

**Safety Guide for REVOLADE™
(eltrombopag) in chronic immune
thrombocytopenic purpura (ITP)**

Important safety information for healthcare professionals regarding the monitoring and management of patients prescribed eltrombopag

Prescribing Information is available at the end of this document.

INTRODUCTION

ADVERSE EVENTS OF SPECIAL INTEREST:

- 1. Hepatotoxicity
- 2. Thrombotic/thromboembolic complications
- 3. Bone marrow reticulin formation and risk for bone marrow fibrosis
- 4. Haematological malignancies
- 5. Post therapy thrombocytopenia

OTHER CONSIDERATIONS

SUMMARY

- Safety management essentials

Eltrombopag for the treatment of adults with chronic idiopathic thrombocytopenic purpura (ITP)¹

Eltrombopag is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Revolade should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.

Revolade should not be used in attempt to normalize platelet counts. Eltrombopag may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.¹ The active ingredient, eltrombopag, is an oral, thrombopoietin (TPO)-receptor agonist that maintains platelet counts at a haemostatic level by stimulating differentiation and proliferation of cells in the megakaryocyte lineage.^{1,2} The objective of treatment with eltrombopag should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk (>50,000/ μ L).¹

The safety and tolerability of eltrombopag have been evaluated in approximately 500 patients with chronic ITP in the eltrombopag clinical development programme.¹⁻⁶ At the most recent data cut-off point of the ongoing EXTEND study (February 2013), 302 patients had been treated for up to 6 months, with 218, 179, 74 and 4 patients for up to 1, 2, 4 and 6 years, respectively.^{6,12}

Summary of eltrombopag clinical studies in patients with chronic ITP:

Study	Phase	N (n)	Design	Dosing group	Study aim and status
773A ²	II	117 (88)	6-week randomized, double-blind, placebo-controlled study*	Eltrombopag 30 mg, 50 mg, 75 mg, and placebo	Dose-ranging efficacy and safety Completed
773B ³	III	114 (76)	6-week randomized, double-blind, placebo-controlled study*	Eltrombopag 50 mg starting dose, and placebo	Short-term efficacy and safety Completed
RAISE ⁴	III	197 (135)	6-month randomized, double-blind, placebo-controlled study*	Eltrombopag 50 mg starting dose, and placebo	6-month efficacy and safety Completed
REPEAT ⁵	II	66 (66)	Open-label, repeat-dose, Phase II study	Eltrombopag 50 mg starting dose	Repeated intermittent use efficacy and safety (3 x 6-week cycles, 4-week washout between cycles) Completed
EXTEND ^{6,7,12}	III	302	Open-label, long-term, extension study	Eltrombopag 50 mg starting dose	Long-term safety and efficacy Ongoing (enrolment completed)
Bone marrow study ^{8,9}	IV	167 [†]	Two-year, open-label, multi-centre study	Eltrombopag 50 mg starting dose (25 mg in patients of East Asian ancestry)	To evaluate the long-term effect of eltrombopag on bone marrow reticulin and/or collagen fibers Ongoing
LENS ¹⁰	IV	164	Observational study monitoring ocular safety in subjects previously enrolled in a eltrombopag trial and who received either eltrombopag or placebo	N/A – observational only	Long-term ocular safety with respect to changes in the lens Completed

N = total study population; n = number of patients who received eltrombopag.

*The use of standard-of-care (SOC) in addition to eltrombopag or placebo was permitted in these studies.

~ 25 mg dose adjustments were permitted in these studies.

†Number of patients enrolled in the study by the 2-year interim analysis

Study ID numbers: TRA100**773A**, TRA100**773B** and RAISE [TRA102537], **REPEAT** [TRA108057], and **EXTEND** [TRA105325] and **Bone marrow study** [TRA11294001]

Results showed that eltrombopag was generally well tolerated in patients with chronic ITP compared to placebo with a low rate of mild-to-moderate, transient adverse events.^{2-4,6,7}

Here we draw attention to some important safety issues that were identified during the clinical development programme and provide guidance on best practice management of these issues should they arise.

1. HEPATOTOXICITY¹

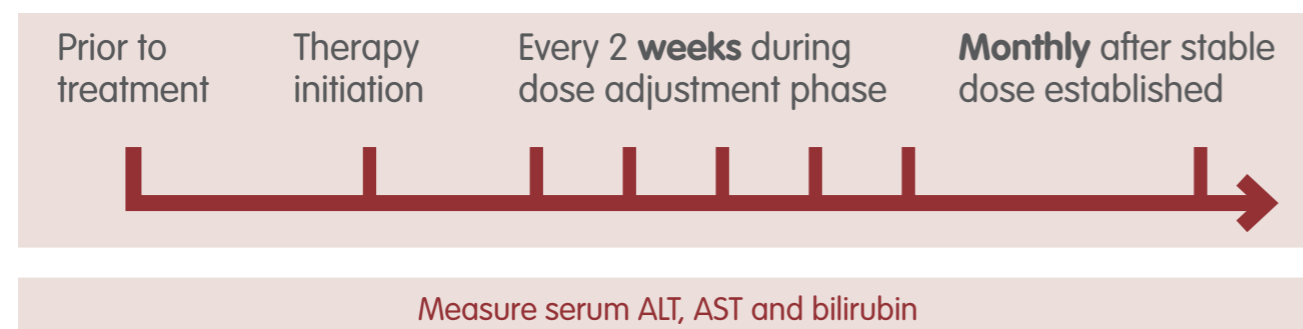
Clinical trials have shown that eltrombopag can cause changes in hepatobiliary function indicated by increases in liver function parameters. Patients should be educated about the potential for abnormal liver function and the importance of laboratory monitoring of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. They should also be reassured that, when they occur, hepatobiliary abnormalities are usually mild (grade 1–2), reversible and without clinical sequelae. Eltrombopag should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of eltrombopag must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Incidence of hepatotoxicity with eltrombopag

The frequency of increases in ALT, AST and bilirubin was classified as ‘common’ with eltrombopag in the overall clinical development programme, occurring in at least 1% but less than 10% of patients.¹

The potential for hepatotoxicity with eltrombopag is being assessed in the ongoing long-term EXTEND study, an open-label extension including patients who had completed a previous eltrombopag ITP study (TRA100773A/B, RAISE and REPEAT).⁷ Analysis of 302 patients with ITP treated with eltrombopag for a median of 121 weeks (range, 2 days–285 weeks [5.5 years]), revealed that a total of 36 patients (12%) experienced hepatobiliary laboratory abnormalities (HBLAs).⁶ Most HBLAs were mild, reversible, and without associated symptoms of impaired liver function; a total of eight patients (3%) discontinued eltrombopag therapy owing to hepatobiliary adverse events.⁶

Patients receiving eltrombopag require regular monitoring of serum liver tests¹

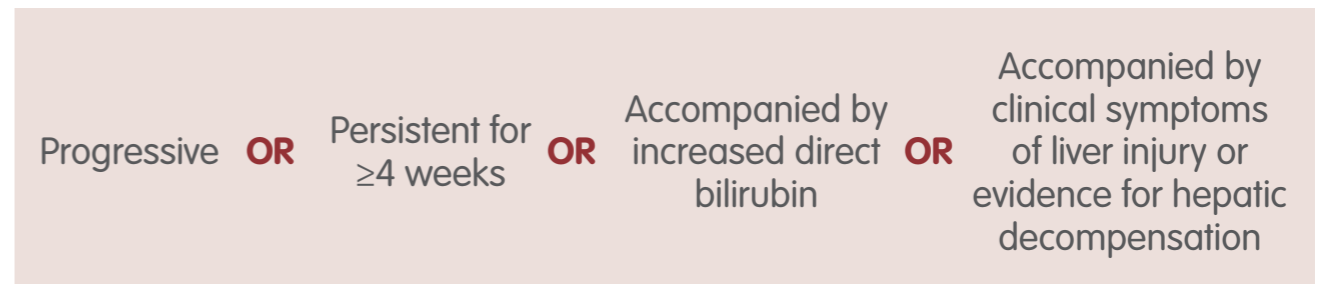


If abnormal levels are detected, repeat the tests **within 3 to 5 days**.

If the abnormalities are confirmed, monitor serum liver tests until the abnormalities resolve, stabilise or return to baseline levels.

When should eltrombopag be discontinued?

The frequency of increases in ALT, AST and bilirubin was classified as ‘common’ with eltrombopag. Discontinue eltrombopag if ALT levels increase to three times upper limit of normal or greater and are:



Can eltrombopag be administered to patients with hepatic impairment?

In ITP patients with hepatic impairment (Child–Pugh score ≥ 5), eltrombopag should not be used unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of eltrombopag must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.

2. THROMBOTIC/THROMBOEMBOLIC COMPLICATIONS

Thromboembolic events (TEEs) may occur in patients with ITP¹; approximately 5% of patients with chronic ITP are reported to have experienced a TEE.¹¹ Thus, there is a potential concern that thrombotic or thromboembolic complications may occur in these patients as a result of excessive increases in platelet counts.¹ As a consequence, eltrombopag should be used with caution in patients with known risk factors for thromboembolism, and these patients should be educated about the potential risks associated with eltrombopag treatment.

Incidence of thrombotic/thromboembolic complications with eltrombopag¹

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n=446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1).¹ In the ongoing long-term EXTEND study, where patients have been treated with eltrombopag for up to 5.5 years, the incidence of thromboembolic events is 2.70 per 100 patient-years (95% CI: 1.62–4.21), with no increased incidence observed with longer duration of therapy.⁶ No relationship between thromboembolic events and elevated platelet counts has been observed.⁶

The risk of TEEs has been found to be increased in thrombocytopenic patients (platelet count $< 50,000/\mu\text{L}$) with chronic liver disease (CLD), without concomitant ITP.¹ In a placebo-controlled study (n=288, safety population), following 2 weeks of treatment in preparation for invasive procedures, six of 143 (4%) adult patients with CLD receiving eltrombopag experienced seven TEEs of the portal venous system and two of 145 (1%) subjects in the placebo group experienced three TEEs.¹ Five of the six patients treated with eltrombopag experienced the TEE at a platelet count $> 200,000/\mu\text{L}$.¹ Eltrombopag should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous

thrombosis.¹ If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment, the starting dose of eltrombopag must be 25 mg once daily.¹ After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.¹

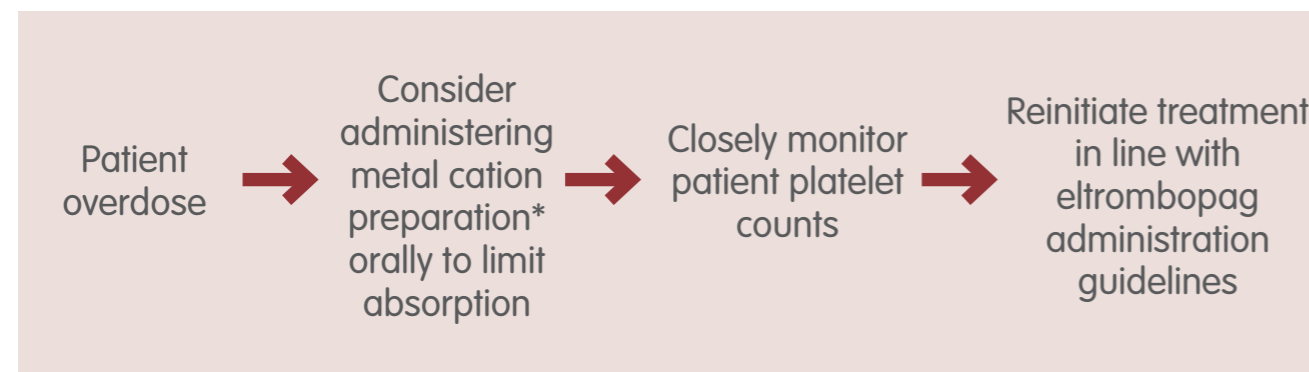
What are the risk factors for thromboembolism?

Risk factors for thromboembolism include, but are not limited to, inherited (e.g. Factor V Leiden) or acquired risk factors (e.g., ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking.¹ The risk of TEEs has been found to be increased in thrombocytopenic patients (platelet count <50,000/ μ L) with CLD, without concomitant ITP, treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures. No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts \geq 200,000/ μ L.¹ Analysis of data from the 446 patients with chronic ITP treated with eltrombopag across the ITP clinical trial programme observed no correlation between high platelet counts and the incidence of TEEs.¹³ Physicians considering prescribing eltrombopag to patients presenting with these risk factors should weigh up the relative risks and benefits of treatment.

How can the risk of thrombotic/thromboembolic complications be minimised?

To minimise the risk for thrombotic/thromboembolic complications, the platelet count should be monitored weekly during treatment until a stable count has been achieved.¹ Thereafter it should be monitored monthly.¹ The eltrombopag dose should be reduced if the platelet count rises above 150,000/ μ L, or discontinued if it rises above 250,000/ μ L.¹ The risk–benefit balance should be considered in patients at risk of TEEs of any aetiology.¹

Overdose with eltrombopag may increase platelet counts excessively and increase the risk of thrombotic/thromboembolic complications. In the event of overdose, follow the steps outlined below:¹



* Preparations containing metal cations, such as calcium, magnesium or aluminium chelate with eltrombopag and prevent absorption.

3. BONE MARROW RETICULIN FORMATION AND RISK FOR BONE MARROW FIBROSIS

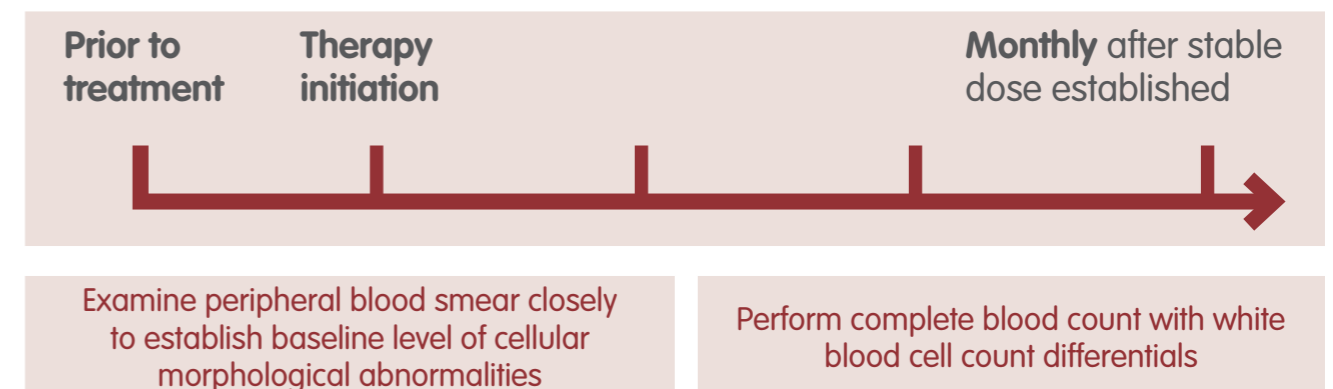
Eltrombopag, as with other TPO-receptor agonists, may increase the risk for development or progression of reticulin fibers within the bone marrow.¹ Interpretation of the impact of the TPO-receptor agonists on reticulin changes is complicated by the fact that patients with ITP are at an increased risk of bone marrow reticulin formation prior to treatment. A retrospective study of bone marrow samples from 40 such ITP patients with ITP identified 67% with grade 1–2 reticulin.¹⁴

Across the overall clinical ITP programme, no patients receiving eltrombopag demonstrated clinically relevant bone marrow abnormalities or signs of bone marrow dysfunction. Eltrombopag treatment was discontinued in one patient owing to bone marrow reticulin.¹

From the most recent analysis of bone marrow data from patients treated with eltrombopag in the ongoing open-label EXTEND study, there was no clinically relevant increase in bone marrow reticulin deposition in patients treated with eltrombopag for up to 4.75 years (n=113).⁶

In an ongoing, Phase IV, 2-year, prospective bone marrow study, bone marrow biopsies are collected at baseline (pre-treatment) and at 1 and 2 years of treatment.⁹ At the 2-year interim analysis, there was no increase in bone marrow reticulin in 73% (33/45) of patients, an increase of 1 grade in 16% (7/45) of patients and a 2-grade increase in 2% (1/45) of patients.⁹ No patient with an increase to MF-2 at 2 years had adverse events or haematological abnormalities considered to be related to impaired bone marrow function and none withdrew due to bone marrow findings.⁹ Analysis from this prospective study indicated that at baseline, approximately 11% of adult chronic ITP patients may have MF-1 reticulin in their bone marrow.⁹ The effects of eltrombopag, as with other TPO-receptor agonists, on bone marrow reticulin formation are continuing to be monitored.

Patients receiving eltrombopag require regular blood count monitoring:¹



If immature or dysplastic cells are observed, peripheral blood smears should be examined. If the patient has developed new or worsening morphological abnormalities or cytopenia(s), discontinue treatment and consider a bone marrow biopsy, including staining for fibrosis.

Other considerations

4. HAEMATOLOGICAL MALIGNANCIES

TPO-receptor agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO receptor is predominantly expressed on the surface of cells of the myeloid lineage and there is a concern that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies, such as myelodysplastic syndrome (MDS).¹ Studies have shown that patients with autoimmune disorders, including ITP, have a significantly increased risk of developing haematological malignancies irrespective of treatment.¹⁵

In clinical studies with a TPO-receptor agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported. Patients should, therefore, be informed that a concern exists that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies, such as MDS.

In all patients and especially the elderly, the diagnosis of ITP should be confirmed by exclusion of other clinical conditions which may present with thrombocytopenia. A diagnosis of MDS must be expressly excluded.

- Physicians should consider performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age and in those with systemic symptoms or abnormal signs such as increased peripheral blast cells.¹

Eltrombopag should not be used outside the context of its license unless in a clinical trial setting.

In a randomized, double-blind, placebo-controlled, Phase III study (RAISE) of eltrombopag in 197 patients with ITP, malignancies were reported for one patient in the eltrombopag group (1%) and one patient in the placebo group (2%).⁴ Two patients were diagnosed with lymphoma (one diffuse large B-cell and one non-Hodgkin) during the 622 patient-years of eltrombopag exposure during an open-label extension study (EXTEND) (as of February 2011 cut-off date).¹⁶

5. POST THERAPY THROMBOCYTOPENIA¹

Platelet counts return to baseline levels within 2 weeks of discontinuing treatment with eltrombopag in most patients, which may increase the risk of bleeding. In three controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively.

This risk of post therapy thrombocytopenia is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support.

Patients should be informed of the risk of bleeding and platelet count should be monitored weekly for 4 weeks following discontinuation of eltrombopag.

Please refer to the Summary of Product Characteristics for additional safety information.

Are there any dose adjustment recommendations for specific populations?¹

Plasma eltrombopag exposure was shown to be 87% higher in a pharmacokinetic study of ITP patients with East Asian ancestry (such as Japanese, Chinese, Taiwanese and Korean) compared with non-East Asian (predominantly Caucasian) patients. Therefore, a lower starting dose of 25 mg once daily should be considered for these patients. Patients of East Asian ancestry should be monitored closely, and the eltrombopag dose increased by 25 mg to a maximum of 75 mg if platelet counts remain below 50,000/ μ L following at least 2 weeks of therapy.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child–Pugh score \geq 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of eltrombopag must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Who is not suitable for eltrombopag therapy?¹

Eltrombopag is not recommended for use in children or adolescents aged less than 18 years. Eltrombopag is also not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether the active ingredient or metabolites of eltrombopag are excreted in human milk, although a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from eltrombopag therapy, taking into account the benefit of breast-feeding for the child and the benefit of eltrombopag therapy for the woman.

The diagnosis of ITP in adults and elderly patients should be confirmed by excluding other clinical entities with thrombocytopenia. Physicians should consider performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age and in those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

Eltrombopag should not be used for the treatment of conditions outside of the indicated patient population, including patients with MDS. The risk-benefit of using eltrombopag to treat thrombocytopenia outside of the registered indication has not been established.

Is eltrombopag associated with any significant food or medicinal interactions?

Polyvalent cation-containing antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must not be administered 4 hours before or after taking eltrombopag. Polyvalent cations, including iron, calcium, magnesium, aluminium, selenium and zinc chelate with eltrombopag and significantly reduce absorption of the drug.¹ Eltrombopag may be taken with food containing little (<50 mg) or preferably no calcium, such as fruit, lean beef or ham and unfortified soy milk.¹⁷ Food with moderate or high levels of calcium has been shown to reduce exposure to eltrombopag.¹ For patients who require an antacid, you may be able to consider an alternative timing or non-heavy-metal-containing antacid, such as an H2 blocker or proton pump inhibitor.¹⁷

ELTROMBOPAG - SAFETY MANAGEMENT ESSENTIALS¹

Patients should be informed about these potential food interactions, and it may be useful to assist your patients in developing an individualized plan to administer eltrombopag at a time each day that fits into their daily schedule.

Other drug considerations¹

- **Statins:** in clinical studies with eltrombopag, reducing statin dose by 50% was recommended
- **OATP1B1 and BCRP substrates (e.g. topotecan and methotrexate):** co-administration of eltrombopag should be undertaken with caution
- **Contraceptive pill and hormone therapy:** caution should be taken when administering eltrombopag owing to the observed risk of thromboembolic events in clinical trials
- **Lopinavir/ritonavir (LPV/RTV):** caution should be taken, as the concentration of eltrombopag may be decreased when co-administered with LPV/RTV
- **Other medicinal products for the treatment of ITP:** platelet counts should be monitored when eltrombopag is co-administered with other medicinal products for the treatment of ITP such as corticosteroids, danazol or azathioprine

When should the dose of eltrombopag be reduced or treatment interrupted?¹

Eltrombopag dosing should be adjusted to the minimum dose required to achieve and maintain a platelet count $\geq 50,000/\mu\text{L}$ as necessary to reduce the risk for bleeding. The eltrombopag dose should be reduced if the platelet count rises above $150,000/\mu\text{L}$ or discontinued if it rises above $250,000/\mu\text{L}$. Additional information on dose adjustment with eltrombopag can be found in the 'Safety Management Essentials' on the next page.

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Note: please refer to the Summary of Product Characteristics for additional information.

INDICATION

Adult chronic ITP in splenectomised patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). Eltrombopag may be considered as second-line treatment for adult non-splenectomised patients where surgery is contraindicated.

SAFETY INFORMATION

Hepatotoxicity	Increases in ALT, AST and bilirubin classified as 'common' (1–10%). Discontinue eltrombopag if ALT levels increase to $\geq 3x$ ULN and are: progressive, persistent for ≥ 4 weeks, accompanied by increased direct bilirubin, or accompanied by liver injury symptoms.
Thrombotic/Thromboembolic complications	DVT and pulmonary embolism classified as 'uncommon' (0.1–1%). Use with caution in patients with known risk factors for thromboembolism. Patients with chronic liver disease may have an increased risk of portal venous thrombosis.
Haematological concerns	Eltrombopag as a TPO-receptor agonist may increase the risk of reticulin fibers within the bone marrow. There is also a concern that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies such as MDS.

DOSING

Start with:

- 50 mg/d for most patients
- 25 mg/d for patients of East-Asian origin
- 25 mg/d for patients with hepatic impairment (Child–Pugh score ≥ 5)*

*Eltrombopag should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.

DOSE ADJUSTMENT

Goal: achieve and maintain a platelet count $\geq 50,000/\mu\text{L}$

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Platelet count	Dose adjustment or response
$< 50,000/\mu\text{L}$ following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
$\geq 50,000/\mu\text{L}$ to $\leq 150,000/\mu\text{L}$	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
$> 150,000/\mu\text{L}$ to $\leq 250,000/\mu\text{L}$	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$> 250,000/\mu\text{L}$	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $\leq 100,000/\mu\text{L}$, reinstate therapy at a daily dose reduced by 25 mg.

REGULAR MONITORING

Prior treatment Phase	Eltrombopag initiated	Dose-adjustment Phase	Stable-dose Phase
		CBC (weekly)	CBC (monthly)
Liver Function Tests*		Liver Function Tests (every 2 weeks)	Liver Function Tests (monthly)
Peripheral blood smears		Peripheral blood smears (weekly)	Peripheral blood smears (monthly)

*Liver: Serum ALT, AST and bilirubin. CBC = complete blood count including platelets and white blood cells.

Additional monitoring may be required. Refer to the eltrombopag label for more information.

FOOD INTERACTIONS

Polyvalent cation-containing antacids, dairy products (or other calcium-containing food products) and other products containing polyvalent cations, such as mineral supplements, must not be administered **4 hours before or after** taking eltrombopag.

OVERDOSE: Consider using metal cation preparation to limit absorption.

STOPPING: Platelets return to baseline within 2 weeks (consider bleeding risk); monitor platelet count weekly for 4 weeks after stopping.

Prescribing Information is available at the end of this document.

PRESCRIBING INFORMATION

REVOLADE®

Important note: Before prescribing, consult full prescribing information.

Presentation: Film-coated tablets containing eltrombopag olamine equivalent to 25 mg, or 50 mg of eltrombopag free acid.

Indications: Eltrombopag is indicated for the treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Dosage and administration: Dosing regimens must be individualized based on the patient's platelet counts. **Dose regimen:** Starting dose between 25 to 50 mg once daily. Monitoring and individual dose adjustment. Maintenance doses with maximum daily doses between 75 to 150 mg depending on patient population and indication.

Special populations: Elderly: No clinically significant differences in safety. Renal impairment: Caution and close monitoring recommended. Hepatic impairment: Caution and close monitoring, starting dose 25 mg once daily.

Contraindications: None.

Warnings and precautions: Hepatic monitoring. Hepatic decompensation. Close monitoring for signs and symptoms of hepatic decompensation. Thrombotic/thromboembolic complications: Use with caution in patients with known risk factors for thromboembolism. Monitoring of platelet counts and potentially dose reduction or discontinuation. Increased risk for bleeding after discontinuation of treatment. Monitoring weekly for 4 weeks following discontinuation. Risk for malignancies and progression of malignancies. Patient with cataracts: Routine monitoring.

Women of child-bearing potential, pregnancy: Should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Breast-feeding: Not recommended unless the expected benefit justifies the potential risk to the infant.

Adverse drug reactions (by highest reporting frequency):

ITP study population: Very common ($\geq 10\%$): Nausea, diarrhea. **Common (1 to 10%):** Pharyngitis, urinary tract infection, dry mouth, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, alopecia, rash, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia.

ITP pediatric study population (1 to 17 years of age) – Additional ADRs: Very common ($\geq 10\%$): Nasopharyngitis, upper respiratory tract infection. **Common (1 to 10%):** Rhinitis, abdominal pain, toothache, cough, oropharyngeal pain, rhinorrhea, pyrexia.

Adverse reaction from spontaneous reports: Rare (0.01 to 0.1%): Thrombotic microangiopathy with acute renal failure.

For a complete list of ADRs, consult full prescribing information.

Novartis Page 3 BSS v1.1 16-Dec-2015 Revolade

Interactions: Rosuvastatin: Dose reduction and monitoring. Other OATP1B1 and BCRP substrates to be used with caution. Cyclosporine (BCRP inhibitor): monitoring weekly for 2 to 3 weeks, eltrombopag dose may need to be increased: Polyvalent cations (chelation): staggered administration. Food interactions. Lopinavir/ritonavir: Caution and monitoring of platelet count weekly for 2 to 3 weeks.

References

1. REVOLADE Summary of Product Characteristics. July 2012.
2. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; 357: 2237–2247.
3. Bussel JB, Provan D, Shamsi T, Cheng G, Psaila B, Kovaleva L, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 373: 641–648.
4. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377: 393–402. Erratum in *Lancet* 2011; 377: 382.
5. Bussel JB, Saleh MN, Vasey S, Mayer B, Arning M, Stone NL, et al. Repeated short-term use of eltrombopag in patients with chronic immune thrombocytopenia (ITP). *Br J Haematol* 2013; 160: 538–546.
6. Saleh MN, Cheng G, Bussel JB, Burgess P, Bakshi K, Brainsky A, et al. Long-term safety and efficacy of eltrombopag in adults with chronic immune thrombocytopenia (ITP): report of up to 5.5 years of treatment in EXTEND. *Blood* 2012; 120: Abstract 2198.
7. Saleh MN, Bussel JB, Cheng G, Meyer O, Bailey CK, Arning M, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia (ITP): results of the long-term, open-label EXTEND study. *Blood* 2013; 121: 537–545.
8. NCT01098487. A longitudinal 2-year bone marrow study of eltrombopag in previously treated adults, with chronic immune (idiopathic) thrombocytopenic purpura (ITP). Available from: <http://clinicaltrials.gov/ct2/show/NCT01098487> (Last accessed February 2012).
9. Brynes R, Orazi A, Wong RSM, Bakshi K, Bailey CK, Chan G. A longitudinal prospective study evaluating the effects of eltrombopag treatment on bone marrow in patients with chronic immune thrombocytopenia: interim analysis at 2 years. Abstract P465 from the 18th Congress of the European Hematology Association, Stockholm, Sweden, 14 June 2013.
10. NCT00643929. LENS - Long-term Eltrombopag Observational Study. Available from: <http://clinicaltrials.gov/ct2/show/NCT00643929> [Accessed June 2013].
11. Aledort LM, Hayward CP, Chen MG, Nichol JL, Bussel J. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol* 2004; 76: 205–213.
12. Bussel JB, Saleh MN, Wong R, Burgess P, et al. Update on the safety and efficacy of EXTENDED treatment with eltrombopag (EPAG) in adults with chronic immune thrombocytopenia (cITP). Poster presented at 55th Annual Meeting of the American Society of Hematology, New Orleans, USA, December 7–10 2013.
13. Bussel J, Cheng G, Saleh M, Mayer B, Vasey S, Brainsky A. Incidence of thromboembolic events across eltrombopag clinical trials in chronic immune thrombocytopenia (ITP). Presented at the 52nd Annual Meeting of the American Society of Hematology, Orlando, Florida, December 4–7 2010: Abstract 70.
14. Mufti G, Bagg A, Hasserjian R, Bain B, Kuter D, Dreiling L, et al. Bone marrow reticulin in patients with immune thrombocytopenic purpura. Presented at the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida. *Blood* 2006; 108: Abstract 3982.
15. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. *Eur J Cancer* 2006; 42: 3028–3033.
16. Saleh MN, Cheng G, Bussel J, Sun H, Mayer B, Bailey C, et al. Safety and efficacy of extended treatment with eltrombopag in adults with chronic immune thrombocytopenia (ITP) from June 2006 to February 2011. Poster presented at the 53rd Annual Meeting of the American Society of Hematology, San Diego, USA, December 10–13, 2011.
17. Williams DD, Peng B, Bailey CK, Wire MB, Deng Y, Park JW, et al. Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. *Clin Ther* 2009; 31: 764–776.

You can report any problem or adverse events through:

Novartis Consulting AG.

Saudi Arabia: P.O. Box 16032, Riyadh 11464, Tel: +966114658882

DS&E

Phone: +996112658100

Fax: +966112658107

Email: adverse.events@novartis.com

National pharmacovigilance and drug safety center.

Toll free phone: 8002490000

Fax: +966112057662

E-mail: npc.drug@sfd.gov.sa

Or by online: <https://ade.sfda.gov.sa>



REV RMP3 JAN 16/SA