

Trade names

Film-coated tablet

REBOZET® 25 mg and 50 mg

Description and composition

Pharmaceutical form

Film-coated tablets

The 25 mg tablets are white or orange, round, biconvex, and film-coated, debossed with 'GS NX3' and '25' on one side.

The 50 mg tablets are blue or brown, round, biconvex, and film-coated, debossed with 'GS UFU' and '50' on one side.

Active substance

Each film-coated tablet contains eltrombopag olamine equivalent to either: 25 mg or 50 mg of eltrombopag as eltrombopag free acid.

Excipients

Film-coated tablets

Tablet core:

Magnesium stearate, Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate.

Tablet coating:

Hypromellose, Macrogol 400, Polysorbate 80, Titanium dioxide (E171).

Indications

Rebozet is indicated for the treatment of thrombocytopenia in patients aged 6 years and above with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

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

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

Rebozet is indicated in adult patients with chronic hepatitis C virus (HCV) infection whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.

Rebozet is indicated for the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.

Dosage regimen and administration

Dosage regimen

Rebozet treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Rebozet dosing requirements must be individualized based on the patient's platelet counts. The objective of treatment with Rebozet should not be to normalize platelet counts but to maintain platelet counts above the level for haemorrhagic risk ($>50,000/\mu\text{L}$). In most patients, measurable elevations in platelet counts take 1-2 weeks (see section Clinical studies).

General target population

Chronic immune (idiopathic) thrombocytopenia (ITP)

The lowest dose of Rebozet should be used to achieve and maintain a platelet count $\geq 50,000/\mu\text{L}$. Dose adjustments are based upon the platelet count response. Rebozet should not be used to normalize platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting Rebozet and decreased within 1 to 2 weeks after discontinuation.

Initial dose regimen

Adults and pediatric patients aged 6 to 17 years

The recommended starting dose of Rebozet is 50 mg once daily.

For patients of East-/Southeast-Asian ancestry, Rebozet should be initiated at a reduced dose of 25 mg once daily (see section Clinical pharmacology, Special populations).

Monitoring and dose adjustment

After initiating Rebozet, the dose should be adjusted to achieve and maintain a platelet count $\geq 50,000/\mu\text{L}$ as necessary to reduce the risk for bleeding. A daily dose of 75 mg should not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with Rebozet and the dose regimen of Rebozet should be modified based on platelet counts as outlined in Table-1. During therapy with Rebozet complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ($\geq 50,000/\mu\text{L}$ for at least 4 weeks) has been achieved. CBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table-1 Dose adjustments of Rebozet in ITP patients

| Platelet count | Dose adjustment or response |
|--|---|
| <50,000/microL following at least 2 weeks of therapy | Increase daily dose by 25 mg to a maximum of 75 mg/day. |
| ≥50,000/microL to ≤ 150,000/microL | Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding. |
| >150,000/microL to ≤ 250,000/microL | Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| >250,000/microL | Discontinue eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤100,000/microL, reinstate therapy at a daily dose reduced by 25 mg. |

Rebozet can be administered in addition to other ITP medicinal products. Modify the dose regimen of concomitant ITP medicinal products, as medically appropriate, to avoid excessive increases in platelet counts during therapy with Rebozet.

To see the effect of any dose adjustment on the patient's platelet response prior to considering another dose increase one should wait for at least 2 weeks.

The standard Rebozet dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days or less frequent dosing may be required.

Discontinuation

Treatment with Rebozet should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section Warnings and precautions).

Chronic Hepatitis C (HCV) associated thrombocytopenia

When Rebozet given in combination with antiviral therapies reference should be made to the full prescribing information of the respective co-administered medicinal products for comprehensive details of administration.

The lowest dose of Rebozet to achieve and maintain a platelet count necessary to initiate and optimize antiviral therapy should be used. Dose adjustments should be based upon the platelet count response. Rebozet should not be used to normalize platelet counts. In clinical studies, platelet counts generally increase within 1 week of starting Rebozet.

Initial dose regimen

Adults

Rebozet should be initiated at a dose of 25 mg once daily.

No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry, or patients with mild hepatic impairment.

Monitoring and dose adjustment

The dose of Rebozet should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy (see Table-2). Platelet counts should be monitored every week prior to starting antiviral therapy.

During antiviral therapy the dose of Rebozet should be adjusted as necessary to avoid dose reduction of peginterferon. Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved. CBC's, including platelet counts and peripheral blood smears should be obtained monthly thereafter.

A dose of 100 mg Rebozet once daily should not be exceeded.

For specific dosage instructions for peginterferon alfa or ribavirin, one should refer to their respective prescribing information.

Table-2 Rebozet dose adjustments in HCV patients during antiviral therapy

| Platelet count | Dose adjustment or response |
|--|---|
| <50,000/microL following at least 2 weeks of therapy | Increase daily dose by 25 mg to a maximum of 100 mg/day. |
| ≥200,000/microL to ≤400,000/microL | Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| >400,000/microL | Discontinue Rebozet; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150,000/microL, reinstate therapy at a lower daily dose*. |

* For patients taking 25 mg Rebozet once daily, consideration should be given to reinitiating dosing at 12.5 mg once daily or alternatively a dose of 25 mg every other day.

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.

Rebozet treatment should be terminated when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table-2 or important liver test abnormalities may also necessitate discontinuation of Rebozet (see section Warnings and precautions).

Children

The safety and efficacy of Rebozet in pediatric patients with chronic HCV have not been established.

Severe Aplastic Anaemia

Initial Dose Regimen

Adults

Rebozet should be initiated at a dose of 50 mg once daily. For SAA patients of East-/Southeast-Asian ancestry, Rebozet should be initiated at a dose of 25 mg once daily (see section Clinical pharmacology, Special populations).

Monitoring and dose adjustment

Hematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting Rebozet (see section Clinical Studies). Adjust the dose of Rebozet in 50 mg increments every 2 weeks as necessary to achieve the target platelet count $\geq 50,000/\text{microL}$.

Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with Rebozet and modify the dosage regimen of Rebozet based on platelet counts as outlined in Table-3.

Table-3: Rebozet dose adjustments in SAA patients

| Platelet count | Dose adjustment or response |
|--|--|
| <50,000/microL following at least 2 weeks of therapy | Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients of East-/Southeast-Asian ancestry or those with hepatic impairment taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg. |
| $\geq 200,000/\text{microL}$ to $\leq 400,000/\text{microL}$ at any time | Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| $> 400,000/\text{microL}$ | Discontinue Rebozet for at least one week. Once the platelet count is $< 150,000/\text{microL}$, reinstitute therapy at a dose reduced by 50 mg. |
| $> 400,000/\text{microL}$ after 2 weeks of therapy at lowest dose of Rebozet | Discontinue Rebozet. |

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

Once platelet count $> 50,000/\text{microL}$, hemoglobin $> 10 \text{ g/dL}$ in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) $> 1 \times 10^9/\text{L}$ for more than 8 weeks, the dose of Rebozet should be reduced by up to 50%. If counts stay stable after 8 weeks at the reduced dose, then discontinue Rebozet and monitor blood counts. If platelet counts drop to

<30,000/microL, hemoglobin to <9 g/dL or ANC <0.5 x 10⁹/L, Rebozet may be reinitiated at the previous dose.

Discontinuation

If no hematological response has occurred after 16 weeks of therapy with Rebozet, discontinue therapy. Consider Rebozet discontinuation if new cytogenetic abnormalities are observed (see section Adverse drug reactions). Excessive platelet count responses (as outlined in Table-3) or important liver test abnormalities also necessitate discontinuation of Rebozet (see section Warnings and precautions).

Children

The safety and efficacy of Rebozet in pediatric patients with SAA have not been established.

Special populations (all indications)

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use Rebozet with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section Clinical pharmacology).

Hepatic impairment

Rebozet 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 (see section Warning and precautions). If the use of Rebozet is deemed necessary for ITP patients with hepatic impairment, the starting dose must be 25 mg once daily. After initiating the dose of Rebozet in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Thrombocytopenic patients with chronic HCV with hepatic impairment and severe aplastic anaemia patients with hepatic impairment should initiate Rebozet at a dose of 25 mg once daily (see section Clinical pharmacology, Special Populations).

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures (see section Warnings and precautions and section Adverse drug reactions).

Pediatric patients

In the clinical studies, Rebozet tablets were administered to patients aged 6-17 years, while Rebozet powder for oral solution (PfOS) were administered to patients aged 1 to 5 years. Since Rebozet is only available as tablet, the use in patients with ITP below the age of 6 years is not recommended as they are unable to swallow whole tablets.

The safety and efficacy of Rebozet has not been established in pediatric patients (<18 years) with chronic HCV related thrombocytopenia.

Geriatric patients (65 years of age or older)

There are limited data on the use of Rebozet in patients aged 65 years and older. In the clinical studies of Rebozet, overall no clinically significant differences in safety of Rebozet were observed between subjects 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 (see section Clinical Pharmacology, Special populations).

East-/Southeast-Asian patients

For adult and pediatric patients of East-/Southeast-Asian ancestry, Rebozet should be initiated at a dose of 25 mg once daily for the treatment of ITP and HCV-associated thrombocytopenia and SAA.

Method of administration

The tablets should be administered orally. It is not recommended to split or crush the tablet. Rebozet should be taken at two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see section Interactions, Drug-food/drink interactions).

Rebozet may be taken with food containing little (<50 mg) or preferably no calcium (see section Interactions, Drug-food/drink interactions).

Contraindications

Hypersensitivity to Rebozet or to any of the excipients.

Warnings and precautions

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels (smaller is equal to) 35 g/l or model for end stage liver disease (MELD) score (bigger is equal to) 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin (smaller is equal to) 35 g/l) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting with thrombocytopenia. 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.

The effectiveness and safety of Rebozet have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia and myelodysplastic syndromes (MDS).

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.

Hepatotoxicity

Rebozet administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury.

In clinical studies of adult and pediatric patients with chronic ITP who received Rebozet, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section Adverse drug reactions).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. In two placebo controlled studies in adults with chronic ITP, adverse events of ALT increase were reported in 5.7% and 4.0% of Rebozet and placebo treated patients, respectively. In two placebo-controlled studies in pediatric subjects with chronic ITP, ALT ≥ 3 times the upper limit of normal (\times ULN) was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In two controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST $> 3 \times$ ULN were reported in 34% and 38% of the Rebozet and placebo groups, respectively. Rebozet administration in combination with peginterferon/ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin $\geq 1.5 \times$ ULN was reported in 76% and 50% of the Rebozet and placebo groups, respectively.

In the single-arm, monotherapy study in patients with SAA, concurrent ALT or AST $> 3 \times$ ULN with total (indirect) bilirubin $> 1.5 \times$ ULN were reported in 5% of patients. Total bilirubin $> 1.5 \times$ ULN occurred in 14% of patients.

In patients with ITP, HCV, and SAA, serum ALT, AST and bilirubin should be measured prior to initiation of Rebozet, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1 (see section Clinical Pharmacology), which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilize, or return to baseline levels. Rebozet should be discontinued if ALT levels increase ($\geq 3 \times$ ULN) in patient with normal liver function or $\geq 3 \times$ baseline in patients with elevations in transaminases before treatment 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 261 decompensation.

Caution should be exercised when administering Rebozet to patients with hepatic disease. In ITP and SAA patients, a lower starting dose of Rebozet should be used when administering to patients with hepatic impairment (see section Dosage regimen and administration, Hepatic impairment).

Isolated cases of severe liver injury were identified in clinical studies. The elevation of liver laboratory values improved or resolved following Rebozet interruption or discontinuation. No cases of severe liver injury related to Rebozet were identified in a clinical study in patients with SAA, however, the number of exposed patients in these indications was limited. As the highest authorized dose is administered to patients in the SAA indications (150 mg/day) and due to the nature of the reaction, drug-induced liver injury might be expected in this patient population.

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤ 35 g/L) or with MELD score ≥ 10 at baseline.

Chronic HCV patients with liver cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving alpha interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV hepatic decompensation were occurred more frequently in the Rebozet arm (13%) than in the placebo arm (7%). Patients with low albumin levels (< 3.5 g/dL) or with a Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon prescribing information for discontinuation criteria should be referred to. Rebozet should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

Platelet counts above the normal range present a theoretical risk of thrombotic/thromboembolic complications. In Rebozet clinical studies in ITP thromboembolic events were observed at low and normal platelet counts.

Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section Dosage

regimen and administration). The risk-benefit balance should be considered in patients at risk of thromboembolic events of any aetiology.

In adult ITP studies, 21 thromboembolic/thrombotic events (TEE) were observed in 42 out of 763 patients (5.5%). The TEEs included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischemic stroke, and suspected PRIND (prolonged reversible ischemic neurologic deficiency).

No cases of TEEs were identified in a clinical study in SAA patients, however, the number of exposed patients in this indication was limited. As the highest authorized dose is administered to patients in the SAA indication (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

Rebozet should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering Rebozet to patients with hepatic impairment (see section Dosage regimen and administration and Adverse drug reactions, Hepatic impairment).

In two controlled Phase III studies in thrombocytopenic patients with HCV receiving interferon based therapy, 31 out of 955 patients (3%) treated with Rebozet experienced a TEE (3%) and 5 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1% in patients treated with Rebozet versus $< 1\%$ for placebo). No specific temporal relationship between start of treatment and occurrence of TEE was observed. The majority of TEEs resolved and did not lead to the discontinuation of antiviral therapy.

In a controlled study in thrombocytopenic patients with chronic liver disease (n = 288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg Rebozet once daily for 14 days. Six of 143 (4%) adult patients with chronic liver disease receiving Rebozet experienced TEEs (all of the portal venous system) and two out of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five Rebozet treated patients with a TEE experienced the event within 14 days of completing Rebozet dosing and at a platelet count above 200,000 microL.

Rebozet is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with Rebozet. Following discontinuation of Rebozet, platelet counts returned to baseline levels within 2 weeks in the majority of patients (see section Clinical studies), which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if Rebozet treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with Rebozet 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 Rebozet.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Rebozet may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of Rebozet the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of Rebozet, 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 Rebozet should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

In clinical studies with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Malignancies and progression of malignancies

There is a theoretical concern that they may stimulate the progression of existing hematopoietic 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.

The effectiveness and safety of Rebozet have not been established for the treatment of thrombocytopenia due to MDS. Rebozet should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

A randomized, double-blind, placebo-controlled, multicenter study in patients with International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2 or high risk myelodysplastic syndrome (MDS) with thrombocytopenia, receiving azacitidine in combination with either Rebozet or placebo, was terminated due to futility and increased MDS progression, including to AML. A total of 356 patients (179 on Rebozet, 177 on placebo) were randomized 1:1 and stratified by the International Prognostic Scoring System (IPSS): intermediate-1 (n = 64 [36%]), intermediate-2 (n = 79 [44%]), high-risk (n = 36 [20%]) in the Rebozet arm versus intermediate-1 (n = 65 [37%]), intermediate-2 (n = 79 [45%]), high-risk (n = 33 [19%]) in the placebo arm. Patients were treated with either Rebozet, at a starting dose of 200 mg once daily, up to a maximum of 300 mg once daily, or placebo in combination with azacitidine for at least six cycles. Based on central review assessment, there were 76 (42%) and 67 (38%) progression-free survival events, in the Rebozet group and the placebo group, respectively. Twenty-one (12%) and 10 (6%) patients progressed to AML by central review assessment in the Rebozet group and the placebo group, respectively. In the final analysis, overall survival favored the placebo arm: a total of 57 (32%) patients died on the Rebozet arm versus 51 (29%) patients in the placebo arm.

Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section Non-clinical safety data).

In controlled studies in thrombocytopenic patients with HCV receiving interferon based therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the Rebozet group and 5% of the placebo group.

Routine monitoring of patients for cataracts is recommended.

Interference with laboratory tests

Eltrombopag is highly colored and has the potential to interfere with some laboratory tests. Serum discoloration and interference with total bilirubin and creatinine testing have been reported in patients taking Rebozet. If the laboratory results and clinical observations are inconsistent, evaluation of contemporaneous aminotransferase values may help in determining the validity of low total bilirubin levels in the presence of clinical jaundice and blood urea should be evaluated in the event of an unexpectedly high serum creatinine. Re-testing using another method may also help in determining the validity of the result.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with Rebozet treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Interactions

Effects of other drugs on Rebozet

Cyclosporine

A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg cyclosporine (a BCRP inhibitor, see Pharmacokinetics). Administration of a single dose of Rebozet 50 mg with 200 mg cyclosporine decreased the C_{max} and the AUC_{inf} of eltrombopag by 25% (90% CI: 15%, 35%) and 18% (90% CI: 8%, 28%), respectively. The co-administration of 600 mg cyclosporine decreased the C_{max} and the AUC_{inf} of eltrombopag by 39% (90% CI: 30%, 47%) and 24% (90% CI: 14%, 32%), respectively. This decrease in exposure is not considered clinically meaningful. Rebozet dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section Dosage regimen and administration). Platelet count should be monitored at least weekly for 2 to 3 weeks when Rebozet is co-administered with cyclosporine. Rebozet dose may need to be increased based on these platelet counts.

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see section Clinical pharmacology). Administration of a single dose of Rebozet 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag AUC_{inf} by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62 %, 76%) (see section Dosage regimen and administration). Rebozet should be taken at least two hours before or four hours after products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption (see Dosage regimen and administration).

Lopinavir/ritonavir

Co-administration of Rebozet with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of Rebozet with repeat dose lopinavir/ritonavir 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma AUC_{inf} by 17% (90% CI: 6.6%, 26.6%).

Therefore, caution should be used when co-administration of Rebozet with lopinavir/ritonavir takes place. Platelet count should be monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of Rebozet when lopinavir/ritonavir therapy is initiated or discontinued.

HCV protease inhibitors

Co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of Rebozet 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Effects of Rebozet on other drugs

Rosuvastatin

Administration of Rebozet 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 C_{max} 103% (90% CI: 82%, 126%) and AUC_{inf} 55% (90% CI: 42%, 69%). When co-administered with Rebozet, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken. Concomitant administration of Rebozet and other OATP1B1 and BCRP substrates should be undertaken with caution.

Cytochrome P450 substrates

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

HCV Protease inhibitors

Co-administration of a single dose of Rebozet 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure. Co-administration of a single dose of Rebozet 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir AUC_{tau}, increased C_{max} by 19%, and decreased C_{min} by 32%.

Drug-food/drink interactions

Administration of a single 50 mg-dose of Rebozet with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag AUC_{inf} by 59% (90% CI: 54%, 64%) and C_{max} by 65% (90% CI: 59%, 70%). Food low in calcium [<50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see section Dosage regimen and administration).

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 (see section Dosage regimen and administration).

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

There are no or limited amount of data from the use of Rebozet in pregnant women to inform a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of eltrombopag to pregnant rats and rabbits throughout organogenesis resulted in developmental toxicity in rats (see Animal data). The effect of eltrombopag on human pregnancy is unknown. Pregnant women or women of childbearing potential should be advised of the potential risk of Rebozet to a fetus. Rebozet should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Animal data

In embryo-fetal developmental toxicity studies in rats and rabbits, oral eltrombopag was administered to pregnant animals during organogenesis. In rats, a maternally toxic dose of 60 mg/kg/day (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) resulted in decreased fetal weights and a slight increase in the incidence of the fetal variation, cervical rib. No evidence of major structural malformations was observed. In rabbits, there was no evidence of embryo- fetal toxicity or teratogenicity up to 150 mg/kg/day (0.5 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

In a pre-and postnatal developmental toxicity study in pregnant rats, oral eltrombopag was administered from gestation day 6 through lactation Day 20. No adverse effects on maternal reproductive function or on the development of the offspring were observed 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 was detected in the plasma of offspring. The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

Lactation

Risk summary

There is no information regarding the presence of eltrombopag or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. However, eltrombopag was detected in the pups of lactating rats 10 days postpartum suggesting the potential for transfer during lactation. A decision must be made whether to discontinue breastfeeding or to continue/abstain from Rebozet therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Females and males of reproductive potential

Contraception

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

Infertility

There is no effect of Rebozet on fertility based on animal studies (see section Non-clinical safety data). Eltrombopag did not affect female or male fertility in rats at doses 2 and 3 times respectively the human clinical exposure based on AUC in patients with ITP at 75 mg/day and in patients with chronic Hepatitis C at 100 mg/day (see section Non-clinical safety data).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse drug reactions

Summary of the safety profile

Chronic immune (idiopathic) thrombocytopenia (ITP) in adult and pediatric patients

The safety of Rebozet was assessed in adult patients (N=763) with previously treated ITP using data from pooled double-blind, placebo controlled studies TRA100773A and B, TRA102537 (RAISE), and TRA113765 in which patients were exposed to Rebozet (N=403) and to placebo (N=179), in addition to data from completed open label studies (N=360) TRA108057, TRA105325 (EXTEND), and TRA112940. Patients received study medication for up to 8 years (in EXTEND). The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea and increased alanine aminotransferase.

The safety of Rebozet was assessed in pediatric patients (aged 1 to 17 years) with previously treated chronic ITP using the all-treated population from two studies (N=171). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomised, placebo controlled study. Patients were randomized 2:1 and received eltrombopag (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a three-part, staggered cohort, open-label and double blind, randomised, placebo controlled study. Patients were randomised 2:1 and received eltrombopag (n=44) or placebo (n=21) for up to 7 weeks. The profile of adverse reactions was comparable to that seen in adults with some additional adverse drug reactions, marked ♦ in the table below. The most common adverse drug reactions in pediatric ITP patients 1 year and older ($\geq 3\%$ and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain,

oropharyngeal pain, toothache and rhinorrhoea. Adverse drug reactions for the adult (N=763) and pediatric (N=171) ITP study population are shown in Table-4.

Chronic Hepatitis C (HCV) associated thrombocytopenia in adult patients

ENABLE 1 (TPL103922 n = 716, 715 treated with Rebozet) and ENABLE 2 (TPL108390 n = 805) were randomized, double-blind, placebo-controlled, multicenter studies to assess the efficacy and safety of Rebozet in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomized patients who received double-blind study drug during Part 2 of ENABLE 1 (Rebozet treatment n = 450, placebo treatment n = 232) and ENABLE 2 (Rebozet treatment n = 506, placebo treatment n = 253). Patients are analysed according to the treatment received (total safety double blind population, Rebozet n = 955 and placebo n = 484). Adverse drug reactions for the HCV study population (N=1520) are shown in Table-5. The most common adverse drug reactions ($\geq 10\%$) for Rebozet were anaemia, pyrexia, fatigue, headache, nausea, influenza like illness, diarrhoea, decreased appetite, asthenia, pruritus, cough, chills, and myalgia.

Severe aplastic anemia in adult patients

The safety of Rebozet in severe aplastic anemia was assessed in a single-arm, open-label study (N=43) in which 11 patients (26%) were treated for >6 months and 7 patients (16%) were treated for >1 year. Adverse drug reactions for the SAA study population (N=43) are shown in Table-6.

The most common adverse drug reactions ($\geq 10\%$) for Rebozet were nausea, fatigue, cough, headache, diarrhoea, pain in extremity, dizziness, oropharyngeal pain, pyrexia, rhinorrhoea, abdominal pain, transaminases increased, arthralgia and muscle spasms.

Most adverse drug reactions associated with Rebozet in ITP, HCV and SAA were mild to moderate in severity, early in onset and rarely treatment-limiting.

Tabulated summary of reactions from clinical trials

Adverse drug reactions from clinical trials are listed below by MedDRA body system organ class and by frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

The adverse drug reactions identified in patients treated with Rebozet are presented below.

Table-4 Adverse drug reactions in the ITP study 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 pediatric 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 | Very common | Back pain |
| | Common | Myalgia, muscle spasm, musculoskeletal pain, bone 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 pediatric 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 |
| <p>* Additional adverse reactions observed in pediatric studies (aged 1 to 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</p> | | |

Table-5 Adverse drug reactions in the HCV study population (Rebozet in combination with interferon anti-viral 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, gastroesophageal 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 | | |

Table-6: Adverse drug reactions in the SAA study population

| System organ class | Frequency | Adverse reaction |
|---|-------------|---|
| Blood and lymphatic system | Common | Neutropenia, splenic infarction |
| Metabolism and nutrition disorders | Common | Iron overload, decreased appetite, hypoglycaemia, increased appetite |
| Psychiatric disorders | Common | Anxiety, depression |
| Nervous system disorders | Very common | Headache, dizziness |
| | Common | Syncope |
| Eye disorders | Common | Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters |
| Respiratory, thoracic and mediastinal disorders | Very common | Cough, oropharyngeal pain, rhinorrhoea |
| | Common | Epistaxis |
| Gastrointestinal disorders | Very common | Diarrhoea, nausea, gingival bleeding, abdominal pain |
| | Common | Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence |
| Hepatobiliary disorders | Very common | Transaminases increased |
| | Common | Blood bilirubin increased (hyperbilirubinemia), jaundice |
| | Not known | Drug-induced liver injury* *Cases of drug-induced liver injury have been reported in patients with ITP and HCV |
| Skin and subcutaneous tissue disorders | Common | Petechiae, rash, pruritus, urticaria, skin lesion, rash macular |
| | Not known | Skin discolouration, skin hyperpigmentation |

| | | |
|--|-------------|--|
| Musculoskeletal and connective tissue disorder | Very common | Arthralgia, pain in extremity, muscle spasms |
| | Common | Back pain, myalgia, bone pain |
| Renal and urinary disorders | Common | Chromaturia |
| General disorders and administration site conditions | Very common | Fatigue, pyrexia, chills |
| | Common | Asthenia, oedema peripheral, malaise |
| Investigations | Common | Blood creatine phosphokinase increased |

Description of selected adverse reactions

Thrombotic/thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see section Warnings and precautions).

In a placebo-controlled study, following 2 weeks treatment in preparation for invasive procedures, 6 of 261 patients with chronic liver disease experienced 7 thromboembolic events of the portal venous system. One additional patient developed a myocardial infarction 20 days after the last dose of study medication, which remains blinded.

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section Warnings and precautions).

Increased bone marrow reticulin

Across the programme, no subjects had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see Section Warnings and precautions).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been reported during post-approval use of Rebozet. These include spontaneous case reports as well as serious adverse events from registries, investigator sponsored studies, clinical pharmacology studies and exploratory studies in unapproved indications. Because they are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table-7 Adverse drug reactions identified during post-approval use**Skin and subcutaneous tissue disorders**

Not known Skin discolouration*

* In patients taking eltrombopag reversible skin discolouration including hyperpigmentation and skin yellowing was observed at eltrombopag doses higher than 100mg per day. Skin discolouration was particularly observed in patients taking eltrombopag for indications that require administration of high doses of eltrombopag including severe aplastic anaemia

Overdosage

In the clinical studies there was one report of overdose where the patient ingested 5000 mg of Rebozet. Reported adverse events included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin. The platelet counts were 672,000/microL on day 18 after ingestion and the maximum platelet count was 929,000/microL. All events were resolved without sequelae following treatment.

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption should be considered. Platelet counts should be closely monitored. Treatment with Rebozet should be reinitiated in accordance with dosing and administration recommendations (see section Dosage regimen and administration).

Because Rebozet is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of Rebozet.

Clinical pharmacology**Pharmacotherapeutic group, ATC**

Thrombopoietin-receptor agonist, B02BX 05.

Mechanism of action (MOA)

Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-receptor. Eltrombopag interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes and bone marrow progenitor cells.

Pharmacodynamics (PD)

Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, eltrombopag treatment of normal human platelets does not enhance adenosine

diphosphate (ADP)-induced aggregation or induce P-selectin expression. Eltrombopag does not antagonize platelet aggregation induced by ADP or collagen.

Clinical studies

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Adults

Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

TRA102537 (RAISE)

RAISE: 197 patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All subjects initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16,000/microL for both treatment groups and in the eltrombopag group were maintained above 50,000/microL at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained $< 30,000$ /microL throughout the study.

Platelet count response between 50,000-400,000/microL in the absence of rescue medication was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table-8: Secondary efficacy results from RAISE

| | Eltrombopag n = 135 | Placebo n = 62 |
|---|--------------------------------|---------------------------|
| Key secondary endpoints | | |
| Number of cumulative weeks with platelet counts \geq 50,000-400,000/microL, Mean (SD) | 11.3 (9.46) | 2.4 (5.95) |

| | | |
|--|----------|---------|
| Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/microL), n (%) | 51 (38) | 4 (7) |
| <i>P</i> -value ^a | < 0.001 | |
| Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%) | 106 (79) | 56 (93) |
| <i>P</i> -value ^a | 0.012 | |
| Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%) | 44 (33) | 32 (53) |
| <i>P</i> -value ^a | 0.002 | |
| Requiring rescue therapy, n (%) | 24 (18) | 25 (40) |
| <i>P</i> -value ^a | 0.001 | |
| Patients receiving ITP therapy at baseline (n) | 63 | 31 |
| Patients who attempted to reduce or discontinue baseline therapy, n (%) ^b | 37 (59) | 10 (32) |
| <i>P</i> value ^a | 0.16 | |

^a Logistic regression model adjusted for randomisation stratification variables

^b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medication at baseline permanently discontinued all baseline ITP medications.

At baseline, more than 70% of patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B

In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to $\geq 50,000$ /microL at Day 43 from a baseline platelet count $< 30,000$ /microL; patients who withdrew prematurely due to a platelet count $> 200,000$ /microL were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomized 2:1, with 76 randomized to Rebozet and 38 randomized to placebo.

Table-9: Efficacy results from TRA100773B

| | Eltrombopag n = 74 | Placebo n = 38 |
|--|-------------------------------|---------------------------|
| Key primary endpoints | | |
| Eligible for efficacy analysis, n | 73 | 37 |
| Patients with platelet count $\geq 50,000$ /microL after up to 42 days of dosing (compared to a baseline count of $< 30,000$ /microL), n (%) | 43 (59) | 6 (16) |
| <i>P</i> value ^a | < 0.001 | |
| Key secondary endpoints | | |
| Patients with a Day 43 bleeding assessment, n | 51 | 30 |

| | | |
|---------------------------------|---------|---------|
| Bleeding (WHO Grades 1-4) n (%) | 20 (39) | 18 (60) |
| <i>P</i> value ^a | 0.29 | |

^a Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count ($\leq 15,000/\text{microL}$, $>15,000/\text{microL}$) at randomization.

In RAISE and TRA100773B studies, in the subgroup of patients with baseline platelet count $\leq 15,000/\text{microL}$ the median platelet counts did not reach the target level ($>50,000/\text{microL}$), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count $\leq 15,000/\text{microL}$ treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was $19,500/\text{microL}$ prior to eltrombopag administration.

Median platelet counts at 12, 18 and 24 months on study were $68,000/\text{microL}$, $75,000/\text{microL}$ and $119,000/\text{microL}$, respectively.

Open label studies

TRA108057 (REPEAT)

TRA108057 was an open-label, repeat-dose, study which evaluated the efficacy, safety and consistency of response following repeated, intermittent, short-term dosing of eltrombopag over 3 cycles of therapy in adults with previously treated chronic ITP. A cycle was defined as an up to 6-week on-therapy period followed by an up to 4-week off-therapy period. The duration of both the on-therapy and the off-therapy periods was defined by the patient's platelet count. Patients were to interrupt treatment for the cycle if they achieved a platelet count $>200,000/\text{microL}$, or when they reached Week 6. Patients were to begin the next cycle when their platelet counts fell below $20,000/\text{microL}$, or when they reached Week 4 of the off-therapy period. The primary endpoint in REPEAT was the proportion of 854 subjects who achieved a platelet count $\geq 50,000/\text{microL}$ and at least 2x baseline in Cycle 2 or 3, given this response in Cycle 1.

Table-10 Evaluable and responding patients in TRA108057

| | Rebozet 50 mg (N=66) |
|------------------------------|----------------------|
| Evaluable in Cycle 1, n | 65 |
| Responders in Cycle 1, n (%) | 52 (80) |
| Evaluable in Cycle 2 or 3, n | 52 |

| | |
|--|--------------|
| Responders in Cycle 1 and in Cycle 2 or 3, n (%) | 45 (87) |
| Proportion | 0.87 |
| 95% CI for Proportion (Exact Methods) | (0.74, 0.94) |

Of the 52 patients who responded in Cycle 1, 33 (63%) achieved a platelet count of $\geq 50,000$ microL and at least 2x baseline on Day 8 in Cycle 1; on Day 15, 37 (79%) of 47 evaluable patients achieved this level of response.

A reduction in any bleeding (WHO Grade 1-4) and clinically significant bleeding (WHO Grade 2-4) during the treatment phases was demonstrated in each cycle. At the baseline 863 visit of Cycle 1, 50% and 19% of patients reported any bleeding and clinically significant bleeding, respectively. At the Day 43 Visit of Cycle 1, the proportion of patients bleeding was reduced; 12% and 0% of patients reported any bleeding and clinically significant 866 bleeding, respectively. Similar results were found during the subsequent treatment cycles.

Eight patients successfully managed 10 hemostatic challenges without need for additional therapy to elevate platelet counts and without unexpected bleeding.

TRAI05325 (EXTEND)

TRAI05325 was an open label extension study which has evaluated the safety and efficacy of Rebozet in patients with chronic ITP at least 6 months from diagnosis who were previously enrolled in an eltrombopag study. In this study, patients were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

Rebozet was administered to 302 ITP patients; 218 completed 1 year of treatment, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 year of years of therapy. The median baseline platelet count was 19,000/microL prior to Rebozet administration. Median platelet counts at 1, 2, 3, 4, 5, 6, and 7 years on study were 85,000/microL, 85,000/microL, 105,000/microL, 879 64,000/microL, 75,000/microL, 119,000/microL and 76,000/microL, respectively. The median daily dose of Rebozet following 6 months of therapy was 50 mg (n=74).

At baseline, 59% of patients had any bleeding (WHO Bleeding Grades 1–4) and 18% had clinically significant bleeding. The proportion of patients with any bleeding and clinically significant bleeding decreased from baseline by approximately 50% for the 884 majority of assessments up to 1 year.

One-hundred and one patients were taking ITP medications at baseline upon entry into EXTEND study, and 39 patients were able to permanently discontinue or achieve a sustained reduction of at least one baseline ITP medication without needing rescue medication. Sixty-five percent of these patients maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of patients completely discontinued at least one baseline ITP medication, and 55% of patients permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

Twenty-four patients experienced at least one hemostatic challenge during the study. No patients experienced unexpected bleeding complications related to the procedure while on study.

Pediatric patients

The safety and efficacy of Rebozet in pediatric patients with previously treated ITP have been demonstrated in two studies.

Double-blind placebo-controlled studies

TRAI15450 (PETIT2)

The primary endpoint was a sustained response, defined as the proportion of patients receiving Rebozet, compared to placebo, achieving platelet counts $\geq 50,000/\text{microL}$ for at least 6 out of 8 weeks (in the absence of rescue therapy), between Weeks 5 to 12 during the double-blind randomized period. Patients were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count $< 30,000/\text{microL}$. Ninety-two patients were randomized by three age cohort strata (2:1) to Rebozet (n = 63) or placebo (n = 29). The dose of Rebozet could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Rebozet patients (40%) compared with placebo patients (3%) achieved the primary endpoint (OR: 18.0 [95% CI: 2.3, 140.9] $p < 0.001$) which was similar across the three age cohorts (Table-11).

Table-11 Sustained platelet response rates by age cohort in pediatric patients with ITP at least 12 months from diagnosis in PETIT2*

| | Rebozet n/N (%) [95% CI] | Placebo n/N (%) [95% CI] |
|---------------------------|-----------------------------|-----------------------------|
| Cohort 1 (12 to 17 years) | 9/23 (39%) [20%, 61%] | 1/10 (10%) [0%, 45%] |
| Cohort 2 (6 to 11 years) | 11/26 (42%) [23%, 63%] | 0/13 (0%) [N/A] |
| Cohort 3 (1 to 5 years) | 5/14 (36%) [13%, 65%] | 0/6 (0%) [N/A] |

* Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation. Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia.

A significantly greater proportion of patients treated with Rebozet (75%) compared with placebo (21%) had a platelet response (at least one platelet count $> 50,000/\text{microL}$ during the first 12 weeks of randomized treatment in absence of rescue therapy) (OR: 11.7 [95% CI: 4.0, 34.5], $p < 0.001$). The proportion of patients who responded to Rebozet in the open-label 24-week period (80%) was similar to that observed during the randomized portion of the study. Statistically fewer Rebozet patients required rescue treatment during the randomized period compared to placebo patients (19% [12/63] vs. 24% [7/29] $p=0.032$).

At baseline, 71% of patients in the Rebozet group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of Rebozet patients reporting any

bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo patients reported any bleeding.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of patients were able to reduce (n = 1) or discontinue (n = 7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRAI08062 (PETIT)

The primary endpoint was the proportion of patients achieving platelet counts $\geq 50,000/\text{microL}$ at least once between Weeks 1 and 6 of the randomized period. Patients were refractory or relapsed to at least one prior ITP therapy with a platelet count $< 30,000/$ (n = 67). During the randomized period of the study, patients were randomized by 3 age cohort strata (2:1) to Rebozet (n = 45) or placebo (n = 22). The dose of Rebozet could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Rebozet patients (62%) compared with placebo patients (32%) met the primary endpoint (OR: 4.3 [95% CI: 1.4, 13.3] p = 0.011). Table-12 shows platelet response across the three age cohorts.

Table-12 Platelet response rates in pediatric patients with ITP at least 6 months from diagnosis in PETIT*

| | Rebozet n/N (%) [95% CI] | Placebo n/N (%) [95% CI] |
|---------------------------|-----------------------------|-----------------------------|
| Cohort 1 (12 to 17 years) | 10/16 (62%) [35%, 85%] | 0/8 (0%) [N/A] |
| Cohort 2 (6 to 11 years) | 12/19 (63%) [44%, 90%] | 3/9 (33%) [7%, 70%] |
| Cohort 3 (1 to 5 years) | 6/10 (60%) [26%, 88%] | 4/5 (80%) [28%, 99%] |

* Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation. Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia.

A significantly greater proportion of patients treated with Rebozet (36%) compared with placebo (0%) had a platelet response (platelet counts $> 50,000/\text{microL}$ for at least 60% of assessments between Weeks 2 and 6) (OR: 5.8, [95% CI: 1.2, 28.9], p = 0.002).

Statistically fewer Rebozet-treated patients required rescue treatment during the randomized period compared to placebo treated patients (13% [6/45] vs. 50% [11/22], p = 0.002).

At baseline, 77.7% of patients in the Rebozet group and 81.8% in the placebo group reported any bleeding (WHO Grades 1-4). The proportion of Rebozet patients reporting any bleeding decreased to 22.2% at Week 6. In comparison, 72.7% of placebo patients reported any bleeding at Week 6.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 46% (6/13) of patients were able to reduce (n = 3) or discontinue (n = 3) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of Rebozet for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomized, double-blind, placebo- controlled studies. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. In both studies, patients with a platelet count of <75,000/microL were enrolled and stratified by platelet count (<50,000/microL and ≥50,000/microL to <75,000/microL), screening HCV RNA (<800,000 IU/mL and ≥800,000 IU/mL), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label Rebozet to increase the platelet count to ≥90,000/microL for ENABLE 1 and ≥100,000/microL for ENABLE 2. Rebozet was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25 mg increments over 2 to 3 week periods to achieve the required platelet count for phase 2 of the study. The maximal time patients could receive open-label Rebozet was 9 weeks. If sufficient platelet counts were achieved, patients were randomized (2:1) to the same dose of Rebozet at the end of the pre-treatment phase or to placebo. Rebozet was administered in combination with antiviral treatment per their respective prescribing information for up to 48 weeks.

The primary efficacy endpoint for both studies was sustained virological response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70% of patients were genotype 1/4/6 and 30% were genotype 2/3. Approximately 31% of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately 60,000/microL) were similar among all treatment groups. The median time to achieve the target platelet count ≥90,000/microL (ENABLE 1) or ≥100,000/microL (ENABLE 2) was 2 weeks.

In both HCV studies, a significantly greater proportion of patients treated with Rebozet achieved SVR compared to those treated with placebo (see Table-11). Significantly fewer patients treated with Rebozet had any antiviral dose reductions compared to placebo. The proportion of patients with no antiviral dose reductions was 45% for Rebozet compared to 27% for placebo. Significantly fewer patients treated with Rebozet prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, $p = < 0.0001$). The majority of patients treated with Rebozet (76 %) had minimum platelet counts that were ≥50,000/vL compared to 19% for placebo. A greater proportion of subjects in the placebo group (20%) had minimum platelet counts fall below 25,000/microL during treatment compared to the Rebozet group (3%). In the Rebozet group, SVR rates in patients with high viral loads (>800,000) were 18% as compared to 8% in the placebo group. Significantly more patients reached the later antiviral milestones of early virologic response (EVR), complete early virologic response (cEVR), end of treatment response (ETR) and sustained virologic response at 12-week follow-up (SVR12) when treated with Rebozet.

Table-13: ENABLE 1 and ENABLE 2 virologic response

| Pre-antiviral Phase | Treatment | ENABLE 1 ^a | | ENABLE 2 ^b | |
|--|-----------|-----------------------|--------------------|-----------------------|--------------------|
| | | Rebozet n = 450 | Placebo n = 232 | Rebozet n = 506 | Placebo n = 253 |
| % Achieving target platelet counts and initiating antiviral therapy ^c | | | | | |
| | | N = 715 95% | | N = 805 94% | |
| Antiviral Phase | Treatment | % | % | % | % |
| Overall SVR ^d | | 23 | 14 | 19 | 13 |
| Overall EVR ^d | | 66 | 50 | 62 | 41 |

a Rebozet given in combination with peginterferon alfa-2a (180 microg once weekly for 48 weeks for genotypes 1 or 4; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Rebozet given in combination with peginterferon alfa-2b (1.5 microg/kg once weekly for 48 weeks for genotype 1; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1400 mg orally)

c Target platelet count was $\geq 90,000/\text{microL}$ for ENABLE 1 and $\geq 100,000/\text{microL}$ for ENABLE 2

d P value <0.05 for Rebozet versus placebo

Severe Aplastic Anaemia

CETB115AUS28T

Rebozet was studied in a single-arm, single-center open-label study in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count $\leq 30,000/\text{microL}$.

Rebozet was administered at an initial dose of 50 mg once daily for 2 weeks and increased over 2 week periods up to a maximum dose of 150 mg once daily. The primary endpoint was hematological response assessed after 12 weeks of Rebozet treatment.

Rebozet was discontinued after 16 weeks if no hematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study.

Hematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/microL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by >1.5 g/dL (for patients with pre-treatment hemoglobin <9 g/dL), or a reduction in the volume of RBC transfusions of at least 4 units for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% (for patients with pre-treatment ANC <500/microL) or an ANC increase 500/microL.

The treated population had median age of 45 years (range 17 to 77 years) and 56% of patients were male. At baseline the median platelet count was 20,000/microL, hemoglobin was 8.4 g/dL, and ANC was 580/microL. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

A total of 17 patients (40%) met the hematologic response criteria in at least 1 lineage at the Primary Response Assessment (95% CI: 25, 56).

Multi-lineage responses were observed in 4/17 responders (24%) at the initial response assessment and in 9/17 responders (53%) at last assessment. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off Rebozet, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

The majority of responders met platelet response criteria (65%), followed by neutrophil and hemoglobin response criteria (47% and 18% respectively). The 15 responders who had at least 2 response assessments were evaluable for assessment of response duration and had a median duration of response of 12.0 months.

Nine of the 17 responders had a multi-lineage best response. Of the 14 patients who entered the extension, seven had improvement in more than one lineage following continuation of treatment: five patients with uni-lineage response improved to multi-lineage response (bi- or tri-lineage) and two patients with bi-lineage response improved to tri-lineage response. Three of the four bi-lineage responders also had meaningful improvements in hemoglobin (>1.5 g/dL); however, as their baseline hemoglobin was above 9 g/dL they are not counted as having an erythroid response.

The longest platelet transfusion free period in responders ranged from 8 to 1,190 days with a median of approximately 287 days. The longest RBC transfusion free period in responders ranged from 15 to 1,190 days with a median of approximately 266 days. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off Rebozet, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

Pharmacokinetics Interactions

Pharmacokinetics (PK)

The plasma eltrombopag concentration-time data collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag AUC(0- τ) and C_{max} estimates for ITP subjects are presented (Table-14).

Table-14 Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

| Eltrombopag dose, once daily | N | AUC(0- τ) ^a , microgram.h/mL | C _{max} ^a , microgram/mL |
|------------------------------|----|--|---|
| 30 mg | 28 | 47 (39, 58) | 3.78 (3.18, 4.49) |
| 50 mg | 34 | 108 (88, 134) | 8.01 (6.73, 9.53) |
| 75 mg | 26 | 168 (143, 198) | 12.7 (11.0, 14.5) |

^a AUC(0- τ) and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from subjects with HCV enrolled in the Phase II study TPL102357 and healthy adult patients in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase III studies are presented for each dose studied in Table-15. A higher eltrombopag exposure was observed in patients with HCV at a given Rebozet dose.

Table-15 Geometric mean (95 % CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

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

Data presented as geometric mean (95%CI). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each subject.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see Dosage regimen and administration). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

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

Biotransformation/metabolism

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon AUC_{inf} . Minor metabolites due to glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20% of a dose is metabolized by oxidation.

Elimination

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

In Vitro evaluation of drug interaction potential

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section Interactions).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section Interactions). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see section Dosage regimen and administrations and section Interactions).

In vitro studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC₅₀ value of 2.7 microM (1.2 microgram/mL)). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC₅₀ value of 2.7 microM (1.2 microgram/mL)).

Special populations

Renal impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the AUC_{inf} of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and 60 % lower in subjects with severe renal impairment compared with healthy

volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section Dosage regimen and administrations).

Hepatic impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the AUC_{inf} of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 subjects with hepatic impairment (673 subjects with HCV and 41 subjects with chronic liver disease of other aetiology). Of the 714 subjects, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, subjects with mild hepatic impairment had approximately 111% (85% CI: 45% to 283%) higher plasma eltrombopag AUC_(0-τ) values and subjects with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag AUC_(0-τ) values.

Therefore, 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 (see section Dosage regimen and administration and section Warning and precautions). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section Dosage regimen and administration).

Race/Ethnicity

The influence of East-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (31 East-Asians) and 88 subjects with ITP (18 East-Asians). Based on estimates from the population PK analysis, East-Asian ITP subjects had approximately 87% higher plasma eltrombopag AUC_(0-τ) values as compared to non-East-Asian subjects who were predominantly Caucasian, without adjustment for body weight differences (see section Dosage regimen and administrations).

The influence of Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 663 patients with HCV (214 East-Southeast-Asians). Based on estimates from the population PK analysis, East-Southeast-Asian patients had similar pharmacokinetics of eltrombopag. On average, East-Southeast-Asian patients had approximately 55% higher plasma eltrombopag AUC_(0-τ) values as compared to subjects of other races who were predominantly Caucasian (see section Dosage regimen and administration).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (14 females) and 88 subjects with ITP (57 females). Based on estimates from the population PK analysis, female ITP subjects had approximately 50% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male subjects, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using a population PK analysis in 663 patients with HCV (260 females). Based on model estimates, female HCV subjects had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male subjects.

Geriatric patients (60 years of age or above)

The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects and 635 subjects with HCV ranging from 19 to 74 years old. Based on model estimates, elderly (>60 years) subjects had approximately 36% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section Dosage regimen and administration).

Pediatric population

The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT- 2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Approximately 30% lower plasma eltrombopag CL/F was observed in subjects of East/Southeast-Asian race and 20% lower CL/F was observed in female subjects.

The pharmacokinetic parameters of eltrombopag in pediatric subjects with ITP are shown in Table-16.

Table-16 Geometric Mean (95% CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Pediatric Subjects with ITP (50 mg Once Daily Dosing Regimen)

| Age | C _{max} (microgram/mL) | AUC _{tau} (microgram.hr/mL) |
|-----------------------|------------------------------------|---|
| 12 to 17 years (n=62) | 6.80 (6.17, 7.50) | 103 (91.1, 116) |
| 6 to 11 years (n=68) | 10.3 (9.42, 11.2) | 153 (137, 170) |
| 1 to 5 years (n=38) | 11.6 (10.4, 12.9) | 162 (139, 187) |

Data presented as geometric mean (95%CI). AUC_{tau} and C_{max} based on population PK post-hoc estimates for a 50 mg once daily dose.

Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation.

Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia.

Non-clinical safety data

Safety pharmacology and repeat dose toxicity

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 3 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing (2 times the human clinical exposure based on AUC) (see section Warnings and precautions).

Renal tubular toxicity was observed in studies of up to 14 days 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. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on AUC in HCV patients at 100 mg/day. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times respectively, the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times and equivalent, respectively, to the human clinical exposure in HCV patients at 100 mg/day.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC.

At poorly tolerated doses in rats and dogs (>10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times maximum human clinical exposure based on AUC.

Carcinogenicity and mutagenicity

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 ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients 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 ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day). In the in vitro mouse lymphoma assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency). These in vitro and in vivo findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.5 times the human clinical exposure based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. 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 the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F1). Eltrombopag was detected in the plasma of all F1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Juvenile animal studies

At non-tolerated doses in pre-weaning rats, ocular opacities were observed. However, at tolerated doses, no ocular opacities were observed (see section Non-clinical safety data, Safety pharmacology and repeat dose toxicity).

Pharmaceutical information

Incompatibilities

No known incompatibilities

Shelf-life

The expiry date is indicated on the packaging.

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

Blister packs containing either 25 mg or 50 mg tablets

Each pack of Rebozet contains 14 film-coated-tablets in aluminium foil – aluminium foil blisters.

Not all presentations are available in every country.

Instructions for use and handling

No special requirements

HARUS DENGAN RESEP DOKTER

Rebozet Tablet 25 mg, Box, 2 blisters @ 7 tablets, Reg. No.

Rebozet Tablet 50 mg, Box, 2 blisters @ 7 tablets, Reg. No.

Manufactured, packed and released by:

Novartis Pharmaceutical Manufacturing LLC, Ljubljana, Slovenia for Novartis Pharma AG, Basel, Switzerland.

Imported by

PT Novartis Indonesia, Jakarta, Indonesia

*PI based on CDS update v3.0 13-Aug-2020 (pediatric ITP and 2nd line SAA) **NPM LLC***

REBOZET[®] (Eltrombopag)

Tablet salut selaput 25 mg dan 50 mg

Informasi Produk untuk Pasien

Bacalah brosur ini dengan seksama sebelum Anda mengonsumsi REBOZET.

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter atau apoteker Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Jika Anda mengalami efek samping yang berat, atau jika Anda mengalami efek samping yang tidak tertera pada brosur ini, mohon informasikan kepada dokter ataupun apoteker Anda.

DAFTAR ISI

1. **Apakah Rebozet dan apa kegunaannya**
2. **Apa yang harus diketahui sebelum dan selama mengonsumsi Rebozet**
3. **Bagaimana cara mengonsumsi Rebozet**
4. **Efek samping yang mungkin terjadi**
5. **Penyimpanan Rebozet**
6. **Informasi lebih lanjut**

1 APAKAH REBOZET DAN APA KEGUNAANNYA

Apakah Rebozet

Rebozet mengandung zat aktif eltrombopag olamine, yang termasuk dalam kelompok obat yang disebut '*Thrombopoietin receptor agonists*'. Rebozet adalah obat yang dapat meningkatkan jumlah trombosit, sejenis sel darah yang membantu mengurangi atau mencegah pendarahan.

Apakah kegunaan Rebozet

Rebozet diindikasikan untuk pengobatan trombositopenia pada pasien purpura trombositopenik imun/idiopatik (*immune/idiopathic thrombocytopenic purpura, ITP*) kronis usia 6 tahun ke atas yang tidak respons dengan pengobatan dengan kortikosteroid, imunoglobulin atau splenektomi.

Rebozet digunakan hanya pada pasien ITP yang derajat trombositopenia dan kondisi klinisnya meningkatkan risiko perdarahan.

Rebozet tidak digunakan dalam upaya menormalkan jumlah trombosit.

Rebozet diindikasikan untuk pasien dengan infeksi virus hepatitis C (*hepatitic C virus, HCV*) dewasa yang derajat trombositopenianya menghambat inisiasi dari terapi berbasis interferon atau membatasi kemampuan untuk mempertahankan terapi berbasis interferon.

Rebozet diindikasikan untuk pengobatan pasien dewasa dengan anemia aplastik berat (*severe aplastic anemia, SAA*) yang tidak memperlihatkan respons adekuat terhadap terapi imunosupresif.

Bagaimana kerja Rebozet

Di dalam tubuh, hormon yang disebut '*Thrombopoietin*' menstimulasi produksi trombosit dengan menempel pada reseptor tertentu di sumsum tulang. Rebozet dapat menyebabkan peningkatan produksi trombosit.

2 APA YANG HARUS DIKETAHUI SEBELUM DAN SELAMA MENGONSUMSI REBOZET

Mohon agar mengikuti instruksi dari dokter dengan hati-hati karena instruksi tersebut dapat berbeda dari informasi umum yang terdapat dalam brosur ini.

Peringatan dan perhatian

Jangan mengonsumsi Rebozet jika Anda:

- Memiliki hipersensitifitas terhadap Rebozet atau salah satu bahan yang terkandung di dalam Rebozet.

Jika ini berlaku untuk Anda, beritahukan dokter, apoteker, atau tenaga profesional kesehatan Anda sebelum mengonsumsi Rebozet:

- Memiliki masalah pada hati (*liver*). Anda mungkin membutuhkan dosis Rebozet yang lebih rendah.
- Memiliki riwayat pembentukan gumpalan di dalam pembuluh darah yang mengganggu aliran darah (trombosis), atau Anda mengetahui riwayat trombosis dalam keluarga Anda.
- Jika Anda memiliki kondisi darah berbeda, seperti *myelodysplastic syndrome (MDS)*. Dokter Anda akan melakukan tes untuk memeriksa bahwa Anda tidak memiliki kondisi darah ini sebelum Anda menggunakan Rebozet. Jika Anda memiliki *MDS* dan menggunakan Rebozet, *MDS* Anda mungkin menjadi memburuk.
- Memiliki riwayat gangguan pada penglihatan (katarak).

Beritahukan dokter, apoteker, atau tenaga profesional kesehatan Anda segera jika Anda mendapatkan gejala-gejala ini saat mengonsumsi Rebozet:

- Jika Anda mengalami gejala-gejala yang disebabkan oleh gumpalan darah di kaki Anda seperti pembengkakan atau nyeri/sakit satu kaki.
- Jika Anda mengalami gejala-gejala yang disebabkan oleh masalah-masalah hati seperti menguningnya kulit atau putihnya mata (sakit kuning), penggelapan urin yang tidak biasa, rasa lelah yang tidak biasa, nyeri di daerah perut kanan.

Pemantauan selama pengobatan dengan Rebozet

Mohon perhatian pada awal terapi, jumlah trombosit Anda dan parameter darah rutin lainnya seperti beberapa enzim hati perlu sering dipantau.

Dalam penelitian pada hewan, ditemukan bahwa Rebozet menyebabkan perkembangan katarak (kekeruhan lensa di mata). Dalam uji coba HCV pada manusia peningkatan risiko kejadian katarak juga terlihat. Dokter Anda mungkin menyarankan agar Anda diperiksa untuk katarak sebagai bagian dari pemeriksaan mata rutin.

Dokter Anda dapat merekomendasikan pemantauan fungsi hati Anda sebelum dan selama pengobatan.

Orang yang lebih tua (65 tahun ke atas)

Data terbatas tentang penggunaan Rebozet pada pasien berusia 65 tahun dan lebih tua. Perhatian harus diberikan ketika mengonsumsi Rebozet jika Anda berusia 65 tahun atau lebih.

Anak - anak

Rebozet dapat digunakan pada anak berusia 6 sampai 17 tahun untuk mengobati *chronic immune (idiopathic) thrombocytopenic purpura* (ITP).

Rebozet tidak dianjurkan pada anak-anak dengan infeksi virus hepatitis C (HCV) untuk mengobati jumlah trombosit yang rendah (trombositopenia).

Mengonsumsi obat lain

Beritahukan dokter, apoteker, atau tenaga profesional kesehatan Anda segera jika Anda baru saja mengambil atau mungkin mengambil obat lain. Ini termasuk obat-obatan yang diperoleh tanpa resep dan vitamin.

Ada beberapa kelompok obat, termasuk obat resep, obat non-resep dan vitamin yang berinteraksi dengan Rebozet sehingga tidak dapat dikonsumsi bersamaan atau memerlukan penyesuaian dosis saat digunakan bersamaan dengan Rebozet. Obat-obat ini termasuk beberapa produk dalam kelompok berikut:

- Obat antasida untuk mengobati maag,
- Golongan obat penurun kolesterol (statin),
- Golongan obat pengobatan HIV (lopinavir/ritonavir),
- Golongan mineral seperti aluminium, kalsium, zat besi, magnesium, selenium dan zinc yang dapat ditemukan dalam suplemen mineral,
- Obat-obatan untuk kanker seperti methotrexate dan topotecan.

Dokter Anda akan meninjau kembali obat-obatan yang sedang Anda konsumsi untuk memastikan Anda tidak sedang mengonsumsi obat-obatan yang tidak dapat digunakan bersamaan dengan Rebozet. Jika Anda membutuhkan obat-obatan ini dan tidak ada obat pengganti yang tersedia, silakan diskusikan dengan dokter Anda.

Beritahukan dokter atau apoteker Anda jika Anda sedang mengonsumsi atau pernah mengonsumsi obat-obat lain belakangan ini, termasuk obat-obat non-resep.

Mengonsumsi Rebozet bersama makanan atau minuman

Rebozet dipengaruhi oleh asupan kalsium. Jangan minum obat Rebozet dengan makanan tinggi kalsium. Rebozet dapat dikonsumsi bersamaan dengan makanan rendah kalsium seperti:

- Buah-buahan seperti nanas, kismis dan stroberi
- Daging rendah lemak
- Jus buah yang tidak difortifikasi, susu kedelai dan biji-bijian (tidak difortifikasi maksudnya tidak ada tambahan kalsium, magnesium atau zat besi).

Silakan bicarakan dengan dokter Anda; dokter Anda akan bisa menyarankan makanan yang paling cocok dikonsumsi selama pengobatan dengan Rebozet.

Jangan mengonsumsi Rebozet dalam rentang setidaknya 2 jam sebelum atau 4 jam sesudah konsumsi:

- **Obat antasida**, yang biasa digunakan untuk mengobati gangguan pencernaan
- **Suplemen mineral**, seperti aluminium, kalsium, zat besi, magnesium, selenium atau zinc.
- **Produk olahan susu**

Jika Anda melakukannya, Rebozet tidak akan diserap dengan benar oleh tubuh Anda.

Salah satu cara untuk mencegah hal ini adalah dengan mengonsumsi obat-obatan di atas pada pagi hari dan mengonsumsi Rebozet pada malam hari. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

Kehamilan dan Menyusui

Rebozet dianjurkan untuk dikonsumsi selama kehamilan hanya dibenarkan jika kebutuhan medis dikarenakan pengaruh Rebozet terhadap kehamilan belum diketahui. Anda harus menggunakan metode kontrasepsi yang dapat diandalkan (untuk mencegah Anda hamil).

Jika Anda hamil, Anda mungkin hamil atau berencana untuk hamil, tanyakan kepada dokter atau perawat Anda untuk meminta saran sebelum mengonsumsi obat ini.

Jika Anda hamil saat Anda mengonsumsi Rebozet, beritahukan ke dokter Anda segera.

Tidak dianjurkan untuk menyusui selama mengonsumsi Rebozet. Belum diketahui apakah Rebozet masuk ke dalam ASI.

Mintalah saran dari dokter atau apoteker Anda sebelum mengonsumsi obat apapun jika Anda tidak yakin.

Wanita yang berpotensi untuk melahirkan dan pasien laki-laki

Rebozet dapat membahayakan bayi yang belum lahir. Jika Anda seorang wanita yang bisa hamil, Anda harus menggunakan kontrol kelahiran yang dapat diandalkan (kontrasepsi) saat Anda menggunakan Rebozet dan setidaknya 7 hari setelah Anda berhenti menggunakan Rebozet. Tanyakan kepada dokter Anda tentang opsi pengendalian kelahiran yang efektif.

Mengemudi dan Mengoperasikan Mesin

Rebozet dapat menyebabkan pusing dan mempunyai efek samping lain yang menyebabkan Anda menjadi kurang waspada. Jangan mengemudi atau mengoperasikan mesin kecuali Anda yakin obat ini tidak berpengaruh pada Anda.

3 BAGAIMANA CARA MENGONSUMSI REBOZET

Ikuti dengan seksama instruksi yang diberikan oleh dokter Anda. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.

Kapan mengonsumsi Rebozet

Rebozet harus dikonsumsi setidaknya 2 jam sebelum atau 4 jam sesudah konsumsi antasida, produk olahan susu, atau suplemen mineral seperti aluminium, kalsium, zat besi, magnesium, selenium dan zinc. Salah satu cara untuk mengurangi risiko interaksi obat-obat adalah dengan mengonsumsi produk tersebut pada pagi hari dan mengonsumsi Rebozet pada malam hari.

ITP kronis

Dosis awal untuk pasien dewasa dan anak usia 6 sampai 17 tahun adalah 50 mg Rebozet sekali sehari. Dokter Anda mungkin menyesuaikan dosis dan menganjurkan dosis harian Rebozet untuk dikurangi atau ditambahkan berdasarkan respons Anda terhadap Rebozet. Pasien dengan rumpun Asia-Timur/Tenggara perlu memulai pengobatan dengan dosis yang lebih rendah (25 mg sekali sehari).

HCV

Dosis awal untuk pasien dewasa adalah 25 mg Rebozet sekali sehari. Dokter Anda mungkin menyesuaikan dosis dan menganjurkan dosis harian Rebozet untuk dikurangi atau ditambahkan berdasarkan respons Anda terhadap Rebozet. Tidak ada perbedaan dosis awal untuk pasien dengan rumpun Asia-Timur/Tenggara.

Pada awal pengobatan, jumlah trombosit Anda dan parameter darah lainnya akan dipantau secara rutin. Dokter Anda juga akan melakukan pemeriksaan darah untuk menilai fungsi hati Anda sebelum dan selama pengobatan dengan Rebozet.

Anemia aplastik berat yang tidak memperlihatkan respons adekuat terhadap terapi imunosupresif

Dosis awal untuk pasien dewasa adalah 50 mg Rebozet sekali sehari. Jika Anda tergolong rumpun Asia-Timur/Tenggara, diperlukan dosis permulaan yang lebih rendah, yaitu 25 mg sekali sehari.

Selama 1 hingga 2 minggu pertama pengobatan, pemantauan rutin akan dilakukan. Berdasarkan respons Anda terhadap Rebozet, dokter Anda dapat menganjurkan agar dosis harian Anda diubah.

Bagaimana cara mengonsumsi Rebozet

Rebozet harus ditelan sekali sehari, setiap hari, pada waktu yang sama setiap hari dengan menggunakan segelas air.

Apabila Anda lupa mengonsumsi Rebozet

Apabila Anda melewatkan satu dosis, minum segera setelah Anda ingat pada hari yang sama. Minumlah dosis selanjutnya sesuai jadwal. Jangan mengonsumsi dosis ganda di hari berikutnya untuk menutupi dosis yang telah Anda lewatkan. Jika Anda memiliki pertanyaan lebih lanjut terkait Rebozet, tanyakan kepada dokter atau apoteker Anda.

Berapa lama mengonsumsi Rebozet

Jangan berhenti mengonsumsi Rebozet sampai dokter Anda menyarankan Anda untuk melakukannya.

Apabila Anda berhenti mengonsumsi Rebozet

Jika dokter Anda menyarankan untuk menghentikan pengobatan dengan Rebozet, jumlah trombosit Anda akan diperiksa setiap minggu selama empat minggu.

Jika Anda mengalami masalah atau pertanyaan terkait penggunaan Rebozet, silakan berkonsultasi dengan dokter Anda.

Apabila Anda mengonsumsi Rebozet lebih banyak dari yang seharusnya

Jika Anda telah mengambil terlalu banyak Rebozet, atau jika orang lain secara tidak sengaja mengambil obat Anda, segera hubungi dokter atau rumah sakit untuk meminta saran. Tunjukkan kemasan Rebozet. Perawatan medis mungkin diperlukan.

4 EFEK SAMPING YANG MUNGKIN TERJADI

Seperti obat-obatan lainnya, Rebozet dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Rebozet dapat menyebabkan efek samping yang serius

Masalah hati

Rebozet dapat menyebabkan kerusakan pada hati dan menyebabkan penyakit yang serius dan bahkan mengancam nyawa. Anda harus menjalani pemeriksaan darah untuk menilai kondisi hati Anda sebelum dan selama pengobatan dengan Rebozet. Dokter Anda akan menyarankan pemeriksaan darah ini. Pada beberapa kasus, pengobatan Rebozet dapat dihentikan.

Beritahukan segera kepada dokter Anda jika Anda mengalami tanda dan gejala masalah hati berikut ini:

- Kekuningan pada kulit atau bagian putih di mata (tanda ikterus)
- Urin berwarna gelap
- Kelelahan yang tidak biasa
- Nyeri pada perut kanan atas.

Perdarahan setelah Anda menghentikan pengobatan

Ketika Anda menghentikan pengobatan dengan Rebozet, jumlah trombosit darah Anda dapat menurun ke angka sebelum Anda mengonsumsi Rebozet. Efek ini umumnya terjadi dalam rentang waktu sekitar 4 minggu sejak Anda berhenti mengonsumsi Rebozet. Rendahnya jumlah trombosit akan meningkatkan risiko perdarahan. Dokter Anda akan memeriksa jumlah trombosit Anda sekurang-kurangnya 4 minggu sejak Anda berhenti mengonsumsi Rebozet. Beritahukan kepada dokter atau apoteker Anda jika Anda mengalami lebam atau perdarahan setelah Anda berhenti mengonsumsi Rebozet.

Masalah sumsum tulang

Pengidap penyakit seperti yang Anda alami mungkin mengalami masalah sumsum tulang. Obat seperti Rebozet dapat membuat masalah ini semakin memburuk. Tanda-tanda perubahan pada sumsum tulang dapat berupa hasil pemeriksaan darah yang abnormal. Dokter Anda mungkin juga melakukan uji untuk memeriksa sumsum tulang Anda selama pengobatan dengan Rebozet.

Meningginya jumlah trombosit dan meningkatnya risiko penggumpalan darah (trombosis/tromboemboli)

Risiko penggumpalan darah meningkat jika jumlah trombosit terlalu tinggi selama pengobatan dengan Rebozet, namun penggumpalan darah dapat juga terjadi pada kondisi jumlah trombosit normal atau rendah. Jika Anda memiliki sirosis hati, Anda berisiko mengalami penggumpalan darah pada pembuluh darah hati (trombosis vena portal). Anda dapat pula mengalami komplikasi berat berupa terbentuknya gumpalan darah jenis tertentu, seperti gumpalan darah yang terlepas dari pembuluh darah (tromboemboli) ke paru atau yang dapat menyebabkan serangan jantung atau *stroke*. Dokter Anda akan memeriksa jumlah trombosit Anda dan menyesuaikan dosis atau menghentikan Rebozet jika jumlah trombosit Anda terlalu tinggi. Segera beritahukan kepada dokter Anda jika Anda mengalami gejala penggumpalan darah di kaki, seperti pembengkakan atau nyeri pada salah satu kaki.

Efek samping di bawah ini pernah dilaporkan terkait pengobatan dengan Rebozet.

Efek samping yang dilaporkan pada pasien ITP kronis

| Klasifikasi berdasar sistem organ | Frekuensi | Efek samping |
|--|------------------|--|
| Infeksi dan infestasi | Sangat umum | Pilek dan hidung tersumbat (nasofaringitis)*, infeksi saluran pernapasan bagian atas (ISPA)* |

| | | |
|---|------------|--|
| | Umum | Sakit tenggorokan dan ketidaknyamanan saat menelan (faringitis), influenza, herpes di sekitar mulut, radang paru-paru, sinus, tonsilitis (amandel), infeksi saluran pernapasan, radang gusi |
| | Tidak umum | Infeksi kulit |
| Tumor jinak, ganas atau tidak spesifik (termasuk kista dan polip) | Tidak umum | Kanker rektosigmoid |
| Gangguan darah dan getah bening | Umum | Berkurangnya jumlah sel darah merah (anemia), peningkatan jumlah eosinofil dalam darah, peningkatan jumlah sel darah putih, penurunan jumlah trombosit, penurunan hemoglobin, penurunan jumlah sel darah putih |
| | Tidak umum | Anisositosis, anemia hemolitik, <i>myelocytosis</i> , peningkatan neutrofil batang, adanya mielosit, peningkatan jumlah trombosit, peningkatan hemoglobin |
| Gangguan sistem imun | Tidak umum | Hipersensitivitas |
| Gangguan metabolisme dan nutrisi | Umum | Penurunan kalium, penurunan nafsu makan, peningkatan asam urat darah |
| | Tidak umum | Anoreksia, asam urat, penurunan kalsium |
| Gangguan kejiwaan | Umum | Kesulitan tidur, depresi |
| | Tidak umum | Sikap apatis, gangguan <i>mood</i> , sedih |
| Gangguan sistem saraf | Umum | Kesemutan, kehilangan sensitivitas indera, mudah mengantuk, migren |
| | Tidak umum | Gemetar, gangguan keseimbangan, gangguan sensasi raba/sentuh, layu pada separuh badan (<i>hemiparesis</i>), migren dengan aura, gangguan pada saraf perifer, gangguan bicara, neuropati toksik, nyeri kepala tipe vaskular |
| Gangguan mata | Umum | Mata kering, penglihatan kabur, nyeri pada mata, penurunan ketajaman penglihatan |
| | Tidak umum | <i>Lenticular opacities</i> , astigmatisme, katarak kortikal, sering keluar air mata, perdarahan pada retina, gangguan pada pigmen retina, gangguan penglihatan, peradangan pada kelopak mata, <i>keratoconjunctivitis sicca</i> |
| Gangguan telinga dan labirin | Umum | Nyeri pada telinga, vertigo |
| Gangguan jantung | Tidak umum | Peningkatan denyut jantung (takikardia), infark miokardial akut, gangguan kardiovaskular, sianosis, berdebar-debar (palpitasi), takikardia |

| | | |
|--|-------------|---|
| | | sinus, pemanjangan interval QT pada elektrokardiogram |
| Gangguan pembuluh darah | Umum | Trombosis vena dalam (<i>deep vein thrombosis</i>), penumpukan darah abnormal di luar pembuluh darah (hematoma), perasaan hangat yang datang tiba-tiba dan berlangsung intens di sekujur wajah, leher dan dada (<i>hot flush</i>) |
| | Tidak umum | Embolisme, penggumpalan darah di vena yang terletak tepat di bawah permukaan kulit (<i>thrombophlebitis superficial</i>), kemerahan |
| Gangguan pernapasan, rongga dada dan mediastinum | Sangat umum | Batuk [♦] |
| | Umum | Nyeri pada orofaring (<i>oropharyngeal pain</i>), hidung meler (<i>rhinorrhoea</i>) [♦] |
| | Tidak umum | Emboli paru, infark paru, rasa tidak nyaman pada hidung, lepuh pada orofaring (<i>oropharyngeal blistering</i>), gangguan sinus, sesak napas |
| Gangguan pencernaan | Sangat umum | Mual, diare [♦] |
| | Umum | Luka pada mulut, sakit gigi [♦] , muntah, sakit perut [*] , perdarahan pada mulut, perut kembung [*] sangat umum pada pediatrik ITP |
| | Tidak umum | Mulut kering, peradangan mulut, nyeri pada perut, perubahan warna feses, keracunan makanan, sering buang air besar, muntah darah (<i>haematemesis</i>), gangguan pada rongga mulut |
| Gangguan hati dan empedu | Sangat umum | Peningkatan alanin aminotransferase [†] |
| | Umum | Peningkatan aspartat aminotransferase [†] , peningkatan bilirubin dalam darah, fungsi hati yang tidak normal |
| | Tidak umum | Sumbatan empedu (kolestasis), lesi pada hati, hepatitis, hilangnya fungsi hati karena efek samping dari pengobatan (<i>drug-induced liver injury</i>) |
| Gangguan pada kulit dan jaringan bawah kulit | Umum | Ruam, rambut rontok atau penipisan yang tidak biasa (alopecia), keringat berlebihan (hiperhidrosis), gatal di seluruh tubuh, perdarahan bawah kulit (petekie) |
| | Tidak umum | Biduran (urtikaria), kelainan kulit non-radang (dermatosis), keringat dingin, munculnya bercak kemerahan pada kulit (eritema), perubahan pigmen kulit (melanosis), gangguan pigmentasi, perubahan warna kulit, pengelupasan kulit |
| Gangguan tulang, otot dan jaringan penyokong | Umum | Nyeri otot, kram otot, nyeri sendi, nyeri tulang, nyeri punggung |
| | Tidak umum | Kelemahan otot |

| | | |
|--|------------|---|
| Gangguan ginjal dan saluran kemih | Umum | Peningkatan protein dalam urin, peningkatan kadar kreatinin dalam darah, kerusakan yang terjadi di pembuluh darah terkecil di dalam ginjal yang menyebabkan hilangnya fungsi ginjal (<i>thrombotic microangiopathy with acute renal failure</i>) [‡] |
| | Tidak umum | Gagal ginjal, peningkatan sel darah putih dalam urin, nefritis lupus, sering buang air kecil pada malam hari, peningkatan kadar urea dalam darah, peningkatan rasio protein/kreatinin dalam urin |
| Sistem reproduksi dan gangguan payudara | Umum | Jumlah darah yang keluar saat haid berlebihan (<i>menorrhagia</i>) |
| Gangguan umum dan kondisi pada tempat pemberian obat | Umum | Demam [*] , nyeri dada, tidak berenergi [*] sangat umum pada pediatrik ITP |
| | Tidak umum | Dada terasa panas, perdarahan, tidak berenergi, gelisah, peradangan pada luka, lemas (<i>malaise</i>), terasa seperti ada benda asing |
| Abnormalitas hasil pemeriksaan | Umum | Peningkatan fosfatase alkali dalam darah |
| | Tidak umum | Peningkatan bilirubin dalam darah, peningkatan protein total, penurunan albumin dalam darah, peningkatan pH urin |
| Cedera, keracunan dan komplikasi prosedural | Tidak umum | Kulit terbakar |

[♦] Reaksi efek samping tambahan yang diamati dalam studi pediatrik (usia 1 hingga 17 tahun).

[†] Peningkatan alanin aminotransferase dan aspartat aminotransferase dapat terjadi secara bersamaan, meskipun pada frekuensi yang tidak begitu sering.

[‡] Pengelompokan istilah yang digunakan pada ginjal akut dan gagal ginjal.

Efek samping yang dilaporkan pada pasien HCV kronis (Rebozet dikombinasikan dengan terapi anti viral interferon)

| Klasifikasi berdasar sistem organ | Frekuensi | Efek samping |
|---|-------------|--|
| Infeksi dan infestasi | Umum | Infeksi saluran kemih, infeksi saluran pernapasan bagian atas (ISPA), bronkitis, pilek dan hidung tersumbat (nasofaringitis), influenza, herpes di sekitar mulut |
| | Tidak umum | Muntah dan diare akibat infeksi atau peradangan pada dinding saluran pencernaan (gastroenteritis), sakit tenggorokan dan ketidaknyamanan saat menelan (faringitis) |
| Tumor jinak, ganas atau tidak spesifik (termasuk kista dan polip) | Umum | Kanker hati ganas |
| | Sangat umum | Berkurangnya jumlah sel darah merah (<i>anemia</i>) |

| | | |
|---|-------------|--|
| Gangguan darah dan getah bening | Umum | Penurunan jumlah limfosit dalam darah |
| | Tidak umum | Anemia hemolitik |
| Gangguan metabolisme dan nutrisi | Sangat umum | Kehilangan selera makan |
| | Umum | Kelebihan gula darah, penurunan berat badan yang abnormal |
| Gangguan kejiwaan | Umum | Depresi, kecemasan, gangguan tidur |
| | Tidak umum | Kebingungan, mudah merasa iritasi |
| Gangguan sistem saraf | Sangat umum | Sakit kepala |
| | Umum | Pusing, gangguan konsentrasi, gangguan pengecap, sindrom neuropsikiatri yang dapat terjadi pada gagal hati, tidak antusias (letargi), gangguan ingatan, kesemutan |
| Gangguan mata | Umum | Kekeruhan pada lensa mata (katarak), eksudat pada retina, mata kering, mata kuning, perdarahan pada retina |
| Gangguan telinga dan labirin | Umum | Vertigo |
| Gangguan jantung | Umum | Berdebar-debar |
| Gangguan pernapasan, rongga dada, dan mediastinum | Sangat umum | Batuk |
| | Umum | Sesak napas, nyeri pada mulut dan tenggorok, sesak napas saat beraktivitas, batuk berdahak |
| Gangguan pencernaan | Sangat umum | Mual, diare |
| | Umum | Muntah, pembesaran perut, nyeri perut bagian atas, kembung, mulut kering, sembelit, perut tegang, sakit gigi, peradangan mulut, penyakit refluks gastroesofagus, wasir, rasa tidak nyaman di perut, varises pada esofagus |
| | Tidak umum | Perdarahan akibat varises pada esofagus, maag, peradangan dengan rasa terbakar pada jaringan lunak rongga mulut |
| Gangguan hati dan empedu | Umum | Meningkatnya kadar pigmen bilirubin dalam darah, yang dapat menyebabkan menguningnya kulit atau bagian putih mata (<i>hyperbilirubinaemia</i>), penyakit kuning (<i>jaundice</i>), gangguan fungsi hati karena efek samping dari pengobatan (<i>drug induced liver injury</i>) |
| | Tidak umum | Pembekuan darah (<i>portal vein thrombosis</i>), gangguan fungsi hati yang serius (<i>hepatic failure</i>) |
| Gangguan kulit dan jaringan bawah kulit | Sangat umum | Gatal |
| | Umum | Ruam, kulit kering, eksim, ruam pruritus, munculnya bercak kemerahan pada kulit yang disebabkan oleh pelebaran pembuluh darah di bawah kulit (eritema), keringat berlebihan, rambut rontok atau penipisan yang tidak biasa (<i>alopecia</i>) |

| | | |
|--|-------------|---|
| | Tidak umum | Pengelupasan kulit, perubahan warna kulit, gangguan pigmentasi, berkeringat pada malam hari |
| Gangguan tulang, otot, dan jaringan penyokong | Sangat umum | Nyeri otot |
| | Umum | Nyeri sendi, kram otot, nyeri punggung, nyeri pada tangan dan/atau kaki, nyeri otot, nyeri tulang |
| Gangguan ginjal dan saluran kemih | Tidak umum | Kerusakan yang terjadi di pembuluh darah kecil-kecil pada ginjal yang menyebabkan penurunan fungsi ginjal (<i>thrombotic microangiopathy with acute renal failure</i>) [†] , rasa sakit saat buang air kecil (<i>dysuria</i>) |
| Gangguan umum dan kondisi pada tempat pemberian obat | Sangat umum | Demam, mudah lelah, penyakit mirip influenza, tidak berenergi, menggigil |
| | Umum | Mudah teriritasi, nyeri, lesu, nyeri pada tempat injeksi, nyeri dada non-kardiak, edema, kesulitan untuk menggerakkan bagian tubuh |
| | Tidak umum | Gatal pada tempat injeksi, ruam pada tempat injeksi, perasaan tidak nyaman pada dada |
| Abnormalitas hasil pemeriksaan | Umum | Peningkatan bilirubin dalam darah, penurunan berat badan, penurunan jumlah sel darah putih, penurunan hemoglobin, penurunan jumlah neutrofil, peningkatan INR (<i>international normalised ratio</i>), pemanjangan aPTT (<i>activated partial thromboplastin time</i>), peningkatan kadar gula darah, penurunan albumin dalam darah |
| | Tidak umum | Pemanjangan interval QT pada elektrokardiogram |

[†] Pengelompokan istilah yang digunakan pada oliguria, gagal ginjal dan gangguan ginjal

Efek samping yang dilaporkan pada pasien SAA

| Klasifikasi berdasar sistem organ | Frekuensi | Efek samping |
|-----------------------------------|-------------|--|
| Gangguan darah dan getah bening | Umum | Neutropenia, infark pada limpa |
| Gangguan kejiwaan | Sangat umum | Insomnia |
| | Umum | Kecemasan, depresi |
| Gangguan sistem saraf | Sangat umum | Sakit kepala, pusing |
| | Umum | Pingsan (sinkop) |
| Gangguan mata | Umum | Mata kering, mata gatal, katarak, mata kuning, penglihatan kabur, gangguan penglihatan, <i>vitreous floaters</i> |

| | | |
|---|-------------|---|
| Gangguan pernapasan, rongga dada, dan mediastinum | Sangat umum | Batuk, sesak napas, nyeri pada mulut dan tenggorok, hidung meler |
| | Umum | Mimisan |
| Gangguan pencernaan | Sangat umum | Nyeri perut, diare, mual |
| | Umum | Perdarahan pada gusi, lepuh pada mukosa mulut, nyeri pada mulut, muntah, rasa tidak nyaman di perut, sakit perut, sembelit, perut kembung, gangguan menelan, feses berubah warna, lidah bengkak, gangguan motilitas saluran cerna, sering “buang gas” |
| Gangguan hati dan empedu | Sangat umum | Transaminase meningkat |
| | Umum | Peningkatan bilirubin dalam darah (hiperbilirubinemia), ikterus |
| Gangguan kulit dan jaringan bawah kulit | Sangat umum | Lebam (ekimosis) |
| | Umum | Petekie, ruam, gatal, biduran, lesi kulit, ruam makular |
| Gangguan otot, tulang, dan jaringan penyokong | Sangat umum | Nyeri sendi, kram otot, nyeri pada tangan dan/atau kaki |
| | Umum | Nyeri punggung, nyeri otot, nyeri tulang |
| Gangguan ginjal dan saluran kemih | Umum | Kromaturia |
| Gangguan umum dan kondisi pada tempat pemberian | Sangat umum | Mudah lelah, neutropenia disertai demam (<i>febrile neutropenia</i>), demam |
| | Umum | Tidak berenergi, edema perifer, menggigil, lesu |
| Gangguan metabolisme dan nutrisi | Umum | Kelebihan zat besi, penurunan atau peningkatan nafsu makan, hipoglikemia |
| Abnormalitas hasil pemeriksaan | Umum | Peningkatan kadar kreatinin fosfokinase dalam darah |

Jika salah satu dari efek samping yang tercantum dalam brosur ini menjadi serius, atau jika Anda mengalami efek samping apapun yang tidak tercantum dalam brosur ini, beritahukan kepada dokter atau apoteker Anda.

5 PENYIMPANAN REBOZET

Jauhkan dari jangkauan dan penglihatan anak-anak.
Simpan pada suhu di bawah 30°C.

6 INFORMASI LEBIH LANJUT

Kandungan Rebozet

- Zat aktif Rebozet adalah eltrombopag
- Kandungan lainnya adalah

Tablet inti:

Magnesium stearate, Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate.

Tablet penyalut:

Hypromellose, Macrogol 400, Polysorbate 80, Titanium dioxide (E171)

Bagaimana bentuk Rebozet

Rebozet dijual dalam bentuk tablet salut selaput. Setiap tablet mengandung eltrombopag olamine setara dengan 25 mg atau 50 mg eltrombopag.

- Rebozet 25 mg tablet salut selaput berbentuk bulat, bikonveks, berwarna putih atau orange, bersalut selaput dan dicetak dengan 'GS NX3' dan '25' pada masing-masing sisi.
- Rebozet 50 mg tablet salut selaput berbentuk bulat, bikonveks, berwarna biru atau coklat, bersalut selaput dan dicetak dengan 'GS UFU' dan '50' pada masing-masing sisi.

Kemasan

Rebozet Tablet 25 mg, Dus, 2 blister @ 7 tablet, No. Reg.

Rebozet Tablet 50 mg, Dus, 2 blister @ 7 tablet, No. Reg.

HARUS DENGAN RESEP DOKTER

Pemegang Ijin Edar

PT. Novartis Indonesia

Pabrik Pembuat

Dibuat, dikemas dan dirilis oleh **Novartis Pharmaceutical Manufacturing LLC**, Ljubljana, Slovenia untuk Novartis Pharma AG, Basel, Swiss.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Apabila Anda memiliki pertanyaan mengenai obat ini, mohon hubungi dokter atau apoteker Anda.

*PIL based on BPL v3.0 13-Aug-2020 (pediatric ITP and 2nd line SAA) **NPM LLC***