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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. atin. 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 AUCO-∞ of Eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg spectiver ciclosporin decreased the Cmax and the AUCO-∞ 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 AUCO-∞ 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 in40 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 AUCO-∞ 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 inhibitor 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 AUCO-∞ and Cmax. In contrast, the administration of Eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food 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 Eltropag and thus limit absorption. Platelet counts should be closely monitored. Treatment with Eltropag should be reinitiated in accordance with dosing and administration recommendations.

PRESENTATION

Eltropag 25mg & 50mg Tablet available in blister pack of 10's , 20's & 30's

DOSAGE:

As directed by the physician.

Instructions:

Store at 25°C, (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات :
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔ (درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art No. 1580

Eltropag

(Eltrombopag)

25mg & 50mg Tablets

ایلٹروپیگ

(ایلٹرومبوپیگ)

۲۵ ملی گرام اور ۵۰ ملی گرام گولیاں

COMPOSITION:

Eltropag Tablet 25mg
Each film coated tablet contains:
Eltrombopag as Olamine 25mg

Eltropag Tablet 50mg
Each film coated tablet contains:
Eltrombopag as Olamine 50mg

WARNING: RISK FOR HEPATOTOXICITY

Eltropag may cause hepatotoxicity:
- Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin prior to initiation of ELTROPAG, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation.
- Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.
- Discontinue Eltropag if ALT levels increase to ≥3X the upper limit of normal (ULN) 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.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Description

Eltropag 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.

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 AUCO-∞ and Cmax by 70%. The contribution of sodium alginate to this interaction is not known. An open-label, randomized, crossover study was conducted to assess the effect of food on the bioavailability of Eltropag. A standard high-fat breakfast significantly decreased plasma Eltrombopag AUCO-∞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.

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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 Eltropag 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 AUCO-∞. Metabolites due to glucuronidation and oxidation were we also a detected. 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.

SPECIAL POPULATION

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.

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 ancestry, including those with hepatic impairment, Eltrombopag should be initiated ata 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 uses in children under the age of one year with ITP IT 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.

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THERAPEUTIC INDICATIONS

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

Eltropag 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. Eltropag 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.

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

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

DOSAGE & ADMINISTRATION

Monitor liver tests (ALT, AST, and bilirubin) and complete blood counts (CBCs), including platelet counts and peripheral blood smears, prior to initiation of Eltropag and throughout therapy with Eltropag. If bilirubin is elevated, perform fractionation. Monitor CBCs, including platelet counts, for at least 4 weeks following discontinuation of Eltropag [see Warnings and Precautions]. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting Eltropag and decreased within 1 to 2 weeks after discontinuing Eltropag.

Use the lowest dose of Eltropag to achieve and maintain a platelet count ≥ 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 ELTROPAG in an attempt to normalize platelet counts [see Warnings and Precautions].Take Eltropag on an empty stomach (1 hour before or 2 hours after a meal). Allow at least a 4-hour interval between Eltropag and other medications (e.g., antacids), calcium-rich foods (e.g., diary products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

Initial Dose Regimen

Initiate Eltropag at a dose of 50 mg once daily except in patients who are of East Asian ancestry or who have moderate to severe hepatic impairment.

For patients with moderate or severe hepatic impairment, initiate Eltropag at a reduced dose of 25 mg once daily.

Monitoring and Dose Adjustment

After initiating Eltropag, adjust the dose to achieve and maintain a platelet count≥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 ELTROPAG and modify the dosage regimen of ELTROPAG based on platelet counts as outlined in Table 1.

During therapy with Eltropag, assess CBCs, including platelet count and peripheral blood smears, weekly until a stable platelet count has been achieved. Obtain CBCs including platelet counts and peripheral blood smears, monthly thereafter.

Table 1. Dose Adjustments of ELTROPAG

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of ELTROPAG	Increase daily dose by 25 mg to a maximum of 75 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 ELTROPAG; 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.
>400 x 10^9/L after 2 weeks of therapy at lowest dose of ELTROPAG	Permanently discontinue ELTROPAG.

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

Discontinuation

Discontinue Eltropag if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with ELTROPAG 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 Eltropag.

METHOD OF ADMINISTRATION

For oral administration only.

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).

ADVERSE REACTIONS

The most common adverse reactions (occurring in more than 1 patient receiving ELTROPAG and at a higher rate in Eltropag versus placebo) were: nausea, vomiting, menorrhagia, myalgia, paresthesia, cataract, dyspepsia, ecchymosis, thrombocytopenia, increased ALT/AST and conjunctival hemorrhage.

CONTRAINDICATIONS

Hypersensitivity to Eltropag or to any of the excipients.

WARNING & PRECAUTIONS

- Eltropag may cause hepatotoxicity. Increases in serum aminotransferase levels and bilirubin were observed. Liver chemistries must be measured before the initiation of treatment and regularly during treatment.
- Exercise caution when administering to patients with hepatic impairment.
- Eltropag is a thrombopoietin receptor agonist and TPO-receptor agonists increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Monitor peripheral blood for signs of marrow fibrosis.
- Discontinuation may result in worsened thrombocytopenia than was present prior to therapy. Monitor weekly complete blood counts (CBCs), including platelet counts for at least 4 weeks after discontinuation.
- Excessive doses of Eltropag may increase platelet counts to a level that produces thrombotic/thromboembolic complications.
- Eltropag may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome.
- Monitor CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with Eltropag and then monthly following establishment of a stable dose of ELTROPAG.

Because of the risk for hepatotoxicity and other risks, Eltropag is available only through a restricted distribution program.

Pregnancy

There are no or limited amount of data from the use of Eltropag in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Eltropag is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether Eltropag/metabolites are excreted in human milk. Studies in animals have shown that Eltropag 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 Eltropag therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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