Elbonix
Eltrombopag

COMPOSITION
Elbonix 25 tablet : Each film coated tablet contains Eltrombopag Olamine INN equivalent to Eltrombopag 25 mg.
Elbonix 50 tablet : Each film coated tablet contains Eltrombopag Olamine INN equivalent to Eltrombopag 50 mg.

Therapeutic class: Hematopoietic Agent

PHARMACOLOGICAL ACTION

Mechanism of Action
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.

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%.

Distribution: The concentration of Eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. In vitro studies suggest that Eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

Metabolism: Absorbed Eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation and conjugation with Glucuronic acid, Glutathione or Cysteine. In vitro studies suggest that CYP1A2 and CYP2C8 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 to 35 hours in patients with ITP.

DOSAGE AND ADMINISTRATION
Recommended Dosage

Chronic Immune (Idiopathic) Thrombocytopenia

Use the lowest dose of Eltrombopag to achieve and maintain a platelet count greater than or equal to 50 x 10^9/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. 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 of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C). For patients of East 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 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.
Monitoring and Dose Adjustment: After initiating Eltrombopag, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with Eltrombopag and modify the dosage regimen of Eltrombopag based on platelet counts as outlined in Table 1. During therapy with Eltrombopag, assess CBCs with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.
When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks and then follow standard monthly monitoring.

Table 1. Dose Adjustments of Eltrombopag in Patients with Chronic Immune (Idiopathic) Thrombocytopenia

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/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 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 subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
>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

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 in Table 1, or important liver test abnormalities also necessitate discontinuation of Eltrombopag. 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. Dose adjustments are based upon the platelet count response. Do not use Eltrombopag to normalize platelet counts. In clinical trials, platelet counts generally began to rise within the first week of treatment with Eltrombopag.

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.

Table 2. Dose Adjustments of Eltrombopag in Adults with Thrombocytopenia due to Chronic Hepatitis C

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of Eltrombopag	Increase daily dose by 25 mg to a maximum of 100 mg/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 subsequent dose adjustments.
>400 x 10^9/L	Stop Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/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 in Table 2 or important liver test abnormalities also necessitate discontinuation of Eltrombopag.

Severe Aplastic Anemia

Use the lowest dose of Eltrombopag to achieve and maintain a hematologic response. Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg and may take up to 16 weeks after starting Eltrombopag.

Initial Dose Regimen: Initiate Eltrombopag at a dose of 50 mg once daily.

For patients with severe aplastic anemia of East Asian ancestry or those with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, C), initiate Eltrombopag at a reduced dose of 25 mg once daily.

Monitoring and Dose Adjustment: Adjust the dose of Eltrombopag in 50-mg increments every 2 weeks as necessary to achieve the target platelet count greater than or equal to 50 x 10^9/L as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with Eltrombopag and modify the dosage regimen of Eltrombopag based on platelet counts as outlined in Table 3.

Table 3. Dose Adjustments of Eltrombopag in Patients with Severe Aplastic Anemia

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/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 10^9/L to ≤400 x 10^9/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 10^9/L	Stop Eltrombopag for 1 week. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
>400 x 10^9/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 10^9/L, hemoglobin to less than 9 gm/dl or ANC to less than 0.5 x 10^9/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 (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of Eltrombopag.

Use in Specific Populations
Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of Eltrombopag use in pregnancy. In animal reproduction and developmental toxicity studies, there was evidence of embryolethality and reduced fetal weights at maternally toxic doses. Eltrombopag should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether Eltrombopag is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Eltrombopag, a decision should be made whether to discontinue nursing or to discontinue Eltrombopag taking into account the importance of Eltrombopag to the mother.

Pediatric Use: The safety and efficacy of Eltrombopag in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled. The pharmacokinetics of Eltrombopag has been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily for dosing recommendations for pediatric patients 1 year and older. The safety and efficacy of Eltrombopag in pediatric patients younger than 1 year with ITP have not yet been established.

The safety and efficacy of Eltrombopag in pediatric patients with thrombocytopenia associated with chronic hepatitis C and severe aplastic anemia have not been established.

Geriatric Use: Of the 106 patients in two randomized clinical trials of Eltrombopag 50 mg in chronic ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. In the two randomized clinical trials of Eltrombopag in patients with chronic hepatitis C and thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients in the placebo-controlled trials, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment: Hepatic impairment influences the exposure of Eltrombopag. Reduce the initial dose of Eltrombopag in patients with chronic ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia who also have hepatic impairment (Child-Pugh Class A, B, C). No dosage adjustment is necessary for patients with chronic hepatitis C and hepatic impairment.

Renal Impairment: No adjustment in the initial dose of Eltrombopag is needed for patients with renal impairment. Closely monitor patients with impaired renal function when administering Eltrombopag.

Ethnicity: Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit higher Eltrombopag exposures. A reduction in the initial dose of Eltrombopag is recommended for patients of East Asian ancestry with ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia. No dose reduction is needed in patients of East Asian ethnicity with chronic hepatitis C.

Warnings and Precautions

Hepatotoxicity: Monitor liver function before and during therapy.

Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving Eltrombopag. Monitor platelet counts regularly.

Side Effects
The most common side effects of Eltrombopag in adults when used to treat chronic ITP are: In adult patients with ITP, the most common adverse reactions (greater than or equal to 5% and greater than placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia and urinary tract infection.

In pediatric patients age 1 year and older with ITP, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were upper respiratory tract infection and nasopharyngitis.

In patients with chronic hepatitis C-associated thrombocytopenia, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were: anemia, pyrexia, fatigue, headache, nausea, diarrhea, decreased appetite, influenza-like illness, asthenia, insomnia, cough, pruritus, chills, myalgia, alopecia and peripheral edema.

In patients with severe aplastic anemia, the most common adverse reactions (greater than or equal to 20%) were: nausea, fatigue, cough, diarrhea and headache.

Contraindications
There is no contraindications for Eltrombopag

Drug interactions
Take Eltrombopag at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, calcium-rich foods and mineral supplements.

Overdosage
In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications.

In one report, a subject who ingested 5,000 mg of Eltrombopag had a platelet count increase to a maximum of 929 x 10^9/L at 13 days following the ingestion. 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.

PHARMACEUTICAL INFORMATION
Storage condition
Store in a cool and dry place, away from light and moisture. Keep out of the reach of children.

Presentation & Packaging
Elbonix 25 Tablet: Each commercial box contains 28 tablets in Alu-Alu blister pack.
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Manufactured By
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Only for Export

For more info:

LF21801