



Revolade®

Systemic hemostatic agent

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Film-coated Tablets

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

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

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

Active substance

Eltrombopag olamine

Active moiety

Eltrombopag

Excipients

Tablet Core:

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Tablet Coating:

Hypromellose

Macrogol 400 (polyethylene glycol 400)

Titanium dioxide (E171)

Polysorbate 80 (25 mg tablet only)

Iron oxide red (E172) (50 mg tablet only)

Iron oxide yellow (E172) (50 mg tablet only)

CLINICAL PARTICULARS

Therapeutic Indications

Revolade is indicated for immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis in patients aged 6 years and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

Revolade is indicated in adult patients with acquired severe aplastic anemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or management of chronic hepatitis C and its complications.

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with Eltrombopag should not be to normalise platelet counts.

Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc) (*see Interactions, Pharmacokinetics – Absorption*).

Eltrombopag may be taken with food containing little (< 50 mg) or preferably no calcium (*see Interactions, Pharmacokinetics*).

Immune thrombocytopenia

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

Initial Dose Regimen

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

For patients of East Asian ancestry (e.g. Chinese, Japanese, Taiwanese, Korean or Thai), Eltrombopag should be initiated at a reduced dose of 25 mg once daily (*see Pharmacokinetic properties, Special populations*).

Monitoring and dose adjustment

After initiating Eltrombopag, adjust the dose to achieve and maintain a platelet count $\geq 50,000/\mu\text{L}$ as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.

Clinical haematology and liver function tests should be monitored regularly throughout therapy with Eltrombopag and the dose regimen of Eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with Eltrombopag, 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.

Table 1: Dose adjustments of Eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/ μL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day. [#]
$\geq 50,000/\mu\text{L}$ to $\leq 150,000/\mu\text{L}$	Use lowest dose of Eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150,000/ μL to $\leq 250,000/\mu\text{L}$	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250,000/ μL	Stop Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $\leq 100,000/\mu\text{L}$, reinstitute therapy at a daily dose reduced by 25 mg.*

- For patients taking 25 mg Eltrombopag once every other day, increase dose to 25 mg once daily.

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

Eltrombopag 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 Eltrombopag.

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

The standard Eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation

Treatment with Eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of Eltrombopag 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. In non-splenectomised patients, this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (*see Special warnings & precautions for use*).

Chronic hepatitis C (HCV) associated thrombocytopenia

When Eltrombopag is given in combination with antiviral therapies, reference should be made to the full prescribing information of the respective coadministered medicinal products for comprehensive details of administration.

Use the lowest dose of Eltrombopag to achieve and maintain a platelet count necessary to initiate and optimise antiviral therapy. Dose adjustments are based upon the platelet count response. Do not use Eltrombopag to normalize platelet counts. In clinical studies, platelet counts generally increase within 1 week of starting Eltrombopag.

Adult

Initial Dose Regimen

Initiate Eltrombopag at a dose of 25 mg once daily.

No dosage adjustment is necessary for HCV patients of East Asian ancestry (e.g. Chinese, Japanese, Taiwanese, Korean or Thai), or patients with mild hepatic impairment.

Monitoring and dose adjustment

Adjust the dose of Eltrombopag in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy (see Table 2). Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy adjust the dose of Eltrombopag as necessary to avoid dose reduction of peginterferon. Monitor platelet counts 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.

Do not exceed a dose of 100 mg Eltrombopag once daily.

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

Table 2: Dose adjustments of Eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/ μ L following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
\geq 200,000/ μ L to \leq 400,000/ μ L	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000/ μ L	Stop Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/ μ L, reinstate therapy at a lower daily dose*.
>400,000/ μ L after 2 weeks of therapy at lowest dose of Eltrombopag	Discontinue Eltrombopag

For patients taking 25 mg Eltrombopag once every other day, increase dose to 25 mg once daily.

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

Discontinuation

In patients with HCV genotype 1/4/6, independent of the decision to continue interferon therapy, discontinuation of Eltrombopag therapy should be considered in patients who do not achieve virological response at week 12. If HCV-RNA remains detectable after 24 weeks of treatment, Eltrombopag therapy should be discontinued.

Eltrombopag 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 Eltrombopag (*see Warnings and Precautions*).

Children

The safety and efficacy of Eltrombopag in children with chronic HCV have not been established.

Severe Aplastic Anaemia

Adults

Initial Dose Regimen

Initiate Eltrombopag at a dose of 50 mg once daily.

For SAA patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), Eltrombopag should be initiated at a dose of 25 mg once daily (*see Pharmacokinetic, Special populations*).

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting Eltrombopag (*see Clinical Studies*). Adjust the dose of Eltrombopag in 50 mg increments every 2 weeks as necessary to achieve the target platelet count $\geq 50,000/\mu\text{L}$. Do not exceed a dose of 150 mg daily. Monitor clinical haematology and liver tests regularly throughout therapy with Eltrombopag and modify the dosage regimen of Eltrombopag based on platelet counts as outlined in Table 3.

Table 3: Dose adjustments of Eltrombopag in patients with severe aplastic anaemia

Platelet Count Result	Dose Adjustment or Response
< 50,000/ μL following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients of East 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.
$\geq 200,000/\mu\text{L}$ to $\leq 400,000/\mu\text{L}$ at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400,000/ μL	Stop Eltrombopag for at least one week. Once the platelet count is < 150,000/ μL , reinstitute therapy at a dose reduced by 50 mg.
> 400,000/ μL after 2 weeks of therapy at lowest dose of Eltrombopag	Discontinue Eltrombopag

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

Once platelet count > 50,000/ μL , haemoglobin > 10 g/dL in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) > 1 x 10⁹/L for more than 8 weeks, the dose of Eltrombopag should be reduced by up to 50%. If counts stay stable after 8 weeks at the reduced dose, then discontinue Eltrombopag and monitor blood counts. If platelet counts drop to < 30,000/ μL , haemoglobin to < 9 g/dL or ANC < 0.5 x 10⁹/L, Eltrombopag may be reinitiated at the previous dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with Eltrombopag, discontinue therapy. Consider Eltrombopag discontinuation if new cytogenetic abnormalities are observed (*see Adverse Reactions*). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of Eltrombopag (*see Warnings and Precautions*).

Children

The safety and efficacy of Eltrombopag in children with SAA have not been established.

Other Populations (All Indications)

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use Eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (*see Pharmacokinetic, Special populations*).

Hepatic impairment

ITP patients with liver cirrhosis (hepatic impairment, Child-Pugh score ≥ 5) should use Eltrombopag with caution and close monitoring (*see Warnings and Precautions, Pharmacokinetics, Special populations*).

If the use of Eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of Eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose.

Thrombocytopenic patients with chronic HCV with hepatic impairment should initiate Eltrombopag at a dose of 25 mg once daily (*see Pharmacokinetics, Special Populations*).

The risk of thromboembolic events (TEEs) has been found to be increased in thrombocytopenic patients (platelet count $< 50,000/\mu\text{L}$) with chronic liver disease (CLD), without concomitant ITP, treated with 75 mg Eltrombopag once daily for two weeks in preparation for invasive procedures (*see Special warnings & precautions for use*).

Chronic HCV patients with hepatic impairment and severe aplastic anaemia patients with hepatic impairment should initiate Eltrombopag at a dose of 25 mg once daily (*see Pharmacokinetic, Special populations*).

Paediatric population

The safety and efficacy of Eltrombopag have not been established in paediatric ITP patients younger than one year. In paediatric clinical trials, subjects between 1 to 5 years of age were administered Eltrombopag as a *powder for oral suspension* formulation. Eltrombopag is only available as tablets and cannot be used in patients who are unable to swallow Eltrombopag tablets whole. The safety and efficacy of Eltrombopag in paediatric patients with chronic HCV related thrombocytopenia or SAA have not been established.

Elderly

There are limited data on the use of Eltrombopag in subjects aged 65 years and older. In the clinical studies of Eltrombopag, overall no clinically significant differences in safety of Eltrombopag were observed between subjects aged at least 65 years and younger subjects. 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 Pharmacokinetics, Special populations*).

Contraindications

Hypersensitivity to Eltrombopag or to any of the excipients.

Special warnings and precautions for use

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 Eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia and myelodysplastic syndromes (MDS).

Hepatotoxicity

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

In clinical studies of adult and paediatric subjects (aged 1 to 17 years) with chronic ITP who received Eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed (*see Undesirable effects*).

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 adult with chronic ITP, adverse events of ALT increase were reported in 5.7% and 4.0% of Eltrombopag and placebo treated patients respectively. In two placebo-controlled studies in paediatric subjects (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the Eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in thrombocytopenic subjects with HCV, ALT or AST >3 x ULN were reported in 34% and 38% of the Eltrombopag and placebo groups, respectively. Eltrombopag administration in combination with peginterferon/ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76% and 50% of the Eltrombopag and placebo groups, respectively.

Measure serum ALT, AST and bilirubin prior to initiation of Eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests until the abnormalities resolve, stabilise, or return to baseline levels. Discontinue Eltrombopag if ALT levels increase (≥ 3 x ULN) in patients with normal liver function or ≥ 3 x baseline (or > 5 x ULN, whichever is the lower) in patients with elevations in transaminases before treatment and that are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Exercise caution when administering Eltrombopag to patients with hepatic disease. In ITP and SAA patients, use a lower starting dose of Eltrombopag and monitor closely when administering to patients hepatic impairment (*see Posology and method of administration*).

Hepatic decompensation (Use with interferon)

Chronic HCV patients with 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 where Eltrombopag was used as necessary to achieve the target platelet count required to enable antiviral therapy, safety findings suggestive of hepatic decompensation were reported more frequently in the Eltrombopag arm (13%) than in the placebo arm (7%). Subjects with low albumin levels (< 3.5 g/dL) or 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. Refer to the respective interferon prescribing information for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

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

Thrombotic/Thromboembolic Complications

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

Use caution when administering Eltrombopag to patients with known risk factors for thromboembolism (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, advanced age, prolonged periods of immobilisation, malignancies, contraceptives, 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 platelets count exceeds the target levels (*see Posology and method of administration*). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

In adult ITP studies, 21 thromboembolic/thrombotic events (TEEs) were observed in 17 out of 446 subjects (3.8%). The TEEs included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke, and suspected prolonged reversible ischemic neurologic deficiency.

Eltrombopag 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 Eltrombopag to ITP patients with hepatic impairment (*see Posology and method of administration and Undesirable effects*).

In 2 controlled studies in thrombocytopenic subjects with HCV receiving interferon based therapy, 31 out of 955 subjects (3%) treated with Eltrombopag experienced a TEE (3%) and 5 out of 484 subjects (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1% in subjects treated with Eltrombopag 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 subjects with chronic liver disease (n = 288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in subjects treated with 75 mg Eltrombopag once daily for 14 days. Six of 143 (4%) adult subjects with chronic liver disease receiving Eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five Eltrombopag treated subjects with a TEE experienced the event within 14 days of completing Eltrombopag dosing and at a platelet count above 200,000 μL .

Eltrombopag 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 re-occur in ITP patients upon discontinuation of treatment with Eltrombopag. Following discontinuation of Eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients (*see clinical studies*), which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if Eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with Eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of Eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and Eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Malignancies and progression of malignancies

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a theoretical concern that they may stimulate the progression of existing haematological malignancies such as MDS.

Across the adult clinical trials in ITP (n = 493) and HCV (n=1439) no difference in the incidence of malignancies or haematological malignancies was demonstrated between placebo and Eltrombopag treated subjects. This is consistent with information derived from non-clinical research, where no malignant cell proliferation has been demonstrated upon co-incubation of Eltrombopag with MDS cell lines, multiple leukemic cell lines and solid tumour cell lines (colon, prostate, ovary and lung).

Cataracts

Cataracts were observed in toxicology studies of Eltrombopag in rodents (*see Preclinical safety data*). Routine monitoring of patients for cataracts is recommended.

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

Loss of response to Eltrombopag

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

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.

Interference with serological testing

Eltrombopag is highly colored and so 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 Revolade. 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.

Interactions with other medicinal products and other forms of interaction

Effects of Eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that Eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that Eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of Eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% CI: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin, however, clinically significant interactions are not expected between Eltrombopag and atorvastatin or fluvastatin. When co-administered with Eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken.

OATP1B1 and BCRP substrates

Concomitant administration of Eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

Cytochrome P450 substrates

In studies utilising human liver microsomes, Eltrombopag (up to 100 μ M) 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 Eltrombopag 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.

Effects of other medicinal products on Eltrombopag

Cyclosporine

In vitro studies also demonstrated that Eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. A decrease in Eltrombopag exposure was observed with co-administration of 200 mg and 600 mg cyclosporine (a BCRP inhibitor, see Pharmacokinetics). This decrease in exposure is not considered clinically meaningful. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (*see Posology and Method of Administration*). Platelet count should be monitored at least weekly for 2 to 3 weeks when Eltrombopag is co-administered with cyclosporine. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (Chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of Eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma Eltrombopag $AUC_{(0-inf)}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in Eltrombopag absorption due to chelation (*see Posology and method of administration*).

Food Interaction

Administration of a single 50 mg-dose of Eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma Eltrombopag $AUC_{(0-inf)}$ 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 Posology and method of administration*).

Lopinavir/ritonavir

Co-administration of Eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of Eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose of Eltrombopag 100 mg with repeat dose LPV/RTV 400/100 mg

twice daily resulted in a reduction in Eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of Eltrombopag with LPV/RTV 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 Eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

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 Posology and method of administration*).

Fertility, pregnancy and lactation

Fertility

Eltrombopag did not affect female or male fertility in rats at doses 2 and 3 times respectively the human clinical exposure based on AUC (*see Preclinical safety data*).

Pregnancy

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

Breast-feeding

It is not known whether Eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that Eltrombopag is likely secreted into milk (*see Preclinical safety data*); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Eltrombopag therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Lactation

It is not known whether Eltrombopag is excreted in human milk. Eltrombopag is not recommended for nursing mothers unless the expected benefit justifies the potential risk to the infant.

Ability to perform tasks that require judgement, motor or cognitive skills

There have been no studies to investigate the effect of Eltrombopag on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of Eltrombopag. The clinical status of the patient and the adverse event profile of Eltrombopag should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

Adverse Reactions

In 4 controlled and 2 uncontrolled clinical studies, 530 chronic adult ITP patients were treated with Eltrombopag. The mean duration of exposure to Eltrombopag was 260 days. 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: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

In 2 controlled clinical studies 955 thrombocytopenic patients with HCV infection were treated with Eltrombopag. The median duration of exposure was 183 days. The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

The safety of Eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28%) were treated for > 6 months and 9 patients (21%) were treated for > 1 year.

The most important serious adverse reactions were febrile neutropenia and sepsis/infection.

The most common adverse reactions occurring in at least 10% of patients included: headache, dizziness, insomnia, cough, dyspnoea, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, ecchymosis, arthralgia, muscle spasms, pain in extremity, fatigue, febrile neutropenia, and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=550), paediatric ITP studies (N=107), the HCV studies (N=955), the SAA studies (N=43) and post-marketing reports are listed below by

MedDRA system organ class and by frequency.

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	($< 1/10,000$)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

<i>Very common</i>	Nasopharyngitis*, upper respiratory tract infection*
<i>Common</i>	Rhinitis*
<i>Uncommon</i>	Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

<i>Uncommon</i>	Rectosigmoid cancer
-----------------	---------------------

Blood and lymphatic system disorders

<i>Uncommon</i>	Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased
-----------------	---

Immune system disorders

<i>Uncommon</i>	Hypersensitivity
-----------------	------------------

Metabolism and nutrition disorders

<i>Uncommon</i>	Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased
-----------------	--

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered,
Tearfulness

Nervous system disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder,
Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral,
Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy,
Vascular headache

Eye disorders

Common Dry eye, Cataract

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye
pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment
epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity
tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder,
Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis
superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Common Cough*, Oropharyngeal pain*, Rhinorrhoea*

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea*, Mouth ulceration, Toothache*

* Very common in paediatric ITP

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis, Drug-induced liver injury

* Increase of alanine aminotrasferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatitis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculoskeletal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Common Pyrexia*

Uncommon Chest pain, Feeling hot, Pain, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

* Additional adverse reactions observed in paediatric studies (aged 1 to 17 years).

HCV study population (Eltrombopag in combination with interferon anti-viral therapy)

Blood and lymphatic system disorders

Very Common Anaemia

Metabolism and nutrition disorders

Very Common Decreased appetite

Psychiatric disorders

Very Common Insomnia

Nervous systems disorders

Very Common Headache

Eye disorders

Common Cataract

Respiratory, thoracic and mediastinal disorders

Very Common Cough

Gastrointestinal disorders

Very Common Nausea, Diarrhoea

Hepatobiliary disorders

Common Hyperbilirubinaemia, Drug-induced liver injury

Skin and subcutaneous tissue disorders

Very Common Pruritus, Alopecia

Common Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion

Musculoskeletal and connective tissue disorders

Very Common Myalgia

Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

General disorders and administration site conditions

Very Common Fatigue, Pyrexia, Chills, Asthenia, Oedema peripheral, Influenza like illness

Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Renal and urinary disorders

Uncommon Dysuria

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, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia
Common Anxiety, Depression

Nervous systems disorders

Very Common Headache

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very Common Cough, Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very Common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal

distension, Dysphagia, Faeces discoloured, Swollen tongue,
Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very Common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Skin and subcutaneous tissue disorders

Very Common Ecchymosis

Common Rash

Musculoskeletal and connective tissue disorders

Very Common Arthralgia, Muscle spasms, Pain in extremity

Common Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common Chromaturia

General disorders and administration site conditions

Very Common Dizziness, Fatigue, Febrile neutropenia, Pyrexia

Common Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common Blood creative phosphokinase increased

In the single-arm, open-label trial in SAA, subjects had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight subjects had a new cytogenetic abnormality reported, including 5 subjects who had changes in chromosome 7. In the two ongoing studies, cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Postmarketing Data

The following adverse reactions have been reported during post-approval use of Eltrombopag. 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.

Vascular disorders

Rare Thrombotic microangiopathy with acute renal failure

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 myelodysplastic syndrome and severe aplastic anaemia.

Thromboembolic events (TEE)

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 Special warnings and precautions for use*).

In a placebo-controlled study (n=288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving Eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with Eltrombopag experienced the TEE at a platelet count of >200,000/ μ L.

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts \geq 200,000/ μ l (*see Special warnings and precautions for use*).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% of the Eltrombopag and placebo groups, respectively (*see Special warnings and precautions for use*).

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 a small number of ITP patients, Eltrombopag treatment was discontinued due to bone marrow reticulin (*see Special warnings and precautions for use*).

Overdose

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

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of Eltrombopag. 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/ μ L on day 18 after ingestion and the maximum platelet count was 929,000/ μ L. All events were resolved without sequelae following treatment.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, ATC code: B02BX05.

Mechanism of Action

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

Clinical studies

Immune thrombocytopenia (ITP) studies

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 subjects with previously treated chronic ITP. Overall, Eltrombopag was administered to 277 ITP subjects for at least 6 months and 202 subjects for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP subjects 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/ μ L for both treatment groups and in the Eltrombopag group were maintained above 50,000/ μ L at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained $< 30,000/\mu$ L throughout the study.

Platelet count response between 50,000/ μ L - 400,000/ μ L in the absence of rescue medication was achieved by significantly more subjects in the Eltrombopag treated group during the 6 month treatment period, $p < 0.001$. 54% of the Eltrombopag-treated subjects and 13% of placebo-treated subjects achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of subjects responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts $\geq 50,000$ - $400,000/\mu\text{l}$, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with $\geq 75\%$ of assessments in the target range (50,000 to $400,000/\mu\text{l}$), 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	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with Eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

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

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP subjects who had an increase in platelet counts to $\geq 50,000/\mu\text{L}$ at Day 43 from a baseline $< 30,000/\mu\text{L}$; subjects who withdrew prematurely due to a platelet count $> 200,000/\mu\text{L}$ were

considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 subjects with previously treated chronic ITP were randomised 2:1 Eltrombopag (n=76) to placebo (n=38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count $\geq 50,000/\mu\text{l}$ after up to 42 days of dosing (compared to a baseline count of $< 30,000/\mu\text{l}$), 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	0.029	

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 ($\leq 15,000/\mu\text{L}$, $>15,000/\mu\text{L}$) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP subjects with baseline platelet count $\leq 15,000/\mu\text{L}$ the median platelet counts did not reach the target level ($>50,000/\mu\text{L}$), although in both studies 43% of these subjects treated with Eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of subjects with baseline platelet count $\leq 15,000/\mu\text{L}$ treated with Eltrombopag responded at the end of the 6-month treatment period. 42% to 60% of the Eltrombopag-treated subjects 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 302 ITP subjects in the open-label extension study EXTEND (TRA105325), 218 subjects completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19,000/ μ L prior to Eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/ μ L, 85,000/ μ L, 105,000/ μ L, 64,000/ μ L, 75,000/ μ L, 119,000/ μ L and 76,000/ μ L, respectively.

Clinical studies comparing Eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of Eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)

The safety and efficacy of Eltrombopag in paediatric subjects with previously treated chronic ITP have been demonstrated in two studies.

TRA115450 (PETIT2): The primary endpoint was a sustained response, defined as the proportion of subjects receiving Eltrombopag, compared to placebo, achieving platelet counts $\geq 50,000/\mu$ L for at least 6 out of 8 weeks (in the absence of rescue therapy), between Weeks 5 to 12 during the double-blind randomised period. Subjects 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 $< 30,000/\mu$ L. Ninety-two subjects were randomised by three age cohort strata (2:1) to Eltrombopag (n = 63) or placebo (n = 29). The dose of Eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Eltrombopag subjects (40%) compared with placebo subjects (3%) achieved the primary endpoint (Odds Ratio:18.0 [95% CI: 2.3, 140.9] p < 0.001) which was similar across the three age cohorts (Table 6).

Table 6: Sustained platelet response rates by age cohort in pediatric patients with ITP at least 12 months from diagnosis

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

A significantly greater proportion of subjects treated with Eltrombopag (75%) compared with placebo (21%) had a platelet response (at least one platelet count $>50,000/\mu\text{L}$ during the first 12 weeks of randomised treatment in absence of rescue therapy) (Odds Ratio: 11.7, [95% CI: 4.0, 34.5], $p < 0.001$). The proportion of subjects who responded to Eltrombopag in the open-label 24-week period (80%) was similar to that observed during the randomized portion of the trial.

Statistically fewer Eltrombopag subjects required rescue treatment during the randomised period compared to placebo subjects (19% [12/63] vs. 24% [7/29], $p = 0.032$).

At baseline, 71% of subjects in the Eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of Eltrombopag subjects reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo subjects reported any bleeding.

Subjects were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of subjects 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 subjects achieving platelet counts $\geq 50,000/\mu\text{L}$ at least once between Weeks 1 and 6 of the randomised period. Subjects were refractory or relapsed to at least one prior ITP therapy with a platelet count $<30,000/\mu\text{L}$ ($n = 67$). During the randomised period of the study, subjects were randomised by 3 age cohort strata (2:1) to Eltrombopag ($n = 45$) or placebo ($n = 22$). The dose of Eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Eltrombopag subjects (62%) compared with placebo subjects (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] $p = 0.011$). Table 7 shows platelet response across the three age cohorts.

Table 7: Platelet response rates in pediatric patients with ITP at least 6 months from diagnosis

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

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

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

At baseline, 82% of subjects in the Eltrombopag group and 78% in the placebo group reported any bleeding (WHO Grades 1-4). The proportion of Eltrombopag subjects reporting any bleeding decreased to 22% at Week 6. In comparison, 73% of placebo subjects reported any bleeding at Week 6.

Subjects were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 46% (6/13) of subjects 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 Eltrombopag for the treatment of thrombocytopenia in subjects 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, subjects with a platelet count of $< 75,000/\mu\text{L}$ were enrolled and stratified by platelet count ($< 50,000/\mu\text{L}$ and $\geq 50,000/\mu\text{L}$ to $< 75,000/\mu\text{L}$), screening HCV RNA ($< 800,000$ IU/ml and $\geq 800,000$ 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, subjects received open-label Eltrombopag to increase

the platelet count to $\geq 90,000/\mu\text{l}$ for ENABLE 1 and $\geq 100,000/\mu\text{L}$ for ENABLE 2. Eltrombopag 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 subjects could receive open-label Eltrombopag was 9 weeks. If sufficient platelet counts were achieved, subjects were randomized (2:1) to the same dose of Eltrombopag at the end of the pre-treatment phase or to placebo. Eltrombopag 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 subjects with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70% of subjects were genotype 1/4/6 and 30% were genotype 2/3. Approximately 30% of subjects had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately $60,000/\mu\text{l}$) were similar among all treatment groups. The median time to achieve the target platelet count $\geq 90,000/\mu\text{L}$ (ENABLE 1) or $\geq 100,000/\mu\text{L}$ (ENABLE 2) was 2 weeks.

In both HCV studies, a significantly greater proportion of subjects treated with Eltrombopag achieved SVR compared to those treated with placebo (see Table 8). Significantly fewer subjects treated with Eltrombopag had any antiviral dose reductions compared to placebo. The proportion of subjects with no antiviral dose reductions was 45% for Eltrombopag compared to 27% for placebo. Significantly fewer subjects treated with Eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, $p = < 0.0001$). The majority of subjects treated with Eltrombopag (76%) had minimum platelet counts that were $\geq 50,000/\mu\text{L}$ compared to 19% for placebo. A greater proportion of subjects in the placebo group (20%) had minimum platelet counts fall below $25,000/\mu\text{L}$ during treatment compared to the Eltrombopag group (3%). In the Eltrombopag group, SVR rates in subjects with high viral loads ($> 800,000$) were 18% as compared to 8% in the placebo group. Significantly more subjects 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 Eltrombopag.

Table 8: ENABLE 1 and ENABLE 2 Virologic Response

	ENABLE 1 ^a		ENABLE 2 ^b	
Pre-antiviral Treatment Phase	N = 715		N = 805	
% Achieving target platelet counts and initiating antiviral therapy ^c	95%		94%	
	Eltrombopag	Placebo	Eltrombopag	Placebo
Antiviral Treatment Phase	n = 450	n = 232	n = 506	n = 253

	%	%	%	%
Overall SVR ^d	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7
Overall EVR ^d	66	50	62	41
HCV Genotype 2,3	84	67	83	56
HCV Genotype 1,4,6	58	41	53	34

^aEltrombopag given in combination with peginterferon alfa-2a (180 mcg 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)

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

^cTarget platelet count was $\geq 90,000/\mu\text{l}$ for ENABLE 1 and $\geq 100,000/\mu\text{l}$ for ENABLE 2.

^dP value < 0.05 for Eltrombopag versus placebo

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 subjects with severe aplastic anaemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count $\leq 30,000/\mu\text{L}$.

Eltrombopag 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 haematological response assessed after 12 weeks of Eltrombopag treatment.

Haematological response was defined as meeting one or more of the following criteria:

1) platelet count increases to $20,000/\mu\text{L}$ above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by $> 1.5\text{g/dL}$, or a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase $> 0.5 \times 10^9/\text{L}$.

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

The treated population had median age of 45 years (range 17 to 77 years) and 56% of subjects were male. At baseline the median platelet count was $20,000/\mu\text{L}$, haemoglobin was 8.4 g/dL, and ANC was $0.58 \times 10^9/\text{L}$. Eighty-six percent of subjects were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of subjects (84%) had received at least 2 prior immunosuppressive therapies. Three subjects had cytogenetic abnormalities at baseline.

The haematological response rate was 40% (17/43 subjects; 95% CI: 25, 56).

Bi- or tri-lineage responses were observed in 4/17 responders (24%) at the initial response assessment and in 8/17 responders (47%) at last assessment. The longest platelet transfusion free period in responders ranged from 8 to 1,190 days with a median of 287 days. The longest RBC transfusion free period in responders ranged from 15 to 1,190 days with a median of approximately 266 days. No major differences were observed in responses between cohorts regarding the number of prior ISTs received.

In the extension phase, 9 patients achieved a multi-lineage response; 5 of these patients subsequently tapered off of treatment with REVOLADE and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months).

Pharmacokinetic properties

Pharmacokinetics

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 $AUC_{(0-\tau)}$ and C_{max} estimates for ITP subjects are presented (Table 9).

Table 9: Steady-state plasma eltrombopag pharmacokinetic parameters in adults with immune thrombocytopenia

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$ ^a , $\mu\text{g}\cdot\text{h}/\text{ml}$	C_{max} ^a , $\mu\text{g}/\text{ml}$
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 - $AUC_{(0-\tau)}$ 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 subjects in a population PK analysis. Plasma Eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for subjects with HCV enrolled in the Phase III studies are presented for each dose studied in Table 10. A higher Eltrombopag exposure was observed in subjects with HCV at a given Eltrombopag dose.

Table 10: Geometric Mean (95% CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Patients with Chronic HCV

Eltrombopag Dose (once daily)	N	C _{max} (µg/ml)	AUC _(0-τ) (µg.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-τ) and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each subject.

Absorption and bioavailability

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 Posology & method of 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.

Metabolism

Eltrombopag is primarily metabolised 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_(0-inf). Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of Eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed Eltrombopag is extensively metabolised. The predominant route of Eltrombopag excretion is via faeces (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 faeces accounts for approximately 20% of the dose. The plasma elimination half-life of Eltrombopag is approximately 21-32 hours.

Pharmacokinetic Interactions

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 Interaction with other medicinal products and other forms of interaction*).

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 Interaction with other medicinal products and other forms of interaction*). 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 Posology & method of administration and Interaction with other medicinal products and other forms of interaction*).

Administration of a single 50 mg dose of Eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma Eltrombopag $AUC_{(0-inf)}$ and C_{max} . Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma Eltrombopag exposure, regardless of calorie and fat content (*see Posology & method of administration and Interaction with other medicinal products and other forms of interaction*).

Special Patient Populations

Renal Impairment

The pharmacokinetics of Eltrombopag has been studied after administration of Eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{(0-inf)}$ 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.

Hepatic Impairment

The pharmacokinetics of Eltrombopag has been studied after administration of Eltrombopag to adult subjects with liver cirrhosis (hepatic impairment). Following the administration of a single 50 mg dose, the $AUC_{(0-\infty)}$ 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. Unbound Eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of Eltrombopag following repeat administration was evaluated using a population PK analysis in 28 healthy adults and 79 subjects with chronic liver disease (37 mild hepatic impairment, 40 with moderate hepatic impairment, and 2 with severe hepatic impairment). Based on estimates from the population PK analysis, subjects with liver cirrhosis (hepatic impairment) had higher plasma Eltrombopag $AUC_{(0-\tau)}$ values as compared to healthy volunteers, and $AUC_{(0-\tau)}$ increased with increasing Child-Pugh score. Compared to healthy volunteers, subjects with mild hepatic impairment had approximately 87% to 110% higher plasma Eltrombopag $AUC_{(0-\tau)}$ values and subjects with moderate hepatic impairment had approximately 141% to 240% higher plasma Eltrombopag $AUC_{(0-\tau)}$ values.

A similar analysis was also conducted in 28 healthy adults and 635 subjects with HCV. A majority of subjects had Child Pugh score of 5-6. Based on estimates from the population PK analysis, subjects with HCV had higher plasma Eltrombopag $AUC_{(0-\tau)}$ values as compared to healthy subjects, and $AUC_{(0-\tau)}$ increased with increasing Child-Pugh score, HCV patients with mild hepatic impairment had approximately 100-144% higher plasma Eltrombopag $AUC_{(0-\tau)}$ compared with healthy subjects. For subjects with HCV initiate Eltrombopag at a dose of 25 mg once daily (*see Dosage and Administration*).

Race

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 (i.e. Japanese, Chinese, Taiwanese and Korean) ITP subjects had approximately 87% higher plasma Eltrombopag $AUC_{0-\tau}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (*see Posology and method of administration*).

The influence of East Asian ethnicity on the pharmacokinetics of Eltrombopag was evaluated using a population pharmacokinetic analysis in 635 subjects with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population PK analysis, East Asian and Southeast Asian subjects had similar pharmacokinetics of Eltrombopag. On average, East/Southeast Asian subjects had approximately 55% higher plasma

Eltrombopag AUC_(0-τ) values as compared to patients of other races who were predominantly Caucasian (*see Dosage 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 23% higher plasma Eltrombopag AUC_{0-τ} 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 635 subjects with HCV (260 females). Based on model estimates, female HCV subjects had approximately 41% higher plasma Eltrombopag AUC_(0-τ) as compared to male subjects.

Elderly Population

The age difference of Eltrombopag pharmacokinetics was evaluated using population PK 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-τ) as compared to younger subjects (*see Dosage and Administration*).

Preclinical safety data

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 subjects at 75mg/day and 3 times the human clinical exposure based on AUC in HCV patients at 100mg/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 subjects at 75mg/day and 2 times the human clinical exposure based on AUC in HCV subjects at 100mg/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). The clinical relevance of these findings is unknown (*see Special warnings and precautions for use*).

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 characterised 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 subjects at 75mg/day and 0.6 times the human clinical exposure based on AUC in

HCV subjects at 100mg/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 subjects. The clinical relevance of these findings is unknown.

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 in ITP subjects.

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 in ITP subjects.

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 in ITP subjects.

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 subjects at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV subjects 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 subjects at 75 mg/day and 7 times the human clinical exposure in HCV subjects 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.

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 in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV subjects at 100 mg/day, 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 (0.3 to 0.5 times the human clinical exposure in ITP subjects at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP subjects at 75 mg/day and 3 times the human clinical exposure in HCV subjects at 100 mg/day 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 should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (*see Pregnancy and Lactation*). 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 in ITP subjects at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day 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, neurobehavioural 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.

In vitro studies with Eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure in ITP patients and 5 times the human clinical exposure in HCV subjects based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of Eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

PHARMACEUTICAL PARTICULARS

Special Precautions for Storage

Store below 30°C.

Nature and Contents of Container

Each pack of REVOLADE contains 14 or 28 film-coated tablets in aluminium foil-aluminium foil blisters.

Not all presentations will be available locally.

Instructions for Use/Handling

No special requirements.

Manufacturer:

See folding box.

Information issued: Nov 2017.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland