RISK MANAGEMENT PLAN
For
Eltrombopag
Version 1.0.

RMP Version to be Assessed as Part of this Application:

RMP Version Number	1.0
Data Lock Point for this RMP	19-Aug-2024
Date of Final Sign Off	15-Oct-2024
Rationale for Submitting an Updated RMP	RMP has been amended based on the comments received in Day 150 Joint Assessment Report dated 26-Aug-2024 for procedure EMEA/H/C/006417.
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: • RMP has been amended based on the comments received in 150 Joint Assessment Report dated 26-Aug-2024, for procedure EMEA/H/C/006417.

Other RMP Versions Under Evaluation:

RMP Version Number	0.3
Submitted On	26-Sep-2024
Procedure Number	EMEA/H/C/006417

Details of the Current RMP:

Version Number	Not applicable
Approved with Procedure	Not applicable
Date of Approval (Opinion Date)	Not applicable

QPPV: Dr Eiko Soehlke, MD MPH

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
ITP	Immune thrombocytopenia
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
SmPC	Summary of Product Characteristics
TPO	Thrombopoietin

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Eltrombopag
Pharmacotherapeutic Group(s) (ATC Code)	Antihemorrhagics, other systemic hemostatics (B02BX 05)
Marketing Authorisation Holder	Viatris Limited (IE)
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)/UK	Eltrombopag Viatris 12.5 mg film-coated tablets Eltrombopag Viatris 25 mg film-coated tablets Eltrombopag Viatris 50 mg film-coated tablets Eltrombopag Viatris 75 mg film-coated tablets
Marketing Authorisation Procedure	Centralised procedure (H0006417)
Brief Description of the Product	Chemical class Eltrombopag is a thrombopoietin receptor agonist. Summary of mode of action Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells. Important information about its composition Daily oral administration of eltrombopag to healthy and thrombocytopenic humans results in a dose-dependent increase in platelet counts within 1-2 weeks for patients with immune thrombocytopenia (ITP) and chronic hepatitis C virus associated thrombocytopenia.
Hyperlink to the Product Information:	Please refer to 1.3.1 of the current eCTD sequence
Indication(s) in the EEA	Proposed: Eltrombopag is indicated for: • For the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). • 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). • 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. Current: Not applicable
Dosage in the EEA	Proposed: Eltrombopag Viatris 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. Eltrombopag containing medicinal products may be available as a powder for oral suspension under other brand names. This should be taken into consideration for patients who experience difficulty in swallowing the tablet formulation, such as paediatric patients. The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation. When switching between the tablet and the powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks. ***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, 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. Eltrombopag Viatris is intended for oral use. Current: Not applicable

Pharmaceutical Form(s) and Strengths	Proposed: Film-coated tablets, 12.5 mg Film-coated tablets, 25 mg Film-coated tablets, 50 mg Film-coated tablets, 75 mg Current: Not applicable
Will the Product Be Subject to Additional Monitoring in the EU?	No

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

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

This is a MAA for a generic medicine in which the safety concerns available in the EPAR – Risk Management Plan for the reference medicinal product *Revolade* (eltrombopag) version 54.1, last updated on the EMA website on 16-May-2023 (EMEA/H/C/001110, date of final sign off 07-Jul-2022) have been adopted by the MAH.

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	***Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and***

Summary of Safety Concerns	
	severe aplastic anaemia* • Hepatotoxicity • Thromboembolic events ***HCV-associated thrombocytopenia*** • Hepatic decompensation
Important Potential Risks	***Adult ITP, Paediatric ITP, 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, 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 Viatris

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP/RMP in public domain have been considered in this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial RMP for eltrombopag.

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 as this RMP for eltrombopag follows the same safety concerns as the safety concerns of the reference substance RMP available on the EMA website.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for eltrombopag follows the same safety concerns as the safety concerns of the reference substance RMP available on the EMA website.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

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, 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, 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 Viatris

PART III: PHARMACOVILIGANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH/Applicant has in place to identify and/or characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

In line with the originator product, the Applicant proposes the implementation of specific adverse reaction follow-up questionnaires to obtain structured information on the following safety concerns:

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

The forms are provided in Annex 4 - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

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

Safety Concern	Routine Risk Minimisation Activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Hepatotoxicity	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. The signs and symptoms were included in in SmPC sections 4.4, and PL section 2. Medicine's legal status: restricted medical prescription
Thromboembolic events	Routine risk communication: SmPC section 4.2, 4.4, 4.8 and 4.9 PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Platelet counts should be closely monitored, and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels. Medicine's legal status: restricted medical prescription
HCV-associated thrombocytopenia Hepatic decompensation	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety Concern	Routine Risk Minimisation Activities
	Warning about Hepatic decompensation and recommendation for monitoring of low albumin levels or MELD score included in SmPC sections 4.4, and PL section 2 and 4. Medicine's legal status: restricted medical prescription
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Increased Bone Marrow Reticulin Formation	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Medicine's legal status: restricted medical prescription
Haematological malignancies	Routine risk communication: SmPC section 4.4 and 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells. Medicine's legal status: restricted medical prescription
Severe aplastic anaemia* Cytogenetic abnormalities	Routine risk communication: SmPC section 4.2, 4.4 and 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: For SAA patient's refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Safety Concern	Routine Risk Minimisation Activities
	Medicine's legal status: restricted medical prescription
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Patients with hepatic impairment	Routine risk communication: SmPC section 4.2 PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Medicine's legal status: restricted medical prescription
Severe aplastic anaemia* Use in paediatric population	Routine risk communication: SmPC section4.2 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Medicine's legal status: restricted medical prescription

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

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Hepatotoxicity	Routine risk minimization measures: SmPC section 4.2, 4.4 and 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Thromboembolic events	Routine risk communication: SmPC section 4.2, 4.4, 4.8 and 4.9 PL section 2 and 4. Additional risk minimisation measures	Routine pharmacovigilance activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	None	
HCV-associated thrombocytopenia Hepatic decompensation	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8. PL section 2 and 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Increased Bone Marrow Reticulin Formation	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Haematological malignancies	Routine risk minimization measures: SmPC section 4.4 and 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Severe aplastic anaemia* Cytogenetic abnormalities	Routine risk minimization measures: SmPC section 4.2, 4.4 and 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Patients with hepatic impairment	Routine risk minimization measures: SmPC section 4.2 PL section 2. Additional risk minimisation measures None	Routine pharmacovigilance activities
Severe aplastic anaemia* Use in paediatric population	Routine risk minimization measures: SmPC section 4.2 PL section 2 Additional risk minimisation measures None	Routine pharmacovigilance activities

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Eltrombopag Viatris (Eltrombopag)

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

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

This summary of the RMP for Eltrombopag Viatris should be read in the context of all the 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 Viatris RMP.

I. The Medicine and What it is Used For

Eltrombopag Viatris is authorised for.

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

- 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).

- 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.

They contain eltrombopag as the active substance and they are given orally.

Further information about the evaluation of Eltrombopag Viatris's benefits can be found in Eltrombopag Viatris's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Eltrombopag Viatris, together with measures to minimise such risks and the proposed studies for learning more about Eltrombopag Viatris's, 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 public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events 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 Viatris is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Eltrombopag Viatris are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. 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 Viatris. 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/use in special patient populations etc.).

Table 4: Part VI.1- Summary of safety concerns

List of important risks and missing information	
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, 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, 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 Viatris

II.B Summary of Important Risks

Table 5: Part VI.2- Hepatotoxicity

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2, 4.4 and 4.8. PL section 4.
Additional risk minimisation measures	None

Table 6: Part VI.2- Thromboembolic events

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8 and 4.9 PL section 2 and 4.
Additional risk minimisation measures	None

Table 7: Part VI.2- Hepatic decompensation

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2, 4.8. PL section 4.
Additional risk minimisation measures	None

Table 8: Part VI.2- Increased Bone Marrow Reticulin Formation

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8.

	PL section 4.
Additional risk minimisation measures	None

Table 9: Part VI.2- Haematological malignancies

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2, 4.8. PL section 4.
Additional risk minimisation measures	None

Table 10: Part VI.2- Cytogenetic abnormalities

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2 PL section 4.
Additional risk minimisation measures	None

Table 11: Part VI.2- Patients with hepatic impairment

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as missing information.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2 PL section 4.
Additional risk minimisation measures	None

Table 12: Part VI.2- Use in paediatric population

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as missing information.
Risk Factors and Risk Groups	Not applicable

Risk Minimisation Measures	Routine risk minimization measures: SmPC section 4.2 PL section 2
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 Eltrombopag Viatris.

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

There are no studies required for Eltrombopag Viatris.

PART VII: ANNEXES

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

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

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Targeted Follow-up Checklist
Eltrombopag - 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) _____
- Date when eltrombopag was started: _____
- 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 _____

Current Liver Function Laboratory Tests

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

Tests	Lab Value	Date	Reference range
Alanine Aminotransferase (ALT)			
Aspartate Aminotransferase (AST)			
Total Bilirubin			
Direct Bilirubin			
Alkaline Phosphatase (Alk Phos)			
Gamma glutamyl-transpeptidase (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 / Fibroscan
☐	☐	CAT Scan
☐	☐	MRI Scan
☐	☐	Endoscopic/Magnetic Retrograde Cholangiopancreatography (ERCP) / (MRCP)
☐	☐	Other_____

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

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**	**Value at Return to baseline**	**Date of Return to baseline**	**Reference range**
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					
Gamma glutamyl-transpeptidase (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 ☐

Any concomitant medication(s)? YES ☐ NO ☐ NONE ☐

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

Please list concurrent disease(s)

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Targeted Follow-up Checklist
Eltrombopag - 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) _____
- Date when eltrombopag was started: _____
- 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 _____

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 ☐ Statin 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?
☐ Avandia/ Avandamet ☐ Sulfonylureas ☐ Metformin ☐ Insulin ☐ Alpha-glucosidase inhibitors ☐ Repaglinide ☐ Troglitazone
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.

☐ RUQ pain ☐ abdominal pain ☐ fever ☐ hepatic encephalopathy / confusion

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

☐ ascites

☐ other (please specify:_____

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

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**	**Value after Return to baseline**	**Date of Return to baseline**	**Reference range**
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					
Gamma glutamyl-transpeptidase (GGT)					
International Normalized Ratio (INR)					

Receipt Date (dd/mm/yyyy): *Case ID #:*_____
_____/_____/_____

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

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

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: _____

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Targeted Follow-up Checklist
Eltrombopag - 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) _____
- Date when eltrombopag was started: _____
- 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 _____
- What is the platelet count most proximal to this event?

  Unit _____ Normal range _____ Date _____
- What was the platelet count after this event? _____ Date _____

Diagnostic tests

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

☐ 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.

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-prothombin 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**	☐	☐	☐

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

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, aminocaproic acid, antifibrinolytic agents, or any recent exposure to drugs associated with TEEs)

☐None

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #*_____

Targeted Follow-up Checklist
Eltrombopag - 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:
- Is the patient still taking eltrombopag?
- If YES, what was the dose of eltrombopag at the time of the event?
- If NO, what were the last dose and the date?
- 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 hemoglobin? ☐Yes ☐No
  If yes, how many? _____Please provide the date(s) _____
- 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 specify:_____

4. Please list concurrent disease(s) ☐ None

Please list concurrent medication(s) (eg. anti-pletelet medications, NSAIDs)
☐ None

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Targeted Follow-up Checklist
Eltrombopag - 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) _____
- Date when eltrombopag was started: _____
- 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 _____

Diagnosis:
Please select one choice regarding this event:
☐ **New diagnosis** ☐ **Relapse of previous malignancy** ☐ **Unknown**

Please select one diagnosis from this list:
☐ Under investigation ☐ MDS (IPSS score):

☐ AML (FAB subtype): ☐ Lymphoma (specify):

☐ Myeloproliferative Disease (MPD)
Please specify: CML IMF PV ET

☐ **Other,** (specify): _____

Is the peripheral blood smear abnormal? ☐ Yes ☐ No

☐ Bone marrow biopsy/Trephine Date_____ Findings_____

☐ Bone marrow aspiration Date_____ Findings _____

☐ Immunophenotype? Date _____ Findings_____

☐ Cytogenetics? Date _____ Findings_____

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

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

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
- ☐ Pallor
- ☐ Fatigue
- ☐ Fever/night sweats
- ☐ Bone pain
- ☐ Hepatospenomegaly
- ☐ Thrombocytopenia
- ☐ Granulocytopenia
- ☐ Lymphadenopathy
- ☐ Increased bruising/bleeding
- ☐ Recurrent infection/poor wound healing
- ☐ 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**)

☐ None

- ☐ Azathioprine
- ☐ Cyclophosphamide
- ☐ Interferon alpha
- ☐ Rituximab
- ☐ Corticosteroids
- ☐ Danazol
- ☐ IVIg
- ☐ Romiplostim

Other (please specify):_____

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Targeted Follow-up Checklist
Eltrombopag - 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) _____
- Date when eltrombopag was started: _____
- 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 _____

Adverse Event description

a. Was the Peripheral Blood Smear Abnormal? ☐ Yes ☐ No
b. Date of this smear: ____ / ____ / ____

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_____ Findings_____

☐ Bone marrow biopsy/Trephine Date_____ Findings_____

☐ Immunophenotype Date_____ Findings_____

☐ Cytogenetics Date_____ Findings_____

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

☐ Recent decrease in hemoglobin
☐ 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_____ Findings_____

☐ Bone marrow biopsy/Trephine Date_____ Findings_____

☐ Immunophenotype Date_____ Findings_____

☐ Cytogenetics Date_____ Findings_____

At baseline 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) _____

Receipt Date (dd/mm/yyyy):
_____/_____/_____

*Case ID #:*_____

Patient History:

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, PUVA/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
- ☐ Cyclophosphamide
- ☐ Danazol Interferon alpha
- ☐ IVIg
- ☐ Rituximab
- ☐ Romiplostim
- ☐ Other (please specify):_____

Please list previous and concurrent disease(s)

_____

_____