141.0 mm

206.0 mm

# ELTROM Tablet

(Eltrombopag)

# الٹروم ٹیبلیٹ

(الٹرومبوپیگ)

**COMPOSITION**

**Eltrom Tablet 25mg**

Each film coated tablet contains:

Eltrombopag as olamine.....25mg

**(Innovator's Specifications)**

**Eltrom Tablet 50mg**

Each film coated tablet contains:

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**(Innovator's Specifications)**

**DESCRIPTION**

Eltrom tablets contain eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production. It is used to treat thrombocytopenia or aplastic anemia associated with various etiologies.

**MECHANISM OF ACTION**

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 signaling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

**INDICATIONS**

Eltrom is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Eltrom is indicated for the treatment of pediatric 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).

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

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

Eltrom should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.

Eltrom should not be used in an attempt to normalize platelet counts.

**DOSAGE & ADMINISTRATION**

Eltrombopag treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of hematological diseases or the management of chronic hepatitis C and its complications.

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalize platelet counts.

**I. Immune (primary) thrombocytopenia**

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥50,000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

***Adults and paediatric population aged 6 to 17 years***

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily.

***Paediatric population aged 1 to 5 years***

The recommended starting dose of eltrombopag is 25 mg once daily.

***Monitoring and dose adjustment***

After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

Clinical hematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table A. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

**Table A. Dose adjustments of eltrombopag in ITP patients**

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

* 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.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

***Discontinuation***

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of eltrombopag therapy at 75 mg once daily. Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment.

**II. Chronic hepatitis C (HCV) associated thrombocytopenia**

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective co-administered medicinal products for comprehensive details of relevant safety information or contraindications. In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts >75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

***Initial dose regimen***

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment.

***Monitoring and dose adjustment***

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided.

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peg interferon due to decreasing platelet counts that may put patients at risk of bleeding. Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs (full blood counts) including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

**Table B. Dose adjustments of eltrombopag in HCV patients during antiviral therapy**

| Platelet count | Dose adjustment or response |
|---|---|
| <50,000/µl following at least 2 weeks of therapy | Increase daily dose by 25 mg to a maximum of 100 mg/day. |
| ≥50,000/µl to ≤100,000/µl | Use lowest dose of eltrombopag as necessary to avoid dose reductions of peg interferon. |
| >100,000/µl to ≤150,000/µl | Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| >150,000/µl | Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly.<br>Once the platelet count is ≤100,000/µl, reinitiate therapy at a daily dose reduced by 25mg*. |

* For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

◆ on initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

***Discontinuation***

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued. Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

**III. Severe aplastic anaemia**

Initial dose regimen

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

***Monitoring and dose adjustment***

Hematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag. The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50,000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table C.

**Table C. Dose adjustments of eltrombopag in patients with severe aplastic anaemia**

| Platelet count | Dose adjustment or response |
|---|---|
| <50,000/µl following at least 2 weeks of therapy | Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg. |
| ≥50,000/µl to ≤150,000/µl | Use lowest dose of eltrombopag to maintain platelet counts. |
| >150,000/µl to ≤250,000/µl | Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| >250,000/µl | Stop eltrombopag; for at least one week. Once the platelet count is ≤100,000/µl, reinitiate therapy at a daily dosereduced by 50 mg. |

*Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders*
For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.
If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to <30,000/µl, haemoglobin drops to < 9 g/dl or absolute neutrophil count (ANC) <0.5 x 109/l, eltrombopag may be reinitiated at the previous effective dose

***Discontinuation***
If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate. Excessive platelet count responses (as outlined in Table C) or important liver test abnormalities also necessitate discontinuation of eltrombopag.

**Special populations**
**Renal impairment**
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.

***Hepatic impairment***
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 must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.
No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.
There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events (TEEs), in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

**Elderly**
There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between patients aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients.

***East-/Southeast-Asian patients***
For adult and paediatric patients of East-/Southeast-Asian ancestry, including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily.
Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

***Paediatric population***
Eltrombopag is not recommended for use in children under the age of one year with ITP due to insufficient data on safety and efficacy. The safety and efficacy of eltrombopag has not been established in children and adolescents (<18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

**Method of administration**
Oral use.
The tablets should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminum, selenium and zinc).

**PHARMACOKINETICS**
**Absorption:**
Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg solution dose was estimated to be at least 52%. In a clinical study, administration of a single 75 mg-dose of eltrombopag with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) decreased plasma eltrombopag AUC0-∞ and Cmax by 70%. The contribution of sodium alginate to this interaction is not known [see Drug Interactions (7.4)]. An open-label, randomized, crossover study was conducted to assess the effect of food on the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma eltrombopag AUC0-∞ by approximately 59% and Cmax by 65% and delayed tmax by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

**Distribution:**
The concentration of eltrombopag in blood cells is approximately 50-79% of plasma concentrations based on a radiolabel study. In vitro studies suggest that eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is not a substrate for p glycoprotein (Pgp) or OATP1B1.

**Metabolism:**
Absorbed eltrombopag is extensively metabolized, predominately through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon AUC0-∞. Metabolites due to glucuronidation and oxidation were also detected. In vitro studies suggest that CYP 1A2 and 2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

**Elimination:**
The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26- 35 hours in ITP patients.

**WARNINGS AND PRECAUTIONS**
There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤35 g/l or model for end stage liver disease (MELD) score ≥10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤35g/l) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.
Combination with direct-acting antiviral agents Safety and efficacy have not been established in combination with direct-acting antiviral agents approved for treatment of chronic hepatitis C infection.

**Risk of hepatotoxicity**
Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening.

Serum alanine aminotransferase (ALT), aspartate aminotrasferase (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. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (3 times the upper limit of normal [x ULN] in patients with normal liver function, or ≥3 x baseline or >5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

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

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment.
Hepatic decompensation (use with interferon) Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤35 g/l) or with MELD score ≥10 at baseline.
Chronic HCV patients with liver cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In two controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) occurred more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/l) or with a MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤35 g/l) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

**Thrombotic/thromboembolic complications**
In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1 439), 38 out of 955 patients (4%) treated with eltrombopag and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus 200 000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures. In eltrombopag clinical studies in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but 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. 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 (see section 4.2). The risk-benefit balance should be considered in patients at risk of TEEs of any aetiology. No case of TEE was identified from a clinical study in refractory SAA, however the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population. 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. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment.

**Bleeding following discontinuation of eltrombopag**

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk 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. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag. In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding

**Bone marrow reticulin formation and risk of bone marrow fibrosis**

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet. Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

**Progression of existing myelodysplastic syndrome (MDS)**

There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. In clinical studies with a TPO-R 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. 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. The effectiveness and safety of Eltrombopag have not been established for the treatment of thrombocytopenia due to MDS. Eltrombopag should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

**Cytogenetic abnormalities and progression to MDS/AML in patients with SAA**

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months. In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6. In clinical studies with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment. For SAA patients 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.

**Ocular changes**

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1 439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

**QT/QTc prolongation**

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

**Loss of response to eltrombopag**

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

**Paediatric population**

The above warnings and precautions for ITP also apply to the paediatric population.

Interference with laboratory tests

Eltrombopag is highly coloured and so has the potential to interfere with some laboratory tests. Serum discolouration and interference with total bilirubin and creatinine testing have been reported in patients taking Eltrombopag. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

**Pregnancy**

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Eltrombopag is not recommended during pregnancy and in women of childbearing potential not using contraception.

**Breast-feeding**

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Eltrombopag therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**SIDE EFFECTS**

| system organ class | Frequency | Adverse reaction |
|---|---|---|
| Infections and infestations | Very common | Nasopharyngitis, upper respiratory tract infection |
| | Common | Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis |
| | Uncommon | Skin infection |
| Neoplasms benign, malignant & unspecified (incl cysts and polyps) | Uncommon | Rectosigmoid cancer |
| Blood and lymphatic system disorders | Common | Anaemia, eosinophilia, leukocytosis, thrombocytopenia, haemoglobin decreased, white blood cell count decreased |
| | Uncommon | Anisocytosis, haemolytic anaemia, myelocytosis, band neutrophil count increased, myelocyte present, platelet count increased, haemoglobin increased |
| Immune system disorders | Uncommon | Hypersensitivity |
| Metabolism and nutrition disorders | Common | Hypokalaemia, decreased appetite, blood uric acid increased |
| | Uncommon | Anorexia, gout, hypocalcaemia |
| Psychiatric disorders | Common | Sleep disorder, depression |
| Nervous system disorders | Uncommon | Apathy, mood altered, tearfulness |
| | Common | Paraesthesia, hypoaesthesia, somnolence, migraine |
| | Uncommon | Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache |
| Eye disorders | Common | Dry eye, vision blurred, eye pain, visual acuity reduced |
| | Uncommon | Lenticular opacities, astigmatism, cataract cortical, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy visual impairment, visual acuity tests abnormal, blepharitis, keratoconjunctivitis sicca |
| Ear and labyrinth disorders | Common | Ear pain, vertigo |

Additional adverse reactions observed in paediatric studies (aged 1 to 17 years).

† Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

‡ Grouped term with preferred terms acute kidney injury and renal failure

**HCV study population (in combination with anti-viral interferon and ribavirin therapy)**

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Infections and infestations | Common | Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes |
| | Uncommon | Gastroenteritis, pharyngitis |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Common | Hepatic neoplasm malignant |
| Blood and lymphatic system disorders | Very common | Anaemia |
| | Common | Lymphopenia |
| | Uncommon | Haemolytic anaemia |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Common | Hyperglycaemia, abnormal loss of weight |
| Psychiatric disorders | Common | Depression, anxiety, sleep disorder |
| | Uncommon | Confusional state, agitation |
| Nervous system disorders | Very common | Headache |
| | Common | Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia |
| Eye disorders | Common | Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage |
| Ear and labyrinth disorders | Common | Vertigo |
| Cardiac disorders | Common | Palpitations |
| Respiratory, thoracic and mediastinal disorders | Very common | Cough |
| | Common | Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough |
| Gastrointestinal disorders | Very common | Nausea, diarrhoea |
| | Common | Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastroesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal |
| Hepatobiliary disorders | Common | Hyperbilirubinaemia, jaundice, drug-induced liver injury |
| | Uncommon | Portal vein thrombosis, hepatic failure |
| Skin and subcutaneous tissue disorders | Very common | Pruritus |
| | Common | Rash, dry skin, eczema, rash pruritic, erythema, hyperhidrosis, pruritus generalised, alopecia |
| | Uncommon | Skin lesion, skin discolouration, skin hyperpigmentation, night sweats |
| Musculoskeletal and connective tissue disorder | Very common | Myalgia |
| | Common | Arthralgia, muscle spasms, back pain, pain in extremity, musculoskeletal pain, bone pain |
| Renal & urinary disorders | Uncommon | Thrombotic microangiopathy with acute renal failure†, dysuria |
| General disorders & administration site conditions | Very common | Pyrexia, fatigue, influenza-like illness, asthenia, chills |
| | Common | Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, oedema peripheral |
| | Uncommon | Injection site pruritus, injection site rash, chest discomfort |
| Investigations | Common | Blood bilirubin increased, weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased |
| | Uncommon | Electrocardiogram QT prolonged |

† Grouped term with preferred terms oliguria, renal failure and renal impairment

**SAA study population**

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Blood and lymphatic system disorders | Common | Neutropenia, splenic infarction |
| Metabolism and nutrition disorders | Common | Iron overload, decreased appetite, hypoglycaemia, increased appetite |
| Psychiatric disorders | Common | Anxiety, depression |
| Nervous system disorders | Very common | Headache, dizziness |
| | Common | Syncope |
| Eye disorders | Common | Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters |
| Respiratory, thoracic and mediastinal disorders | Very common | Cough, oropharyngeal pain, rhinorrhoea |
| | Common | Epistaxis |
| Gastrointestinal disorders | Very common | Diarrhoea, nausea, gingival bleeding, abdominal pain |
| | Common | Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence |
| Hepatobiliary disorders | Very common | Transaminases increased |
| | Common | Blood bilirubin increased (hyperbilirubinemia), jaundice |
| | Not known | Drug-induced liver injury*<br>* Cases of drug-induced liver injury have been reported in patients with ITP and HCV |
| Skin and subcutaneous tissue disorders | Common | Petechiae, rash, pruritus, urticaria, skin lesion, rash macular |
| | Not known | Skin discolouration, skin hyperpigmentation |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia, pain in extremity, muscle spasms |
| | Common | Back pain, myalgia, bone pain |
| Renal and urinary disorders | Common | Chromaturia |
| General disorders and administration site conditions | Very common | Fatigue, pyrexia, chills |
| | Common | Asthenia, oedema peripheral, malaise |
| Investigations | Common | Blood creatine phosphokinase increased |

**DRUG INTERACTIONS**

**Effects of eltrombopag on other medicinal products**

***HMG CoA reductase inhibitors***

Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin. Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken.

**OATP1B1 and BCRP substrates**

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

**HCV protease inhibitors**

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

**Effects of other medicinal products on eltrombopag**

**Ciclosporin**

A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor). The co-administration of 200 mg ciclosporin decreased the Cmax and the AUC0-∞ of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the Cmax and the AUC0-∞ of eltrombopag by 39% and 24%, respectively. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count. Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

**Polyvalent cations (chelation)**

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminum, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminum hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag AUC0-∞ by 70% (90% CI: 64%, 76%) and Cmax by 70% (90% CI: 62%, 76%). 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.

**Lopinavir/ritonavir**

Co-administration of eltrombopag with Lopinavir / ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of eltrombopag with repeat dose lopinavir /ritonavir 400/100 mg twice daily resulted in a reduction in eltrombopag plasma AUC0-∞ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with Lopinavir /ritonavir takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

***CYP1A2 and CYP2C8 inhibitors and inducers***

Eltrombopag is metabolized through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3. Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations, whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

**HCV protease inhibitors**

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

**Medicinal products for treatment of ITP**

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range.

**Food interaction**

The administration of eltrombopag tablet or powder for oral suspension formulations with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag AUC0-∞ and Cmax. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [<50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent.

Food low in calcium (<50 mg calcium), including fruit, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

**OVERDOSE**

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations.

**CONTRAINDICATIONS**

Hypersensitivity to eltrombopag or to any of the excipients.

**STORAGE & INSTRUCTIONS**

Do not store above 30°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of the children.
**To be sold on the prescription of a registered medical practitioner only.**

**HOW SUPPLIED**

**Eltrom Tablet 25mg**
28 Tablets
**Eltrom Tablet 50mg**
28 Tablets

## خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

## ہدایات:

۳۰ ڈگری سینٹی گریڈ درجہ حرارت سے زیادہ پر نہ رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.

206.0 mm