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# Eltrombopag Olamine Tablets 25 mg, 50 mg

# ELTROMBO®

Eltrombopag Olamine Tablets

**Composition**

Each film coated tablet contains:
Eltrombopag Olamine
Eq. to Eltrombopag (as free acid) 25 mg
Excipients q.s
Colours: Red Oxide of Iron & Black Oxide of Iron & Titanium Dioxide IP

Each film coated Tablet contains:
Eltrombopag Olamine
Eq. to Eltrombopag (as free acid) 50 mg
Excipients q.s
Colours: Red Oxide of Iron & Black Oxide of Iron & Titanium Dioxide IP

**Pharmacological Properties**

**Pharmacodynamic properties**

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

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

**Pharmacokinetic Properties**

Pharmacokinetic

The plasma Eltrombopag concentration-time data collected in 88 patients with ITP in studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma EltrombopagAUC(0-τ) and Cmax estimates for ITP patients are presented.

**Geometric mean (95% confidence intervals) of steady-state plasma Eltrombopag**
**Pharmacokinetic parameters in adults with ITP**

| Eltrombopag dose, once daily | N | $AUC_{(0-\tau)}$* µg.h/ml | Cmax *, µg/ml |
|---|---|---|---|
| 30 mg | 28 | 47 (39, 58) | 3.78 (3.18, 4.49) |
| 50 mg | 34 | 108 (88, 134) | 8.01 (6.73, 9.53) |
| 75 mg | 26 | 168 (143, 198) | 12.7 (11.0, 14.5) |

Plasma Eltrombopag concentration-time data collected in 590 patients with HCV enrolled in phase III Studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma Eltrombopag Cmax and AUC(0-τ) estimates for patients with HCV enrolled in the phase III studies are presented for each dose studied in.

**Geometric mean (95% CI) steady-state plasma Eltrombopag pharmacokinetic**
**Parameters in patients with chronic HCV**

| Eltrombopag dose, once daily | N | $AUC_{(0-\tau)}$* µg.h/ml | Cmax a, µg/ml |
|---|---|---|---|
| 25 mg | 330 | 118 (109, 128) | 6.40(5.97, 6.86) |
| 50 mg | 119 | 166 (143, 192) | 9.08(7.96, 10.35) |
| 75 mg | 45 | 301 (250, 363) | 16.71 (14.26, 19.58) |
| 100 mg | 96 | 354 (304, 411) | 19.19 (16.81, 21.91) |

Data presented as geometric mean (95% CI).
AUC (0-τ) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of Eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces Eltrombopag exposure . In a relative bioavailability study in adults, the Eltrombopag powder for oral suspension delivered 22% higher plasma AUC (0-τ) than the film-coated tablet formulation. The absolute oral bioavailability of Eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg Eltrombopag solution dose was estimated to be at least 52%.

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, Eltrombopag accounted for approximately 64% of plasma radiocarbon AUC0-∞. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of Eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed Eltrombopag is extensively metabolised. The predominant route of Eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (Eltrombopag) is not detected in urine. Unchanged Eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of Eltrombopag is approximately 21-32 hours.

**Therapeutic indications**

Eltrombopag is indicated for the treatment of 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. orticosteroids, immunoglobulins) .
Eltrombopag 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 .
Eltrombopag 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 .

**DOSAGE AND ADMINISTRATION:**

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

**Immune (primary) thrombocytopenia:** Initiate Eltrombopag at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East-/Southeast Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 000/µl. Do not exceed 75 mg per day.

**Chronic Hepatitis C-associated Thrombocytopenia**: Initiate Eltrombopag at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg.

**Severe Aplastic Anemia**: Initiate Eltrombopag at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than 50 000/µl. Do not exceed 150 mg per day. The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Method of administration

Oral use

Eltrombopag 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, aluminium, selenium and zinc) .

**Contraindications**

Hypersensitivity to Eltrombopag or to any of the excipients .

**Specialwarningsandprecautionsforuse**

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 ≤35 g/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 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 <1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.
The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg Eltrombopag once daily for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving Eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with Eltrombopag experienced the thrombotic complication at a platelet count >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 . 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 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. 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.

**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.
In the clinical studies there was one report of overdose where the patient ingested 5000 mg of Eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on Day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.
Because Eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of Eltrombopag

**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 OATP1B1and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin Cmax 103% (90% confidence interval [CI]: 82%, 126%) and AUC0-∞ 55% (90% CI: 42%, 69%). 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 .

*Cytochrome P450 substrates*
In studies utilising human liver microsomes, Eltrombopag (up to 100 µM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of Eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when Eltrombopag and CYP450 substrates are co-administered .

*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. Co-administration of a single dose of Eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir AUC(0-∞), but increased Cmax by 20%, and decreased Cmin by 32%. The clinical relevance of the decrease in Cmin has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

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 Cmaxand 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 (see section 4.2). 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, aluminium, selenium and zinc. Administration of a single dose of Eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium 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 metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). 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 highcalcium 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 highcalcium meal or with low-calcium food [<50 mg calcium] did not alter plasma Eltrombopag exposure to a clinically significant extent.
Administration of a single 50 mg dose of Eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma Eltrombopag mean AUC0-∞ by 59% and mean Cmaxby 65%.
Administration of a single 25 mg dose of Eltrombopag as powder for oral suspension with a highcalcium, moderate-fat and moderate-calorie meal reduced plasma Eltrombopag mean AUC0-∞ by 75% and mean Cmaxby 79%. This decrease of exposure was attenuated when a single 25 mg dose of Eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean AUC0-∞ was decreased by 20% and mean Cmax by 14%).
Food low in calcium (<50 mg calcium), including fruit, lean ham, 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.

**HOW SUPPLIED / STORAGE AND HANDLING**
**Storage: Store below 30°C.**

**Presentation:** Per bottle 28 Tablets

PMA0005215-00

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