For use in india only

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Eltrombopag Tablets 25 mg and 50 mg

MSN **Rebopag** एम एस एन रेबोपैग

To be used as directed by the Hematologist or Doctor of Medicine or Oncologist.

PRESCRIBING INFORMATION

> **WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C and RISK OF HEPATOTOXICITY**
> - In patients with chronic hepatitis C, Eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.
> - Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

1. GENERIC NAME

Eltrombopag Tablets 25 mg and 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eltrombopag Tablets 25 mg
Each Film Coated Tablet Contains Eltrombopag Olamine Equivalent to
Eltrombopag……………..25 mg

Colours:
Titanium Dioxide IP
Ferric Oxide Yellow USP-NF
Ferric Oxide Red USP-NF

Eltrombopag Tablets 50 mg
Each Film Coated Tablet Contains Eltrombopag Olamine Equivalent to
Eltrombopag……………..50 mg

Colours:
Titanium Dioxide IP
Ferric Oxide Yellow USP-NF
FD&C Blue/Indigo Carmine Aluminum Lake

3. DOSAGE FORM AND STRENGTH

Eltrombopag is available as film coated tablets 25 mg and 50 mg.

4. CLINICAL PARTICULARS

4.1. Indications

Eltrombopag is indicated for:

1. The treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.(It should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. It should not be used in an attempt to normalize platelet counts).
2. The treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection to
a. Enable the initiation of interferon based therapy
b. Optimise interferon based therapy

4.2. Posology and Method of Administration

Chronic Immune 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.

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 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 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 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 complete blood counts (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 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 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.

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.

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.

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.

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.

Administration of Eltrombopag Tablets

Take Eltrombopag without a meal or with a meal low in calcium (≤ 50 mg). Take Eltrombopag at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (containing > 50 mg calcium e.g., dairy products, calcium-fortified juices, and certain fruits and vegetables), or supplements containing polyvalent cations such as iron, calcium, aluminium, magnesium, selenium, and zinc.
Do not split, chew, or crush tablets and mix with food or liquids.

4.3. Contraindications

Eltrombopag tablets are contraindicated in patients who are hypersensitivity to Eltrombopag or to any of the excipients.

4.4. Special Warnings and Precautions for Use

Hepatic Decompensation in Patients with Chronic Hepatitis C

In patients with chronic hepatitis C, Eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.

Hepatotoxicity

Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity.

Treatment of ITP, Chronic Hepatitis C-associated Thrombocytopenia:
Measure serum ALT, AST, and bilirubin prior to initiation of Eltrombopag, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. Eltrombopag inhibits UDP-glucuronosyl-transferase (UGT) 1A1 and organic anion-transporting polypeptide (OATP) 1B1, which may lead to indirect hyperbilirubinemia. 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 resolved or stabilized. Discontinue Eltrombopag if ALT levels increase to greater than or equal to 3 x ULN in patients with normal liver function or greater than or equal to 3 x baseline (or greater than 5 x ULN, whichever is the lower) in patients with pre-treatment elevations in transaminases and are:

- progressively increasing, or
- persistent for greater than or equal to 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

If the potential benefit for reinitiating treatment with Eltrombopag is considered to outweigh the risk for hepatotoxicity, then consider cautiously reintroducing Eltrombopag and measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur if Eltrombopag is reinitiated. If liver test abnormalities persist, worsen, or recur, then permanently discontinue Eltrombopag.

Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia

There is a theoretical concern that thrombopoietin receptor (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. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

The diagnosis of ITP 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.

Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with Eltrombopag. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism when administering Eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use Eltrombopag in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet counts.

Cataracts

Cataracts were observed in toxicology studies of Eltrombopag in rodents. Perform a baseline ocular examination prior to administration of Eltrombopag and, during therapy with Eltrombopag, regularly monitor patients for signs and symptoms of cataracts.

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.

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 patients a higher incidence of gastrointestinal bleeding, including serious and fatal cases, were observed 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 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.

QT/QTc prolongation

QTc interval prolongation has been observed in 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.

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 observed 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.

4.5. Drug Interactions

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.
The coadministration of multiple doses of Eltrombopag (75 mg once daily for 5 days) with a single dose of rosuvastatin (OATP1B1 and BCRP substrate; 10 mg) increased plasma rosuvastatin AUC_{0-INF} by 55% and C_{max} by 103%. A dose reduction of rosuvastatin by 50% is 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 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.

Cyclosporine

A decrease in Eltrombopag exposure was observed with co-administration of ciclosporin (a BCRP inhibitor). 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.

Lopinavir/ritonavir

Co-administration of Eltrombopag with lopinavir/ritonavir may cause a decrease in the concentration of Eltrombopag. 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. 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.

Medicinal products for treatment of ITP

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

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

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.

Females and Males of Reproductive Potential

Based on animal reproduction studies, Eltrombopag can cause fetal harm when administered to a pregnant woman. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Eltrombopag during treatment and for at least 7 days after stopping treatment with Eltrombopag.

Pediatric Use

The safety and efficacy of Eltrombopag have been established in pediatric patients 1 year and older with chronic ITP. Safety and efficacy in pediatric patients below the age of 1 year with ITP have not been established. Safety and efficacy in pediatric patients with thrombocytopenia associated with chronic hepatitis C has not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Hepatic Impairment

Patients with Chronic ITP and Severe Aplastic Anemia.

Reduce the initial dose of Eltrombopag in patients with chronic ITP (adult and pediatric patients 6 years and older only) or refractory severe aplastic anemia who also have hepatic impairment (Child-Pugh Class A, B, C).

Patients with Chronic Hepatitis C

No dosage adjustment is recommended in patients with chronic hepatitis C and hepatic impairment.

Ethnicity

Reduce the initial dose of Eltrombopag for patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) with ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia. No reduction in the initial dose of Eltrombopag is recommended in patients of Asian ethnicity with chronic hepatitis C.

4.7. Effects on Ability to Drive and Use Machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8. Undesirable Effects

The following clinically significant adverse reactions associated with Eltrombopag.

- Hepatic decompensation in patients with chronic Hepatitis C
- Hepatotoxicity
- Increased risk of death and progression of myelodysplastic syndromes to acute myeloid leukemia
- Thrombotic/Thromboembolic Complications
- Cataracts

The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Undesirable noticed in ITP population:

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 and 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
	Uncommon	Apathy, mood altered, tearfulness
Nervous system disorders	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
Cardiac disorders	Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged
Vascular disorders	Common	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, thrombophlebitis superficial, flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough⁺
	Common	Oropharyngeal pain, rhinorrhoea⁺
	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, diarrhoea⁺
	Common	Mouth ulceration, toothache⁺, vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in paediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	Very common	Alanine aminotransferase increased†
	Common	Aspartate aminotransferase increased†, hyperbilirubinaemia, hepatic function abnormal
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	Common	Myalgia, muscle spasm, musculoskeletal pain, bone pain, back pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡
	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Pyrexia*, chest pain, asthenia *Very common in paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn

⁺ Additional adverse reactions observed in paediatric studies (aged 1to 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

Undesirable noticed HCV 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, gastrooesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal
	Uncomon	Oesophageal varices haemorrhage, gastritis, aphthous stomatitis
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 and urinary disorders	Uncommon	Thrombotic microangiopathy with acute renal failure†, dysuria
General disorders and 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+91 40-38265227 Ext- 5295**. By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose

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

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.

5. PHARMACOLOGICAL PROPERTIES

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.

5.1 Pharmacodynamic effects

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.

Cardiac Electrophysiology
At doses up to 150 mg (the maximum recommended dose) daily for 5 days, Eltrombopag did not prolong the QT/QTc interval to any relevant extent.

5.2 Pharmacokinetic Properties

Absorption
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%.

Effect of Food
A standard high-fat breakfast (876 calories, 52 g fat, 71 g carbohydrate, 34 g protein, and 427 mg calcium) significantly decreased plasma Eltrombopag AUC_{0-INF} by approximately 59% and C_{max} by 65% and delayed T_{max} by 1 hour. The decrease in exposure is primarily due to the high calcium content.
A meal low in calcium (≤ 50 mg calcium) did not significantly impact plasma Eltrombopag exposure, regardless of calorie and fat content.

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.

Elimination
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.

Excretion: 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.

Specific Populations
Ethnicity: Eltrombopag concentrations in Asian (i.e., Japanese, Chinese, Taiwanese, Korean) patients with ITP or chronic hepatitis C, were 50% to 55% higher compared with non-Asian patients.

Eltrombopag exposure in African-American origin patients was approximately 40% higher than that observed in Caucasian patients.

The effect of African-American ethnicity on exposure and related safety and efficacy of Eltrombopag has not been established.

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. For patients with HCV initiate Eltrombopag at a dose of 25 mg once daily.

Renal Impairment
Patients with impaired renal function should use Eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis. The efficacy and safety of Eltrombopag have not been established in patients with both moderate to severe renal impairment.

Pediatric Patients
In pediatric patients 1 year and older with ITP plasma Eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Asian pediatric patients with ITP had approximately 43% higher plasma Eltrombopag $AUC_{(0-\tau)}$ values as compared with non-Asian patients.
Plasma Eltrombopag $AUC_{(0-\tau)}$ and C_{max} in pediatric patients aged 12 to 17 years was similar to that observed in adults.

6. NONCLINICAL PROPERTIES

Carcinogenesis, Mutagenesis, Impairment of Fertility
Eltrombopag does not stimulate platelet production in rats, mice, or dogs because of unique TPO receptor specificity. Data from these animals do not fully model effects in humans. Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max} in patients with ITP at 75 mg/day and 7 times the human clinical exposure based on C_{max} in patients with chronic hepatitis C at 100 mg/day). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (less than 3-fold increase in mutation frequency). Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

Animal Pharmacology and/or Toxicology
Treatment-related cataracts were detected in rodents in a dose- and time-dependent manner. At greater than or equal to 6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At greater than or equal to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing.

Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.6 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day. No similar effects were observed in mice after 13 weeks at exposures greater than those associated with renal changes in the 2-year study, suggesting that this effect is both dose- and time-dependent.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities
None

7.2 Packing Information
7's Blister Pack

7.3 Storage and Handling Instructions
Do not store above 30°C.

8. PATIENT COUNSELING INFORMATION

Prior to treatment, patients should fully understand and be informed of the following risks and considerations for Eltrombopag.

Hepatotoxicity
- Therapy with Eltrombopag may be associated with hepatobiliary laboratory abnormalities
- Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic decompensation when receiving Eltrombopag with alfa interferon therapy.
- Advise patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away:
  - ➢ yellowing of the skin or the whites of the eyes (jaundice)
  - ➢ unusual darkening of the urine
  - ➢ unusual tiredness
  - ➢ right upper stomach area pain
  - ➢ confusion
  - ➢ swelling of the stomach area (abdomen)

Risk of Bleeding Upon Eltrombopag Discontinuation
- Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing Eltrombopag, particularly if Eltrombopag is discontinued while the patient is on anticoagulants or antiplatelet agents. Advise patients that during therapy with Eltrombopag, they should continue to avoid situations or medications that may increase the risk for bleeding.

Thrombotic/Thromboembolic Complications
- Advise patients that too much Eltrombopag may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.

Cataracts
- Advise patients to have a baseline ocular examination prior to administration of Eltrombopag and be monitored for signs and symptoms of cataracts during therapy. Drug Interactions Advise patients to take Eltrombopag at least 2 hours before or 4 hours after calcium-rich foods, mineral supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

Lactation
- Advise women not to breastfeed during treatment with Eltrombopag.

Administration of Eltrombopag
- For patients with chronic ITP, therapy with Eltrombopag is administered 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.
- For patients with chronic hepatitis C, therapy with Eltrombopag is administered to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin.
- Advice patients to take Eltrombopag without a meal or with a meal low in calcium (≤ 50 mg) and at least 2 hours before or 4 hours after other medications (e.g., antacids) and calcium-rich foods.

9. DETAILS OF MANUFACTURER

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

10. DETAILS OF MANUFACTURING LICENCE NUMBER

Mfg. Lic. No.: 38/MD/AP/2007/F/CC

11. DATE OF REVISION

April-2023

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