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) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Revolade is indicated for immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis in paediatric 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 combination with standard immunosuppressive therapy for the first-line treatment of adult and adolescent patients 12 years and older with severe aplastic anemia.

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. aluminum, 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 ≥50,000/µL. Dose adjustments are based upon the platelet count response. Do not use Eltrombopag to normalize 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-/Southeast-Asian ancestry, 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 ≥50,000/µL 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 (≥50,000/µL 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.[#]
≥50,000/µL to ≤ 150,000/µL	Use lowest dose of Eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150,000/µL to ≤ 250,000/µL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250,000/µL	Discontinue Eltrombopag; increase the frequency of platelet monitoring to twice weekly.

	Once the platelet count is ≤ 100,000/µL, reinitiate 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 increased 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-/Southeast-Asian ancestry, 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/µL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥200,000/µL to ≤ 400,000/µL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000/µL	Discontinue Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/µL, reinitiate therapy at a lower daily dose*.
>400,000/ µL 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.

First-line Severe Aplastic Anemia

Initiate Eltrombopag concurrently with standard immunosuppressive therapy.

Initial Dose Regimen:

The recommended initial dose regimen is listed in Table 3. Do not exceed the initial dose of Eltrombopag.

Table 3. Recommended Initial Eltrombopag Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
Patients 12 Years and Older	150 mg once daily for 6 months

For patients with severe aplastic anemia of East-/Southeast-Asian ancestry or those with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, C), decrease the initial Eltrombopag dose by 50 % as listed in Table 4.

If baseline ALT or AST levels are > 6 x ULN, do not initiate Eltrombopag until transaminase levels are < 5 x ULN. Determine the initial dose for these patients based on Table 3 or Table 4.

Table 4. Recommended Initial Eltrombopag Dose Regimen for Patients of Asian Ancestry or Those with Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh Class A, B, C) in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
Patients 12 Years and Older	75 mg once daily for 6 months

Table 5. Dose of standard immunosuppressive therapy administered with Revolade in the first-line SAA pivotal study

Agent	Dose administered in the pivotal study
Horse antithymocyte globulin (h-ATG)	40 mg/kg/day, based on actual body weight, administered intravenously on Days 1 to 4 of the 6-month treatment period.
Cyclosporine* (therapeutic dose for 6 months, from Day 1 to Month 6, adjusted to obtain a target therapeutic trough level between 200 and 400 micrograms/L)	Patients aged 12 years and older: 3 mg/kg, based on actual body weight, orally every 12 hours (total daily dose of 6 mg/kg/day) for 6 months, starting on Day 1. *Patients >20 years of age with a body mass index >35 or patients aged 12 to 20 years with a body mass index >95th percentile*: 3 mg/kg, based on adjusted body weight$^{\#}$, orally every 12 hours (total daily dose of 6 mg/kg/day) for 6 months, starting on Day 1.
Cyclosporine (maintenance dose, from Month 6 to Month 24)	For patients who achieve a hematologic response at 6 months: 2 mg/kg/day administered orally at a fixed dose for an additional 18 months.

** Dose of cyclosporine may need to be adjusted to achieve the above recommended target trough levels when cyclosporine is used concomitantly with other therapies; refer to the appropriate cyclosporine prescribing information.*

$^{\#}$ Calculated as the midpoint between the ideal body weight and actual body weight.

Monitoring and Dose Adjustment:

Perform clinical hematology and liver tests regularly throughout therapy with Eltrombopag.

Table 6. Dose Adjustments of Eltrombopag for Elevated Platelet Counts in the First-line Treatment of Severe Aplastic Anemia.

Platelet Count Result	Dose Adjustment or Response
> 200 x 10^9/L to ≤ 400 x 10^9/L	Decrease the daily dose by 25 mg every 2 weeks to the lowest dose that maintains platelet count ≥ 50 x 10^9/L.
> 400 x 10^9/L	Discontinue Eltrombopag for one week. Once the platelet count is < 200 x 10^9/L, reinitiate Eltrombopag at a daily dose reduced by 25 mg.

Table 7 summarises the recommendations for dose interruption, reduction, or discontinuation of Eltrombopag in the management of elevated liver transaminase levels and thromboembolic events.

Table 7. Recommended Dose Modifications for Eltrombopag for ALT and AST Elevations and Thromboembolic Events.

Event	Recommendation
ALT or AST Elevations	Increase in ALT or AST > 6 x ULN Discontinue Eltrombopag. Once ALT or AST is < 5 x ULN, reinitiate Eltrombopag at the same dose. Increase in ALT or AST > 6 x ULN after reinitiating Eltrombopag Discontinue Eltrombopag and monitor ALT or AST at least every 3 to 4 days. Once ALT or AST is < 5 x ULN, reinitiate Eltrombopag at a daily dose reduced by 25 mg compared to the previous dose. If ALT or AST returns to > 6 x ULN on the reduced dose Reduce the daily dose of Eltrombopag by 25 mg until ALT or AST is < 5 x ULN.
Thromboembolic events (e.g., deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, myocardial infarction)	Discontinue Eltrombopag but remain on horse antithymocyte globulin (h-ATG) and cyclosporine

The total duration of Eltrombopag treatment is 6 months.

Refractory Severe Aplastic Anaemia

Adults

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

For SAA patients of East-/Southeast-Asian ancestry, 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 ≥ 50,000/µL.

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 8.

Table 8: 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-/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.
≥ 200,000/µL to ≤ 400,000/µL 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	Discontinue Eltrombopag for at least one week. Once the platelet count is < 150,000/µL, reinitiate 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/µL) 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 refractory severe aplastic anaemia patients with hepatic impairment should initiate Eltrombopag at a dose of 25 mg once daily (*see Pharmacokinetic, Special populations*).

In a clinical trial in definitive immunosuppressive therapy-naïve severe aplastic anemia patients with baseline AST/ALT > 5 x ULN were ineligible to participate. The initial dose of Eltrombopag in patients with hepatic impairment in the first-line setting should be determined as necessary based on clinical judgement, tolerability, and close monitoring of liver function.

Paediatric population

The safety and efficacy of Eltrombopag have not been established in paediatric ITP patients younger than one year. In paediatric clinical studies, 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)*.

East-/Southeast-Asian patients
For adult and pediatric patients of East-/Southeast-Asian ancestry, Revolade should be initiated at a dose of 25mg once daily for the treatment of ITP, HCV-associated thrombocytopenia, and refractory SAA. For the treatment of patients with first-line SAA refer to *Posology and method of administration*.

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 (unconjugated) 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 the two placebo controlled Phase III 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 two 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.

In a single-arm open-label clinical trial in definitive immunosuppressive therapy-naïve SAA patients who received Eltrombopag concurrently with h-ATG and cyclosporine, ALT or AST >3 x ULN with total bilirubin >1.5 x ULN was reported in 43.5 % (40/92) of patients. None of these elevations resulted in discontinuation.

In the single-arm phase II monotherapy refractory SAA study, concurrent ALT or AST >3 x ULN with total bilirubin >1.5 x ULN were reported in 5 % of patients. Total bilirubin >1.5 x ULN occurred in 14 % of patients

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 (≥ 3x ULN) in patients with normal liver function or ≥3x 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

In the first-line setting of severe aplastic anemia, ALT, AST, and bilirubin should be measured prior to initiation of Eltrombopag. During treatment, increases in ALT levels should be managed as recommended in Table 6.

Isolated cases of severe liver injury were identified in clinical trials. The elevation of liver laboratory values occurred approximately three months after initiation of Eltrombopag. In all cases, the event resolved following Eltrombopag discontinuation. No cases were identified from clinical trials in refractory SAA, however the number of exposed patients in this indication was limited. As the highest authorized dose is given to patients in SAA indication (150 mg/day) and

due to the nature of the reaction, drug induced liver injury might be expected in this patient's population

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 liver cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving alpha interferon therapy. In the two 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 studies 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, thromboembolic/thrombotic events (TEEs) were observed in 42 out of 763 subjects (5.5%). 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 the two controlled Phase III 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 out 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 returned 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 studies, 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

Thrombopoietin-receptor (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 studies 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 the two controlled Phase III 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 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 µM) 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, aluminum, selenium and zinc. Administration of a single dose of Eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminum hydroxide and 1425 mg magnesium carbonate) decreased plasma Eltrombopag $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})\infty}$ 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

Summary of the safety profile

Immune thrombocytopenia in adult patients
The safety of Revolade 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 Revolade (N=403) and to placebo (N=179), in addition to data from the completed open-label studies TRA108057 (REPEAT), TRA105325 (EXTEND) and TRA112940 *(see Clinical studies)*. 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 and back pain.

Immune thrombocytopenia in paediatric patients

The safety of Revolade in paediatric patients (aged 1 to 17 years) with previously treated ITP has been demonstrated in two studies *(see Clinical studies)*. PETIT2 (TRA115450) was a 2-part, double-blind and open-label, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a 3-part, staggered-cohort, open-label and double-blind, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (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 reactions, marked ♦ in the table 9. The most common adverse reactions in paediatric ITP patients 1 year and older (≥3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache and rhinorrhoea.

Thrombocytopenia with HCV infection in adult patients

ENABLE 1 (TPL103922 n=716, 715 treated with Revolade) and ENABLE 2 (TPL108390 n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of Revolade in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomised patients who received double-blind study medicinal product during Part 2 of ENABLE 1 (Revolade treatment n=450, placebo treatment n=232) and ENABLE 2 (Revolade treatment n=506, placebo treatment n=252). Patients are analysed according to the treatment received (total safety double-blind population, Revolade n=955 and placebo n=484). 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, cough, nausea, diarrhoea, hyperbilirubinaemia, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and oedema.

Definitive immunosuppressive therapy-naïve severe aplastic anaemia in adult and paediatric patients

The safety of Revolade administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine to patients with severe aplastic anaemia who had not received prior definitive immunosuppressive therapy (i.e., ATG therapy, alemtuzumab, or high dose cyclophosphamide) was evaluated in a single-arm, sequential cohort study (see Clinical studies). A total of 154 patients were enrolled and 153 were dosed in this study, of which 92 patients were enrolled to the cohort where Revolade, h-ATG, and cyclosporine were initiated concurrently at the recommended dose and schedule (Cohort 3 regimen): Revolade up to 150 mg once daily on Day 1 to Month 6 (D1-

M6) in combination with h-ATG on Days 1 to 4 and cyclosporine for 6 months, followed by low dose of cyclosporine (maintenance dose) for an additional 18 months for patients who achieved a haematologic response at 6 months. The median duration of exposure to Revolade in this cohort was 183 days with 83.7% of patients exposed for >12 weeks. Adverse drug reactions for the first-line SAA study population (N=92) are shown in Table 11.

The most common adverse drug reactions occurring in at least 10% of patients were alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased (including ocular icterus).

Refractory severe aplastic anaemia in adult patients

The safety of eltrombopag in refractory severe aplastic anaemia 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 *(see Clinical studies)*. Adverse drug reactions for the refractory SAA study population (N=43) are shown in Table 12. 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, cough, oropharyngeal pain, nausea, diarrhoea, abdominal pain, transaminases increased, arthralgia, pain in extremity, fatigue, rhinorrhoea, rhinorrhoea, muscle spasms and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=763), paediatric ITP studies (N=171), the HCV studies (N=1,520), the definitive immunosuppressive therapy-naïve SAA (first-line SAA) study population (N=92), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Table 9: 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,

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
	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 paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn

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

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

‡ Grouped term with preferred terms acute kidney injury and renal failure

Table 10: HCV study population (in combination with anti-viral interferon and ribavirin therapy)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes

	Uncommon	Gastroenteritis, pharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Hepatic neoplasm malignant
Blood and lymphatic system disorders	Very common	Anaemia
	Common	Lymphopenia
	Uncommon	Haemolytic anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hyperglycaemia, abnormal loss of weight
Psychiatric disorders	Common	Depression, anxiety, sleep disorder
	Uncommon	Confusional state, agitation
Nervous system disorders	Very common	Headache
	Common	Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia
Eye disorders	Common	Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal

	Uncommon	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 11: Definitive immunosuppressive therapy-naïve SAA (first-line SAA) study population

Revolade in combination with standard immunosuppressive therapy

System organ class	Frequency	Adverse reaction
Gastrointestinal disorders	common	Nausea, Diarrhoea, Abdominal pain
Skin and subcutaneous tissue disorders	common	Rash, Skin discolouration including hyperpigmentation
Investigations	very common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased (including ocular icterus)

The only adverse drug reaction associated with Eltrombopag reported in definitive immunosuppressive therapy-naïve SAA patients not previously reported in the refractory SAA study population is skin discolouration including skin hyperpigmentation (5.4 %). In definitive immunosuppressive therapy-naïve SAA patients, blood bilirubin increased, was reported more frequently (17.4 %) than in the refractory SAA study population.

New or worsening liver function laboratory abnormalities (CTCAE Grade 3 and Grade 4) in the Revolade D1-M6 cohort were 15.2% and 2.2% for AST, 26.4% and 4.3% for ALT, and 12.1% and 1.1% for bilirubin, respectively.

Paediatric patients

The safety assessment of Revolade in definitive immunosuppressive therapy-naïve paediatric SAA patients 2 to 17 years old is based on 37 patients enrolled in the single-arm, sequential cohort study: 2 patients aged 2 to 5 years, 12 patients aged 6 to 11 years, and 23 patients aged 12 to 17 years *(see Clinical studies)*. The safety profile in paediatric patients was consistent with the safety profile observed in the overall population.

Table 12: SAA study population

System organ class	Frequency	Adverse reaction

Blood and lymphatic system disorders	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	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
Musculosketal and connective tissue disorders	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 ITP patients receiving eltrombopag (n=446), 17 patients 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 4.4).

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%) patients in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count >200,000/µl

No specific risk factors were identified in those patients who experienced a TEE with the exception of platelet counts ≥200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1,439), 38 out of 955 patients (4%) treated with eltrombopag experienced a TEE and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)
Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤35 g/l) or MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal

adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Hepatotoxicity
In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed (see section 4.4).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥3 x ULN was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

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

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% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin
Across the programme, no patients 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 section 4.4).

Cytogenetic abnormalities

In the single-arm study in patients with definitive immunosuppressive therapy-naïve SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. In the entire study across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients

who experienced a cytogenetic abnormality, 7 patients had the loss of chromosome 7, six of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13, which is considered a good prognostic factor in aplastic anemia; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. In the Revolade D1-M6 cohort, 7 patients had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7, occurring within 6.1 months. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with Revolade.

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.

Haematologic malignancies

In the single-arm, open-label study in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) patient has been diagnosed with MDS or AML in each study.

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 Revolade. 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 13 Adverse drug reactions identified during post-approval use

Skin and subcutaneous tissue disorders
Skin discolouration*

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

Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate 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/µL on day 18 after ingestion and the maximum platelet count was 929,000/µL. 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: Antihaemorrhagics, 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. The single-arm phase II study TAPER (CETB115J2411) evaluated the safety and efficacy of Eltrombopag and its ability to induce sustained response after treatment discontinuation in 105 adult ITP patients who relapsed or failed to respond to first-line corticosteroid treatment.

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

Platelet count response between 50,000/µL - 400,000/µL 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 14: Secondary efficacy results from RAISE	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
p-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-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)
p-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 ≥ 50,000/μL at Day 43 from a baseline < 30,000/μL; subjects who withdrew prematurely due to a platelet count > 200,000/μL 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 15: Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/μl after up to 42 days of dosing (compared to a baseline count of < 30,000/μl), n (%)	43 (59)	6 (16)
p-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)
p-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 (≤ 15,000/μL, >15,000/μL) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP subjects with baseline platelet count ≤ 15,000/μL the median platelet counts did not reach the target level (>50,000/μL), 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 ≤ 15,000/µL 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/µL prior to Eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/µl, 85,000/µl, 105,000/µl, 64,000/µl, 75,000/µL, 119,000/µL and 76,000/µl, respectively.

CETB115J2411 (TAPER)

CETB115J2411 was a single-arm phase II study including ITP patients treated with Revolade after first-line corticosteroid failure irrespective of time since diagnosis. A total of 105 patients were enrolled in the study and started treatment with Revolade 50 mg once daily (25 mg once daily for patients of East-/Southeast Asian ancestry except for Japanese patients in Japan who received 12.5 mg once daily). The dose of Revolade was adjusted during the treatment period based on individual platelet counts with the goal to achieve a platelet count ≥100,000/µl.

Of the 126 patients that were screened for inclusion in the TAPER study, 105 patients received at least one dose of Revolade, 70 patients (66.7%) completed treatment and 35 patients (33.3%) discontinued treatment early.

Primary analysis results of sustained response off treatment

Patients who reached a platelet count of ≥100,000/µl and maintained platelet counts for 2 months ≥70,000/µl were eligible for tapering off Revolade and treatment discontinuation. To be considered as having achieved a sustained response off treatment, a patient had to maintain platelet counts ≥30,000/µl, in the absence of bleeding adverse events or any rescue therapy, both during the treatment tapering period and following discontinuation of treatment until Month 12.

The tapering schedule recommended dose reductions of 25 mg every 2 weeks, if the platelet counts were stable, followed by dosing at 25 mg on alternate days for 2 weeks until treatment discontinuation.

The duration of tapering was individualized depending on the starting dose and the response of the patient. The tapering was done in smaller drug decrements of 12.5 mg every second week for patients of East-/Southeast Asian ancestry. If a relapse (defined as platelet count <30,000/µl) occurred during the 12-month treatment period, patients were offered a new course of Revolade at the appropriate starting dose.

The study met the primary objective by demonstrating that Revolade was able to induce sustained response off treatment, in the absence of bleeding events or the use of rescue therapy, by Month 12 in 32 patients of the 105 enrolled patients (30.5%; p<0.0001; 95% CI: 21.9, 40.2).

Eighty-nine patients (84.8%) achieved a complete response (platelet count ≥100,000/μl) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts <70,000/μl. Forty-four patients (41.9%) were able to be tapered off Revolade through treatment discontinuation while maintaining platelet counts ≥30,000/μl in the absence of bleeding adverse events or any rescue therapy (Table 16).

The median duration of sustained response after treatment discontinuation to Month 12 was 33.3 weeks (min-max: 4-51).

The overall safety analysis is consistent with previously reported data and the risk benefit assessment remained unchanged for the use of eltrombopag in patients with ITP.

Table 16 Proportion of patients with sustained response off treatment at month 12 (Full Analysis Set) in TAPER

		All patients N=105		Hypothesis Testing	
		n (%)	95% CI	p-value	Reject H0
Step 1:	Patients who reached platelet count ≥100,000/μl at least once	89 (84.8)	(76.4, 91.0)		
Step 2:	Patients who maintained stable platelet count for 2 months after reaching 100,000/μl (no counts below 70,000/μl)	65 (61.9)	(51.9, 71.2)		
Step 3:	Patients who were able to be tapered off the drug through treatment discontinuation, maintaining platelet count ≥30,000/μl in the absence of bleeding adverse events or use of any rescue therapy	44 (41.9)	(32.3, 51.9)		
Step 4:	Patients with sustained response off treatment until Month 12, maintaining platelet count ≥30,000/μl in the absence of bleeding adverse events or use of any rescue therapy	32 (30.5)	(21.9, 40.2)	<0.0001*	Yes

N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.

n: Number of patients who are at the corresponding category.

The 95% CI for the frequency distribution was computed using Clopper-Pearson exact method.

Clopper Pearson test is used for testing whether the proportion of responders is greater than 15%.

CI and p-values are reported.

** Indicates statistical significance (one-sided) at the 0.05 level.*

Results of an early response on treatment analysis by time since ITP diagnosis

An ad-hoc analysis was conducted on the n=105 patients by time since ITP diagnosis to assess the early response to Revolade treatment across four different ITP duration categories (newly diagnosed ITP <3 months, persistent ITP 3 to <6 months, persistent ITP 6 to ≤12 months, and chronic ITP >12 months).

49% of patients (n=51) had an ITP duration of <3 months, 20% (n=21) of 3 to <6 months, 17% (n=18) of 6 to ≤12 months and 14% (n=15) of >12 months.

Until the cut-off date (22-Oct-2021), patients were exposed to Revolade for a median (25^{th} to 75^{th} percentile) duration of 6.2 months (2.3 to 12.0). The median (25^{th} to 75^{th} percentile) platelet count at baseline was 16,000/µl (7,800 to 28,000/µl).

Platelet count response, defined as a platelet count ≥50,000/µl at least once by Week 9 without rescue therapy was achieved in 84% (95% CI: 71%, 93%) of newly diagnosed patients (ITP duration <3 months), 91% (95% CI: 70%, 99%) and 94% (95% CI: 73%, 100%) of persistent ITP patients (i.e., with ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and in 87% (95% CI: 60%, 98%) of chronic ITP patients.

The rate of complete response, defined as platelet count ≥100,000/µl at least once by Week 9 without rescue therapy, was 75% (95% CI: 60%, 86%) in newly diagnosed patients (ITP duration <3 months), 76% (95% CI: 53%, 92%) and 72% (95% CI: 47%, 90%) in persistent ITP patients (ITP duration 3 to <6 months and 6 to ≤12 months, respectively), and 87% (95% CI: 60%, 98%) in chronic ITP patients.

The rate of durable platelet count response, defined as a platelet count ≥50,000/µl for at least 6 out of 8 consecutive assessments without rescue therapy during the first 6 months on study, was 71% (95% CI: 56%, 83%) in newly diagnosed ITP patients, 81% (95% CI: 58%, 95%) and 72% (95% CI: 47%, 90%) in persistent ITP patients (ITP duration 3 to <6 months and 6 to ≤12 months, respectively), and 80% (95% CI: 52%, 96%) in chronic ITP patients.

When assessed with the WHO Bleeding Scale, the proportion of newly diagnosed and persistent ITP patients without bleeding at Week 4 ranged from 88% to 95% compared to 37% to 57% at baseline. For chronic ITP patients it was 93% compared to 73% at baseline.

The safety of Revolade was consistent across all ITP categories and in line with its known safety profile.

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 ≥50,000/µL 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/µL. 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 17).

Table 17: Sustained platelet response rates by age cohort in pediatric patients with ITP at least 12 months from diagnosis in PETIT2

	Eltrombopag 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]

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/µL 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 study.

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.

TRA108062 (PETIT): The primary endpoint was the proportion of subjects achieving platelet counts ≥50,000/μL 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/μL (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 18 shows platelet response across the three age cohorts.

Table 18: Platelet response rates in pediatric patients with ITP at least 6 months from diagnosis in PETIT

	Eltrombopag 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%]

A significantly greater proportion of subjects treated with Eltrombopag (36%) compared with placebo (0%) had a platelet response (platelet counts >50,000/μL 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/µL were enrolled and stratified by platelet count (< 50,000/µL and ≥50,000/µL to < 75,000/µL), 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, subjects received open-label Eltrombopag to increase the platelet count to ≥90,000/µl for ENABLE 1 and ≥100,000/µL 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/µl) were similar among all treatment groups. The median time to achieve the target platelet count ≥90,000/µL (ENABLE 1) or ≥100,000/µL (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 19). 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 ≥50,000/µL

compared to 19% for placebo. A greater proportion of subjects in the placebo group (20%) had minimum platelet counts fall below 25,000/µL 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 19: 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

[a]Eltrombopag 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)

[b]Eltrombopag 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)

[c]Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2.

[d]P value < 0.05 for Eltrombopag versus placebo

Definitive immunosuppresive therapy-naïve severe aplastic anemia study

Eltrombopag in combination with horse antithymocyte globulin (h-ATG) and cyclosporine was investigated in a single-arm, single-center, open-label sequential cohort trial in patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy (i.e., ATG therapy, alemtuzumab, or high dose cyclophosphamide). The multiple cohorts differed by treatment start day and duration of Eltrombopag-treatment and the initiation of low dose of cyclosporine (maintenance dose) for patients who achieved a hematologic response at 6 months. A total of 153 patients received Eltrombopag in sequential cohorts:

- Eltrombopag on Day 14 to Month 6 (D14-M6) plus h-ATG and cyclosporine (the trial's Cohort 1 regimen, n=30).
- Eltrombopag on Day 14 to Month 3 (D14-M3) plus h-ATG and cyclosporine (the trial's Cohort 2 regimen, n=31), with half of the patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months.
- Eltrombopag on Day 1 to Month 6 (D1-M6) plus h-ATG and cyclosporine (the trial's Cohort 3 regimen, n=92), with all patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months.

The starting dose of Eltrombopag for adults and adolescent patients aged 12 to 17 years was 150 mg once daily (a reduced dose of 75 mg was administered for East-/Southeast-Asians), 75 mg once daily for patients aged 6 to 11 years (a reduced dose of 37.5 mg was administered for East-/Southeast-Asians), and 2.5 mg/kg once daily for patients aged 2 to 5 years (a reduced dose of 1.25 mg/kg was administered for East-/Southeast-Asians). The dose of Eltrombopag was reduced if the platelet count exceeded 200,000/microL and interrupted and reduced if it exceeded 400,000/microL.

All patients received h-ATG 40 mg/kg/day on Days 1 to 4 of the 6-month treatment period and a total daily dose of 6 mg/kg/day of cyclosporine for 6 months in patients aged 12 years and older or a total daily dose of 12 mg/kg/day for 6 months in patients aged 2 to 11 years. A 2 mg/kg/day maintenance dose of cyclosporine was administered for an additional 18 months to 15 patients who achieved a hematologic response at 6 months in the Eltrombopag D14-M3 cohort and all patients who achieved a hematologic response at 6 months in the Eltrombopag D1-M6 cohort.

Data from the recommended schedule of Eltrombopag on Day 1 to Month 6 in combination with h-ATG and cyclosporine (the trial's Cohort 3 regimen) are presented below. This cohort had the highest complete response rates.

In the Eltrombopag D1-M6 cohort, the median age was 28 years (range 5 to 82 years) with 16.3 % and 28.3 % of patients ≥ 65 years of age and < 18 years of age, respectively. 45.7 % of patients were male and the majority of patients were White (62.0 %).

The efficacy of Eltrombopag in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) >1,000/microL, platelet count >100,000/microL and hemoglobin >10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC >500/microL, platelet count >20,000/microL, or reticulocyte count >60,000/microL

Table 20: Efficacy results in definitive immunosuppressive therapy-naïve SAA patients.

	Rev/Pro D1-M6 + h-ATG + cyclosporine N=92
Month 3, n[*a]	**88**
Overall response, n (%)	66 (75.0)
[95 % CI]	[64.6, 83.6]
Complete response, n (%)	24 (27.3)
[95 % CI]	[18.3, 37.8]
Month 6, n[*a]	**87**
Overall response, n (%)	69 (79.3)
[95 % CI]	[69.3, 87.3]
Complete response, n (%)	38 (43.7)
[95 % CI]	[33.1, 54.7]
Median duration of overall response, n[b]	70
Months (95 % CI)	24.3 (21.4, NE)
Median duration of complete response, n[b]	46
Months (95 % CI)	24.3 (23.0, NE)

**a The number of patients who reached the 3- or 6-month assessment or withdrew earlier is the denominator for percentage calculation*

[b] Number of responders at any time

NE = not estimable

The overall and complete hematological response rates at Year 1 (N=78) are 56.4 % and 38.5 % and at Year 2 (N=62) are 38.7 % and 30.6 % respectively.

Pediatric patients

Thirty seven patients aged 2 to 17 years were enrolled in the single-arm, sequential-cohort trial. Of the 36 patients who reached the 6-month assessment point or withdrew earlier, the complete response rate at 6 months was 30.6 % (0/2 in patients aged 2 to 5 years, 1/12 in patients aged 6 to 11 years, and 10/22 in patients aged 12 to 17 years) and the overall response rate at 6 months was 72.2 % (2/2 in patients aged 2 to 5 years, 7/12 in patients aged 6 to 11 years, and 17/22 in patients aged 12 to 17 years). Out of 25 evaluable patients in the Eltrombopag D1-M6 cohort, the complete response rate at 6 months was 28 % (7/12) and the overall response rate at 6 months was 68 %.

Refractory Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label study 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 ≤ 30,000/µL.

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/µL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/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 x 10^9/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/µL, haemoglobin was 8.4 g/dL, and ANC was 0.58 x 10^9/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 21).

Table 21: Steady-state plasma eltrombopag pharmacokinetic parameters in adults with immune thrombocytopenia

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/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 22. A higher Eltrombopag exposure was observed in subjects with HCV at a given Eltrombopag dose.

Table 22: Geometric Mean (95% CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Patients with Chronic HCV

Eltrombopag Dose (once daily)	N	C_{max} (μg/ml)	$AUC_{(0-\tau)}$ (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 Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

The pharmacokinetic parameters of Eltrombopag after administration of Eltrombopag to 45 patients with definitive immunosuppressive therapy-naïve severe aplastic anemia are shown in Table 23.

Table 23: Steady-state plasma Eltrombopag pharmacokinetic parameters in patients with definitive immunosuppressive therapy-naïve severe aplastic anemia

Eltrombopag dose (once daily)	N	Cmax (microg/mL)	AUCtau (microg.h/mL)
150 mg	45	40.1 (44.9 %)	772 (47.2 %)

Data presented as geometric mean (geometric mean coefficient of variation).

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 $AUC_{(0\text{-}inf)}$. 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 radiolabeled 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 $AUC_{(0\text{-}inf)}$. 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 $AUC_{(0\text{-}inf)}$. 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 $AUC_{(0\text{-}inf)}$. 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. 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 $AUC_{(0\text{-}\tau)}$ values as compared to healthy volunteers, and $AUC_{(0\text{-}\tau)}$ increased with increasing Child-Pugh score. Compared to healthy volunteers, subjects with mild hepatic impairment had approximately 87% to 110% higher plasma Eltrombopag $AUC_{(0\text{-}\tau)}$ values and subjects with moderate hepatic impairment had approximately 141% to 240% higher plasma Eltrombopag $AUC_{(0\text{-}\tau)}$ 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 $AUC_{(0\text{-}\tau)}$ values as compared to healthy subjects, and $AUC_{(0\text{-}\tau)}$ increased with increasing Child-Pugh score, HCV patients with mild hepatic impairment had approximately 100-144% higher plasma Eltrombopag $AUC_{(0\text{-}\tau)}$ 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 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-/Southeast-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-/Southeast-Asian subjects had similar pharmacokinetics of Eltrombopag. On average, East-/Southeast-Asian subjects had approximately 55% higher plasma
Eltrombopag $AUC_{(0-\tau)}$ 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 $AUC_{0-\tau}$ 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 635 subjects 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.

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 $AUC_{(0-\tau)}$ 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 F_0 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 (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 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 aluminum foil-aluminum foil blisters.

Not all presentations will be available locally.

Instructions for Use/Handling

No special requirements.

Manufacturer:

See folding box.

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