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

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine. Adverse events should also be reported to Novartis Ireland by calling 01-2080612 or by email to drugsafety.dublin@novartis.com. If you use email please write “reporting of adverse event” in the mail heading.

Eltrombopag is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). This guide forms part of the risk management programme for eltrombopag and is based on the approved SmPC.
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 patients with chronic idiopathic thrombocytopenic purpura (ITP)¹

Eltrombopag is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). 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/μL).¹

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 hepatic enzyme elevations and the importance of laboratory monitoring of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, as well as the signs and symptoms associated with liver injury (e.g. jaundice). 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 Most hepatobiliary lab abnormalities were mild, reversible, and without associated symptoms of impaired liver function.
Patients receiving eltrombopag require regular monitoring of serum liver tests

<table>
<thead>
<tr>
<th>Prior to treatment</th>
<th>Therapy initiation</th>
<th>Every 2 weeks during dose adjustment phase</th>
<th>Monthly after stable dose established</th>
</tr>
</thead>
</table>

Measure serum ALT, AST and bilirubin

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:

- Progressive
- Persistent for ≥4 weeks
- Accompanied by increased direct bilirubin
- Accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

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 ITP; approximately 5% of patients with chronic ITP are reported to have experienced a TEE. 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. 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.

No relationship between thromboembolic events and elevated platelet counts has been observed. The risk of TEEs has been found to be increased in thrombocytopenic patients (platelet count <50,000/μL) with chronic liver disease (CLD), without concomitant ITP. 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. 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. After initiating the dose of eltrombopag in patients with hepatic impairment, wait 3 weeks before increasing the dose.

**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. No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥200,000/μL. Physicians considering prescribing eltrombopag to patients presenting with these risk factors should weigh 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. Thereafter it should be monitored monthly. The eltrombopag dose should be reduced if the platelet count rises above 150,000/μL, or discontinued if it rises above 250,000/μL. The risk–benefit balance should be considered in patients at risk of TEEs of any aetiology.

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. **Patient overdose**
2. **Consider administering metal cation preparation* orally to limit absorption**
3. **Closely monitor patient platelet counts**
4. **Reinitiate treatment in line with eltrombopag administration guidelines**

* 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. 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.

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.

Patients should be educated about the potential for bone marrow reticulin fibre formation.

Patients receiving eltrombopag require regular blood count monitoring:

<table>
<thead>
<tr>
<th>Prior to treatment</th>
<th>Therapy initiation</th>
<th>Monthly after stable dose established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examine peripheral blood smear closely to establish baseline level of cellular morphological abnormalities</td>
<td>Perform complete blood count with white blood cell count differentials</td>
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</table>

If immature or dyplastic 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.
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). Studies have shown that patients with autoimmune disorders, including ITP, have a significantly increased risk of developing haematological malignancies irrespective of treatment. Expand on theoretical risk

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.

Eltrombopag should not be used outside the context of its license unless in a clinical trial setting. Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.

5. POST THERAPY THROMBOCYTOPENIA

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 educated about the potential risk of bleeding after treatment has stopped. 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.
Other considerations

Are there any dose adjustment recommendations for specific populations?\(^1\)

In paediatric ITP patients aged 1 to 5 years, the recommended starting dose of eltrombopag is 25 mg once daily. In paediatric ITP patients aged 6 to 17 years, the recommended starting dose of eltrombopag is 50 mg once daily.

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, Korean, or Thai) compared with non-East Asian (predominantly Caucasian) patients. Therefore, a lower starting dose of 25 mg once daily should be considered for these patients, regardless of age. 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/μL following at least 2 weeks of therapy.

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.

Who is not suitable for eltrombopag therapy?\(^1\)

Eltrombopag is not recommended for use in infants less than 1 year of age. Patients with hypersensitivity to eltrombopag or any of the incipients should not take eltrombopag. 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?

Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation.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.8 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.8

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
- **Ciclosporin:** co-administration of eltrombopag may decrease eltrombopag exposure. Eltrombopag dose adjustment is permitted, but platelet count should be closely monitored
- **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

Note: This is not an exhaustive list of drug considerations. Please refer to the Summary of Product Characteristics for full information on drug interactions.

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 ≥50,000/μL as necessary to reduce the risk for bleeding. The eltrombopag dose should be reduced if the platelet count rises above 150,000/μL or discontinued if it rises above 250,000/μL. 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.
ELTROMBOPAG - SAFETY MANAGEMENT ESSENTIALS¹

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

INDICATION

Eltrombopag is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

SAFETY INFORMATION

<table>
<thead>
<tr>
<th>Hepatotoxicity</th>
<th>Increases in ALT, AST and bilirubin classified as ‘common’ (1–10%). Discontinue eltrombopag if ALT levels increase to ≥3x ULN and are: progressive, persistent for ≥4 weeks, accompanied by increased direct bilirubin, or accompanied by liver injury symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic/Thromboembolic complications</td>
<td>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.</td>
</tr>
<tr>
<td>Haematological concerns</td>
<td>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.</td>
</tr>
</tbody>
</table>

DOSING

Start with: 50 mg/d for most patients aged 6 years and above
25 mg/d for patients aged 1 to 5 years
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 ≥50,000/μL

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

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Dose adjustment or response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50,000/μL following at least 2 weeks of therapy</td>
<td>Increase daily dose by 25 mg to a maximum of 75 mg/day.^</td>
</tr>
<tr>
<td>≥50,000/μL to ≤150,000/μL</td>
<td>Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.</td>
</tr>
<tr>
<td>&gt;150,000/μL to ≤250,000/μL</td>
<td>Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.*</td>
</tr>
<tr>
<td>&gt;250,000/μL</td>
<td>Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤100,000/μL, reinitiate therapy at a daily dose reduced by 25 mg.</td>
</tr>
</tbody>
</table>

^For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
*For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

REGULAR MONITORING

<table>
<thead>
<tr>
<th>Prior treatment Phase</th>
<th>Dose-adjustment Phase</th>
<th>Stable-dose Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eltrombopag initiated</td>
<td></td>
</tr>
<tr>
<td>CBC (weekly)</td>
<td>Liver Function Tests (every 2 weeks)</td>
<td>Liver Function Tests (monthly)</td>
</tr>
<tr>
<td>Liver Function Tests*</td>
<td>Peripheral blood smears (weekly)</td>
<td>Peripheral blood smears (monthly)</td>
</tr>
</tbody>
</table>

*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

Eltrombopag must be administered at least 2 hours before or 4 hours after polyvalent cation-containing antacids, dairy products (or other calcium-containing food products) and other products containing polyvalent cations, such as mineral supplements.

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.

Please see the Important Safety Information on the next page and the accompanying SmPC.
References


