant medication(s) (e.g. IVIg, diuretics, corticosteroids (cortisone, hydrocortisone and prednisone), aminocaproic acid, antifibrinolytic agents, or any recent exposure to drugs associated with TEEs)

☐ None

If any past or concomitant medication(s), please describe:

_____

Targeted Follow-up Questionnaire for Worsening Thrombocytopenia and Bleeding

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- Date when eltrombopag was started:__/___/____ (DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event?
- If NO, what were the last dose and the date? Dose: _____mg; Date: __/___/____(DD/MMM/YYYY)
- What is the platelet count most proximal to this event?
  unit _____ Normal range_____
- Describe any bleeding symptoms during the event?

- Was a transfusion required to maintain the baseline haemoglobin? ☐ Yes ☐ No

  If yes, how many? ____ Please provide the date(s) :__/___/____(DD/MMM/YYYY)
- Outcome of the event(s)

  _____

Please provide up to the last four platelet counts before the first day of treatment with eltrombopag.

☐ Date_____ Platelet Count_____ Normal Range_____

☐ Date_____ Platelet Count_____ Normal Range_____

☐ Date_____ Platelet Count_____ Normal Range_____

☐ Date_____ Platelet Count_____ Normal Range_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached.

Medical Information

1. Were there any similar bleeding events prior to therapy with eltrombopag? ☐ Yes ☐ No

   If YES, please describe:

   _____

2. Has the patient experienced bleeding symptoms on discontinuation of other treatments for ITP? ☐ Yes ☐ No

If YES, please describe:

_____

3. Were there any changes to the concomitant therapy(ies) for ITP prior to this event?

☐ Yes ☐ No

If YES, please describe:

_____

Please list concurrent medication(s) (e.g. anti-platelet medications, NSAIDs)

☐ None

If any concomitant medication(s), please describe:

_____

Targeted Follow-up Questionnaire for Hematological malignancy

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- History of the event(s) _____
- Date of the event(s):__/___/____(DD/MMM/YYYY)
- Date when eltrombopag was started: __/___/____(DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____ mg
  Date:__/___/____(DD/MMM/YYYY)

Diagnosis:

Please select one choice regarding this event:

☐ **New diagnosis** ☐ **Relapse of previous malignancy** ☐ **Unknown**

Please select one diagnosis from this list:

☐ Under investigation

☐ Myelodysplastic syndrome (MDS) (IPSS score):

☐ Acute myeloid leukemia (AML) (FAB subtype):

☐ Lymphoma (specify):

☐ Myeloproliferative Disease (MPD)

☐ Other, (specify):_____

Is the peripheral blood smear abnormal? ☐ Yes ☐ No

☐ Bone marrow biopsy/Trephine Date:_/___/____(DD/MMM/YYYY)

Findings_____

☐ Bone marrow aspiration Date:_/___/____(DD/MMM/YYYY)

Findings_____

☐ Immunophenotype? Date:_/___/____ (DD/MMM/YYYY)

Findings_____

☐ Cytogenetics? Date:_/___/____ (DD/MMM/YYYY)

Findings_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached.

Please provide any additional information on stage, treatment planned, pathology, and x-ray findings.

What clinical features were present at the time of diagnosis? Check all that apply

☐ Anemia	☐ Thrombocytopenia
☐ Pallor	☐ Granulocytopenia
☐ Fatigue	☐ Lymphadenopathy
☐ Fever/night sweats	☐ Increased bruising/bleeding
☐ Bone pain	☐ Recurrent infection/poor wound healing
☐ Hepatosplenomegaly	☐ Abdominal pain and /or weight loss

Patient History:

Does the patient have any of the following past or present conditions that may predispose them to malignancies?

Yes	No	
☐	☐	Family History of malignancy
☐	☐	Smoking
☐	☐	Occupational exposure (e.g. benzene)
☐	☐	Monoclonal gammopathy
☐	☐	History of chemotherapy or radiation therapy
☐	☐	Other (please specify):_____

What are the concomitant medications? (check all that apply)

[redacted]

☐ None

☐ Azathioprine ☐ Corticosteroids

☐ Cyclophosphamide ☐ Danazol

☐ Interferon alpha ☐ IVIg

☐ Rituximab ☐ Romiplostim

Other (please specify):_____

Targeted Follow-up Questionnaire for Bone Marrow Reticulin / Bone Marrow Fibrosis

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s): _/___/____ (DD/MMM/YYYY)
- Date when eltrombopag was started: __/___/____ (DD/MMM/YYYY)
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____ mg
  Date:__/___/____(DD/MMM/YYYY)

Adverse Event description

a. Was the Peripheral Blood Smear Abnormal? ☐ Yes ☐ No

b. Date of this smear: ___/____/_____ (DD/MMM/YYYY)

c. If YES, were any of the following cells present in the peripheral blood smear?

1. Increased peripheral blast cells ☐ Yes Please provide the %_____
2. Increased nucleated red blood cells ☐ Yes Please provide the %_____
3. Tear drop erythrocytes ☐ Yes

Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates and results

☐ Bone marrow aspiration Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

☐ Bone marrow biopsy/Trephine Date:__/___/_____(DD/MMM/YYYY)

Findings_____

☐ Immunophenotype Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

☐ Cytogenetics Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

What clinical features were present at the time of the event? (check all that apply)

☐ Recent decrease in haemoglobin
☐ Recent decrease in platelet counts
☐ Newly diagnosed splenomegaly
☐ Increased nucleated red blood cells
☐ Newly diagnosed hepatomegaly
☐ Change in white blood cells, (please specify) _____

Please quantify the degree of bone marrow reticulin/collagen using the Bauermeister scale.

(Select only one)

0 ☐ No reticulin fibers demonstrable
1 ☐ Occasional fine individual fibers and foci of a fine fiber network
2 ☐ Fine fiber network throughout most of the section; no coarse fibers
3 ☐ Diffuse fiber network with scattered thick coarse fibers but no mature collage (negative trichrome stain)
4 ☐ Diffuse, often coarse fiber network with areas of collagenization (positive trichrome stain)
☐ Other (please describe)

You may attach anonymized copy of the bone marrow report, if available. ☐ Check this box if attached.

Medical History – Baseline Assessments

Please complete baseline information on any of the assessments below indicating that any of the following procedures were performed prior to the patient being treated with eltrombopag?

☐ Bone marrow aspiration Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

☐ Bone marrow biopsy/Trephine Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

☐ Imrnunophenotype Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

☐ Cytogenetics Date:__/___/_____ (DD/MMM/YYYY)

Findings_____

<u>At baseline</u>, please quantify the degree of bone marrow reticulin/collagen using the Bauermeister scale. (Select only one)

0 ☐ No reticulin fibers demonstrable

1 ☐ Occasional fine individual fibers and foci of a fine fiber network

2 ☐ Fine fiber network throughout most of the section; no coarse fibers

3 ☐ Diffuse fiber network with scattered thick coarse fibers but no mature collage (negative trichrome stain)

4 ☐ Diffuse, often coarse fiber network with areas of collagenization (positive trichrome stain)

☐ Other (please describe) _____

<u>Patient History:</u>

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply and provide details as applicable**

☐ Infection

☐ UV exposure, psoralen plus ultraviolet-A (PUVA)/ Ultraviolet B (UVB)

☐ Smoking ☐ Alcohol abuse

☐ Personal history of malignancy ☐ Family history of malignancy

☐ Immunosuppression condition (e.g. HIV, transplantation)

☐ Immunosuppression therapy

☐ Exposure to carcinogens (environmental, occupational) ☐ Radiation therapy

☐ Autoimmune disease (e.g. psoriasis, Sjogren Syndrome, rheumatoid arthritis)

☐ Others (please specify)

Concomitant medications (Check all that apply and provide details as applicable)

☐ Azathioprine

☐ Corticosteroids (please specify either cortisone, hydrocortisone or prednisone) :_____

☐ Cyclophosphamide

☐ Danazol Interferon alpha

☐ IVIg

☐ Rituximab

☐ Romiplostim

☐ Other (please specify): _____

Please list previous and concurrent disease(s)