Olapag-25

Eltrombopag Olamine INN 25 mg Tablet

Composition: Each Film Coated Tablet Contains Eltrombopag 25 mg (as Eltrombopag Olamine INN).

Pharmacology: Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Treatment with Eltrombopag resulted in dose-dependent increases in platelet counts following repeated (daily) dosing. The increase in platelet counts reached a maximum approximately two weeks after the initiation of dosing, and returned to baseline within approximately two weeks after the last dose of Eltrombopag. Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Oral absorption of drug-related material following administration of a single 75-mg solution dose was estimated to be at least 52%. The concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. Eltrombopag is highly bound to human plasma proteins (greater than 99%). Absorbed eltrombopag is extensively metabolized, predominantly through pathways, including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine.The plasma elimination half-life of Eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in patients with ITP.

Indications: Treatment of Thrombocytopenia in Patients With Persistent or Chronic Immune Thrombocytopenia: Eltrombopag is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. **Treatment of Thrombocytopenia in Patients With Hepatitis C Infection:** Eltrombopag is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Eltrombopag should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. **Treatment of Severe Aplastic Anemia:** Eltrombopag is indicated in combination with standard immunosuppressive therapy (IST) for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia. Eltrombopag is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Dosage & administration: Chronic Immune Thrombocytopenia: Use the lowest dose of Eltrombopag to achieve and maintain a platelet count greater than or equal to 50 x 109/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use Eltrombopag to normalize platelet counts (see Warnings and Precautions). In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting Eltrombopag and decreased within 1 to 2 weeks after discontinuing Eltrombopag. **Initial Dose Regimen:** Adult and Pediatric Patients 6 Years and Older with ITP: Initiate Eltrombopag at a dose of 50 mg once daily, except in patients who are East-/Southeast Asian ancestry or who have mild to severe hepatic impairment (Child-Pugh Class A,B,C). For patients of East-/Southeast Asian ancestry with ITP, initiate Eltrombopag at a reduced dose of 25 mg once daily. For patients with ITP and mild, moderate, or severe hepatic impairment(Child-Pugh Class A,B,C), initiate Eltrombopag at a reduced dose of 25 mg once daily. For patients of East-/Southeast Asian ancestry with ITP and hepatic impairment(Child-Pugh Class A,B,C)., consider initiating Eltrombopag at a reduced dose of 12.5 mg once daily. **Pediatric Patients with ITP Aged 1 to 5 Years:** Initiate Eltrombopag at a dose of 25 mg once daily.

Dose Adjustments of Eltrombopag in Patients With Persistent or Chronic Immune Thrombocytopenia:

Platelet Count Result	Dose Adjustment or Response
< 50 x 109/L following at least 2 weeks of Eltrombopag	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥ 200 x 109/L to ≤ 400 x 109/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
> 400 x 109/L	Stop Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 x 109/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at adaily dose of 12.5 mg.
> 400 x 109/L after 2 weeks of therapy at lowest dose of Eltrombopag	Discontinue Eltrombopag.

In patients with ITP and hepatic impairment (Child-Pugh Class A, B, C), after initiating Eltrombopag. or after any subsequent dosing increase, wait 3 weeks before increasing the dose.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with Eltrombopag.Do not administer more than one dose of Eltrombopag. within any 24-hour period.

Discontinuation: Discontinue Eltrombopag. if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with Eltrombopag. at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined. Important liver test abnormalities also necessitate discontinuation of Eltrombopag (see Warnings and Precautions) . Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of Eltrombopag.

Chronic Hepatitis C-Associated Thrombocytopenia: Use the lowest dose of Eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. **Initial Dose Regimen:** Initiate Eltrombopag at a dose of 25 mg once daily. **Monitoring and Dose Adjustment:** Adjust the dose of Eltrombopag in 25-mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy .

During antiviral therapy: adjust the dose of Eltrombopag to avoid dose reductions of peginterferon. Monitor CBCs with differentials, including platelet counts, weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with Eltrombopag. For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Dose Adjustments of Eltrombopag in Adults With Thrombocytopenia Due to Chronic Hepatitis C:

Platelet count result	Dose adjustment or response
< 50x 10^9 /L following at least 2 weeks of Eltrombopag	Incresae daily dose by 25mg to a maximum of 75mg/day.
≥200 x 10^9 /L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequentdose adjustments.
>400 x 10^9 /L	Stop Eltrombopag increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 x 109/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
>400 x 10^9 /L after 2 weeks of therapy at lowest dose of Eltrombopag.	Discontinue Eltrombopag.

Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility. Eltrombopag should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined. Important liver test abnormalities also necessitate discontinuation of Eltrombopag.

Severe Aplastic Anemia: First-Line Severe Aplastic Anemia: Initiate Eltrombopag concurrently with standard immunosuppressive therapy. Recommended Initial dose Regimen of Eltrombopag . Recommended Initial Eltrombopag Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia:

Age	Dose Regimen
Patients 12 years and older	150 mg once daily for 6 months
pediatric Patients 6 to 11 years	75 mg once daily for 6 months
pediatric Patients 2 to 5 years	2.5 mg/kg once daily for 6 months

For patients with severe aplastic anemia of East-/Southeast-Asian ancestry or those with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), decrease the initial Eltrombopag dose by 50% as listed .If baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST).

Recommended Initial Eltrombopag Dose Regimen for Patients of East-/Southeast-Asian Ancestry or Those With Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh Class A, B, C) in the First-Line Treatment of Severe Aplastic Anemia:

Age	Dose Regimen
Patients 12 years and older	75 mg once daily for 6 months
Pediatric patients 6 to 11 years	37.5 mg once daily for 6 months
Pediatric patients 2 to 5 years	1.25 mg/kg once daily for 6 months

Monitoring and Dose Adjustment for Eltrombopag: Perform clinical hematology and liver tests regularly throughout therapy with Eltrombopag (see Warnings and Precautions) Modify the dosage regimen of Eltrombopag based on platelet counts:

Dose Adjustments of Eltrombopag for Elevated Platelet Counts in the First-Line Treatment of Severe Aplastic Anemia:

Platelet Count Result	Dose Adjustment or Response
> 200 x 109/L to ≤ 400 x 109/L	Decrease the daily dose by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥ 50 x 109/L. In pediatric patients under 12 years of age, decrease the dose by 12.5 mg.
> 400 x 109/L	Discontinue Eltrombopag for one week. Once the platelet count is < 200 x 109/L, reinitiate Eltrombopag at a daily dose reduced by 25 mg (or 12.5 mg in pediatric patients under 12 years of age).

Refractory 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 x 109/L. Do not exceed 150 mg per day. **Dose Adjustments of Eltrombopag in Patients With Refractory Severe Aplastic Anemia:**

Platelet Count Result	Dose Adjustment or Response
< 50 x 109/L following at least 2 weeks of Eltrombopag.	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.
≥ 200 x 109/L to ≤ 400 x 109/L at any time.	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400 x 109/L	Stop Eltrombopag for 1 week. Once the platelet count is < 150 x 109/L, reinitiate therapy at a dose reduced by 50 mg.
> 400 x 109/L after 2 weeks of therapy at lowest dose of Eltrombopag	Discontinue Eltrombopag

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 discontinue Eltrombopag and monitor blood counts. If platelet counts drop to less than 30 x 109/L, hemoglobin to less than 9 g/dL, or absolute neutrophil count (ANC) to less than 0.5 x 109/L, Eltrombopag may be reinitiated at the previous effective dose.

Discontinuation: If no hematologic response has occurred after 16 weeks of therapy with Eltrombopag discontinue therapy. If new cytogenetic abnormalities are observed, consider discontinuation of Eltrombopag. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation of Eltrombopag [see Warnings and Precautions].

Or as directed by the registered physician.

Contraindication: It is contraindicated in patients with hypersensitivity to Eltrombopag or any component of the product.

Precautions: In patients with chronic hepatitis C, Eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation. It may increase the risk of severe and potentially life-threatening hepatotoxicity. Thrombotic/thromboembolic complications may result from increases in platelet counts with Eltrombopag. The dose adjustment guidelines should be followed to achieve and maintain target platelet counts. A baseline ocular examination should be performed prior to administration of Eltrombopag and, during therapy, patients should be regularly monitored for signs and symptoms of cataracts.

Side effects: The most common adverse reactions are nausea, diarrhea, upper respiratory tract infection, vomiting, urinary tract infection, myalgia, oropharyngeal pain, increased AST, pharyngitis, back pain, influenza, paresthesia, rash etc.

Use in Pregnancy and Lactation: There are no adequate and well-controlled studies in pregnant women. Nursing Mother: Women should be advised not to breastfeed during treatment with Eltrombopag

Use in Child: There is no data available.

Drug Interactions: Polyvalent Cations (Chelation): Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids.Take Eltrombopag at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, dairy products, and mineral supplements to avoid significant reduction in absorption of Eltrombopag due to chelation. Transporters: Use caution when concomitantly administering Eltrombopag and drugs that are substrates of OATP1B1 (e.g.,atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38 [active metabolite of irinotecan], valsartan) or breast cancer resistance protein (BCRP) (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with Eltrombopag, a dose reduction of rosuvastatin by 50% was recommended.Protease Inhibitors: HIV Protease Inhibitors: No dose adjustment is recommended when Eltrombopag is coadministered with Lopinavir/Ritonavir (LPV/RTV). Drug interactions with other HIV protease inhibitors have not been evaluated. Hepatitis C Virus (HCV) Protease Inhibitors: No dose adjustments are recommended when Eltrombopag is coadministered with Boceprevir or Telaprevir. Drug interactions with other hepatitis C Virus (HCV) protease inhibitors have not been evaluated .Peginterferon Alfa-2A/b Therapy: No dose adjustments are recommended when Eltrombopag is coadministered with peginterferon alfa-2a or -2b

Overdose: In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. The patient also experienced rash, bradycardia, ALT/AST elevations and fatigue. The patient was treated with gastric lavage, oral Lactulose, Intravenous fluids, Omeprazole, Atropine, Furosemide, Calcium, Dexamethasone and Plasmapheresis; however, the abnormal platelet count and liver test abnormalities persisted for 3 weeks. After 2 months follow-up, all events had resolved without sequelae. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as Calcium, Aluminum, or Magnesium preparations to chelate Eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with Eltrombopag in accordance with dosing and administration recommendations.

Storage: Store below 30°C in a dry place.

Packing: Each box contains 28 tablets in blister pack.

Manufactured by
DRUG INTERNATIONAL LTD.
Tongi, Gazipur, Bangladesh