▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – REVOLADE® (ELTROMBOPAG OLAMINE) TABLETS

1 NAME OF THE MEDICINE

Eltrombopag olamine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

REVOLADE film-coated tablets contain eltrombopag olamine. Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

Each film-coated tablet contains eltrombopag olamine equivalent to either 12.5 mg, 25 mg, 50 mg or 75 mg of eltrombopag as eltrombopag free acid.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Presentations

12.5 mg film-coated tablet*

Round, biconvex, white, and film-coated, debossed with 'GS MZ1' and '12.5' on one side.

25 mg film-coated tablets

Round, biconvex, white, and film-coated, debossed with 'GS NX3' and '25' on one side. Blister packs containing 14*, 28, or 84* tablets.

50 mg film-coated tablets

Round, biconvex, brown, and film-coated, debossed with 'GS UFU' and '50' on one side. Blister packs containing 14*, 28, or 84* tablets.

75 mg film-coated tablets*

Round, biconvex, pink, and film-coated, debossed with 'GS FSS' and '75' on one side.

*Not all strengths and pack sizes may be distributed in Australia.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REVOLADE is indicated for the treatment of:

- paediatric patients with chronic immune thrombocytopaenia (ITP) who have failed other treatments and either (a) need an increased platelet concentration for a planned procedure or (b) are at a high risk of bleeding;
- adult patients with ITP who have had an inadequate response or are intolerant to corticosteroids

and immunoglobulins;

- thrombocytopenia in adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy;
- severe aplastic anaemia (SAA) in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older;
- adult patients with SAA who have had an insufficient response to immunosuppressive therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

REVOLADE dosing regimens must be individualised based on the patient's platelet counts. In most patients, measurable elevations in platelet counts take 1-2 weeks (see section 5.1 Pharmacodynamic properties - Clinical trials).

Chronic ITP

Use the lowest dose of REVOLADE to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use REVOLADE in an attempt to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting REVOLADE and decreased within 1 to 2 weeks after discontinuation.

Initial Dose Regimen

Adults and Paediatric Patients Aged 6 to 17 years

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

For adult and paediatric patients aged 6-17 years of East-/Southeast-Asian ancestry, REVOLADE should be initiated at a reduced dose of 25 mg once daily (see section 5.2 Pharmacokinetic properties - Special Patient Populations).

Paediatric Patients Aged 1 to 5 years

The recommended starting dose of REVOLADE is 25 mg once daily. A lower starting dose (12.5 mg) followed by up-titration can be administered on a case-per-case basis after assessing the risk/benefit.

Monitoring and dose adjustment

Adults and Paediatric Patients Aged 1 to 17 years

After initiating REVOLADE, adjust the dose to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding (see Table 1). Do not exceed a dose of 75 mg daily. Monitor clinical haematology and liver function tests regularly throughout therapy with REVOLADE and the dose of REVOLADE modified based on platelet counts as outlined in Table 1. During therapy with REVOLADE, full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ($\geq 50 \times 10^9$/L for at least 4 weeks) has been achieved. FBCs including platelet count and peripheral blood smears should be obtained monthly thereafter.

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

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

After any REVOLADE dose adjustment, platelet counts should be monitored at least weekly for 2 to 3 weeks. 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 adjustment. In patients with liver cirrhosis (i.e. hepatic impairment), wait 3 weeks before increasing the dose (see section 4.2 Dose and method of

administration - Special populations, and section 4.4 Special warnings and precautions for use).

Table 1 Dose adjustments for REVOLADE in chronic ITP patients

Platelet count	Dose adjustment or response
< 50 x 10^9/L following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 25 mg REVOLADE once every other day, increase dose to 25 mg once daily.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg REVOLADE 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.
> 400 x 10^9/L	Stop REVOLADE. Increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a lower daily dose. For patients taking 25 mg REVOLADE 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

Adults and Paediatric Patients Aged 1 to 17 years

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

Chronic hepatitis C associated thrombocytopenia

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

Use the lowest dose of REVOLADE 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 REVOLADE in an attempt to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 week of starting REVOLADE.

Initial Dose Regimen

Adults

Initiate REVOLADE at a dose of 25 mg once daily. No dose adjustment is required in chronic HCV patients of East-/Southeast-Asian ancestry.

Monitoring and dose adjustment

Adults

Adjust the dose of REVOLADE 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 REVOLADE as necessary to avoid dose reduction of peginterferon. Monitor platelet counts weekly during antiviral therapy until a stable platelet count is achieved. FBCs, including platelet counts and peripheral blood smears, should be obtained monthly thereafter.

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

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

Table 2 Dose adjustments of REVOLADE in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
$< 50 \times 10^9$/L following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments*.
$> 400 \times 10^9$/L	Stop REVOLADE. Increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $< 150 \times 10^9$/L, reinitiate therapy at a lower daily dose. For patients taking 25 mg REVOLADE once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

Discontinuation

Adults

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

REVOLADE 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 REVOLADE (see section 4.4 Special warnings and precautions for use).

Children

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

First-line severe aplastic anaemia

REVOLADE should be initiated concurrently with standard immunosuppressive therapy (see Table 3).

The initial dose of REVOLADE should not be exceeded.

Initial dose regimen

Adult and adolescent patients aged 12 to 17 years

The recommended initial dose of REVOLADE is 150 mg once daily for 6 months.

For adult and adolescent SAA patients of East-/Southeast-Asian ancestry, REVOLADE should be initiated at a dose of 75 mg once daily for 6 months.

Paediatric patients aged 6 to 11 years

The recommended initial dose of REVOLADE is 75 mg once daily for 6 months.

For paediatric SAA patients of East-/Southeast-Asian ancestry aged 6 to 11 years, REVOLADE should be initiated at a dose of 37.5 mg once daily for 6 months.

Paediatric patients aged 2 to 5 years

The recommended initial dose of REVOLADE is 2.5 mg/kg once daily for 6 months.

For paediatric SAA patients of East-/Southeast-Asian ancestry aged 2 to 5 years, REVOLADE should be initiated at a dose of 1.25 mg/kg once daily for 6 months.

Table 3 Dose of standard immunosuppressive therapy administered with REVOLADE in the first-line SAA pivotal study (see section 5.1 Pharmacodynamic Properties - Clinical studies)

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.
Ciclosporin* (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 **Paediatric patients aged 2 to 11 years:** 6 mg/kg, based on actual body weight, orally every 12 hours (total daily dose of 12 mg/kg/day) for 6 months, starting on Day 1. **Patients with a body mass index >95th percentile:** 6 mg/kg, based on adjusted body weight#, orally every 12 hours (total daily dose of 12 mg/kg/day) for 6 months, starting on Day 1.
Ciclosporin (Maintenance dose)	**For patients who achieve a haematologic response at 6 months:** 2 mg/kg/day administered orally at a fixed dose for an additional 18 months.

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

 # Calculated as the midpoint between the ideal body weight and actual body weight.

Monitoring and dose adjustment

Clinical haematology and liver tests should be performed regularly throughout therapy with REVOLADE.

The dosage regimen of REVOLADE should be modified based on platelet counts as outlined in Table 4.

Table 5 summarises the recommendations for dose interruption, reduction, or discontinuation of REVOLADE in the management of liver function abnormalities and thrombosis/embolism events.

Table 4 REVOLADE dose adjustments in first-line severe aplastic anaemia

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 lowest dose that maintains platelet count ≥50 x 10^9/L. In paediatric patients under 12 years of age, decrease the dose by 12.5 mg*.
>400 x 10^9/L	Discontinue REVOLADE for one week. Once the platelet count is <200 x 10^9/L, reinitiate REVOLADE at a daily dose reduced by 25 mg (or 12.5 mg in paediatric patients under 12 years of age)*.

* *For patients taking 25 mg REVOLADE 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.*

Table 5 Recommended dose modification for liver function abnormalities and thrombosis/embolism

Event	Recommendation
Liver function abnormalities	**Increase in ALT >6 times the upper limit of normal (x ULN):** Discontinue REVOLADE. Once ALT is <5 x ULN, reinitiate REVOLADE at the same dose. **Increase in ALT >6 x ULN after reinitiating REVOLADE (and is not attributable to other inciting factors, e.g., serum sickness, sepsis, or azole antifungal agents):** Discontinue REVOLADE and monitor ALT at least every 3 to 4 days. Once ALT is < 5 x ULN, reinitiate REVOLADE at a daily dose reduced by 25 mg compared to the previous dose. **If ALT remains >6 x ULN after on repeat blood tests:** Discontinue REVOLADE. Once ALT is <5 x ULN, reinitiate REVOLADE at a daily dose reduced by 25 mg compared to the previous dose. **If ALT returns to >6 x ULN on the reduced dose:** Reduce the daily dose of REVOLADE by 25 mg until ALT is <5 x ULN. *There is no data on dose modification due to liver function abnormalities in paediatric patients. Dose modification proportional to that in adults (e.g., 12.5 mg) should be considered based on clinical judgement.*
Thrombosis/embolism	**Deep vein thrombosis (DVT), pulmonary embolus (PE), transient ischemic attack (TIA) or stroke, myocardial infarction at any time while on REVOLADE:** Discontinue REVOLADE but remain on h-ATG and ciclosporin. If the platelet level is >50 x 10^9/L at the time of thrombosis, treatment with enoxaparin or another appropriate anticoagulant is recommended as clinically indicated until the platelet count drops <200 x 10^9/L or a standard 3 to 6 month course of anticoagulation is completed.

Discontinuation

The total duration of REVOLADE treatment is 6 months.

Excessive platelet count responses (as outlined in Table 4) or certain adverse events (as outlined in Table 5) also necessitate discontinuation of REVOLADE.

Refractory Severe Aplastic Anaemia

Initial Dose Regimen

Adults

Initiate REVOLADE at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, REVOLADE should be initiated at a dose of 25 mg once daily (see section 5.2 Pharmacokinetic properties and section 4.2 Dose and method of administration – Special populations).

Monitoring and dose adjustment

Adults

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting REVOLADE (see section 5.1 Pharmacodynamic properties - Clinical studies). Adjust the dose of REVOLADE in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50 x 10^9/L. Do not exceed a dose of 150 mg daily. Monitor clinical haematology and liver tests regularly throughout therapy with REVOLADE and modify the dosage regimen of REVOLADE based on platelet counts as outlined in Table 6.

Table 6: Dose adjustments of REVOLADE in refractory patients with severe aplastic anaemia

Platelet Count Result	**Dose Adjustment or Response**
< 50 x 10^9/L 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 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400 x 10^9/L	Stop REVOLADE for at least one week. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue REVOLADE

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

Once platelet count > 50 x 10^9/L, haemoglobin > 100 g/L in the absence of red blood cell (RBC)

transfusion, and absolute neutrophil (ANC) > 1 x 10^9/L for more than 8 weeks, the dose of REVOLADE should be reduced by up to 50%. If counts stay stable after 8 weeks at the reduced dose, then discontinue REVOLADE and monitor blood counts. If platelet counts drop to < 30 x 10^9/L, haemoglobin to < 90 g/L or ANC < 0.5 x 10^9/L, REVOLADE may be reinitiated at the previous dose.

Discontinuation

Adults

If no haematological response has occurred after 16 weeks of therapy with REVOLADE, discontinue therapy. Consider REVOLADE discontinuation if new cytogenetic abnormalities are observed (see section 4.8 Adverse effects (Undesirable effects)). Excessive platelet count responses (as outlined in Table 10) or important liver test abnormalities also necessitate discontinuation of REVOLADE (see section 4.4 Special warnings and precautions for use).

Children

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

Special Populations (all indications)

Elderly

There are limited data on the use of REVOLADE in patients aged 65 years and older. In the clinical studies of REVOLADE, overall no clinically significant differences in efficacy and safety of REVOLADE were observed between patients aged 65 years and older compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2 Pharmacokinetic properties - Special Patient Populations).

Paediatric patients

The safety and efficacy of REVOLADE have not been established in paediatric patients with ITP younger than 1 year of age, chronic HCV, refractory SAA, and definitive immunosuppressive therapy-naïve SAA patients younger than 2 years of age (see section 4.8 Adverse effects (Undesirable effects) and section 5.1 Pharmacodynamic properties – Clinical trials).

Hepatic Impairment

ITP patients with liver cirrhosis (hepatic impairment, Child-Pugh score ≥ 5) should use REVOLADE with caution and close monitoring (see section 4.4 Special warnings and precautions for use and also section 5.2 Pharmacokinetic properties - Special Patient Populations). If the use of REVOLADE is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of REVOLADE in patients with hepatic impairment wait 3 weeks before increasing the dose.

Chronic HCV patients with hepatic impairment and severe aplastic anaemia patients with hepatic impairment should initiate REVOLADE at a dose of 25 mg once daily (see section 5.2 Pharmacokinetic properties - Special Patient Populations).

REVOLADE 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 (see section 4.4 Special warnings and precautions for use).

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg REVOLADE once daily for two weeks in preparation for invasive procedures (see section 4.4 Special warnings and precautions for use).

In a clinical study in definitive immunosuppressive therapy-naïve severe aplastic anaemia, patients with baseline AST/ALT >5 x ULN were ineligible to participate. The initial dose of REVOLADE 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.

Renal Impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use REVOLADE with caution and close monitoring; for example, by testing serum creatinine and/or performing urine analysis (see section 5.2 Pharmacokinetic properties - Special Patient Populations).

East-/Southeast-Asian patients

For adult and paediatric patients of East-/Southeast-Asian ancestry, REVOLADE should be initiated at a dose of 25 mg once daily for the treatment of ITP, HCV-associated thrombocytopenia, and refractory SAA. For the treatment of patients with first-line SAA refer to section 4.2 Dose and Method of Administration, Initial dose regimen.

Administration

Swallow REVOLADE with a glass of water, at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium (see below paragraph), iron, magnesium, selenium, and/or zinc) (see section 5.2 Pharmacokinetic properties – Absorption, and section 4.5 Interactions with other medicines and other forms of interactions).

REVOLADE may be taken with food containing little (< 50 mg) or preferably no calcium (see section 4.5 Interactions with other medicines and other forms of interactions, and section 5.2 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

REVOLADE is contraindicated in patients with hypersensitivity to the active substance eltrombopag olamine or to any of the excipients (see section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

REVOLADE should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain optimal interferon-based therapy.

The safety and efficacy of REVOLADE have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C genotype 1 infection.

Hepatotoxicity

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

Clinical data

In clinical studies of adult and paediatric patients (aged 1 to 17 years) with chronic ITP who received REVOLADE, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect (unconjugated) bilirubin were observed (see section 4.8 Adverse effects (Undesirable effects)).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. In the two placebo controlled Phase III studies in adults 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 patients (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 patients with HCV, ALT or AST $\geq$ 3 x ULN were reported in 34% and 38% of the REVOLADE and placebo groups, respectively. REVOLADE 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 REVOLADE and placebo groups, respectively.

In a single-arm open-label clinical study in definitive immunosuppressive therapy-naïve SAA patients who received REVOLADE concurrently with h-ATG and ciclosporin, 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 study in patients with refractory SAA, 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.

Dosage adjustment

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

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

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

recommended in Table 5.

Caution should be exercised when administering REVOLADE to patients with hepatic disease. In ITP and refractory SAA patients, a lower starting dose of REVOLADE should be used when administering to patients with hepatic impartment (see section 4.2 Dose and method of administration).

Severe liver injury

Isolated cases of severe liver injury were identified in clinical studies. The elevation of liver laboratory values improved or resolved following REVOLADE interruption or discontinuation. No cases of severe liver injury related to REVOLADE were identified in a clinical study in patients with definitive immunosuppressive therapy-naïve SAA or refractory SAA, however the number of exposed patients in these indications was limited. As the highest authorised dose is administered 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.

If the potential benefit for reinitiating REVOLADE treatment is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce REVOLADE and measure serum liver tests weekly during the dose adjusted phase. If liver test abnormalities persist, worsen or recur, then permanently discontinue REVOLADE.

Hepatic decompensation in patients with chronic HCV (concomitant use with interferons)

Chronic HCV patients with liver cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving REVOLADE and alpha interferon therapy. In the two controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) occurred more frequently in the REVOLADE arm (13%) than in the placebo arm (7%). In patients with albumin levels ≤ 35 g/L or with a MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increased risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35 g/L) compared with the group overall. REVOLADE 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. The respective interferon product information for discontinuation criteria should be referred to. REVOLADE should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic Complications

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

Caution should be used when administering REVOLADE to patients with known risk factors for thromboembolism (e.g., advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity, smoking, Factor V Leiden, ATIII deficiency, and antiphospholipid syndrome). Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing REVOLADE treatment if the platelet count exceeds the target levels (see section 4.2 Dose and method of administration).

In adult ITP studies thromboembolic/thrombotic events (TEEs) were observed in 42 out of 763 patients

(5.5%). The TEE events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke, and suspected prolonged reversible ischemic neurologic deficiency. Patients who had a prior history of thrombosis AND at least 2 additional proven risk factors for TEE were excluded from the pivotal studies and therefore the safety of the drug in such patients has not been established.

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

In the two controlled Phase III studies in thrombocytopenic patients with HCV (n = 1439, safety population), 31 out of 955 patients (3%) treated with REVOLADE experienced a TEE and 5 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1% in patients treated with REVOLADE versus < 1% for placebo). No specific temporal relationship between start of treatment and occurrence of TEE was observed. The majority of TEEs resolved and did not lead to the discontinuation of antiviral therapy.

In a controlled study in thrombocytopenic patients with chronic liver disease (n=288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg REVOLADE once daily for 14 days. Six of 143 (4%) adult patients with chronic liver disease receiving REVOLADE experienced TEEs (all of the portal venous system) and two out of 145 (1%) patients and one within the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five REVOLADE patients with a TEE experienced the event within 14 days of completing REVOLADE dosing and at a platelet count above 200 x 10^9/L.

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

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

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

Bleeding following discontinuation of REVOLADE

Following discontinuation of REVOLADE in the ITP and HCV settings, platelet counts returned to baseline levels within 2 weeks in the majority of patients (see section 5.1 Pharmacodynamic properties - Clinical trials), which increases the bleeding risk and in some cases may lead to bleeding. Platelet counts must be monitored weekly for 4 weeks following discontinuation of REVOLADE.

Risk of bone marrow fibrosis

Thrombopoietin receptor (TPO-R) agonists, including REVOLADE, may increase the risk for development or progression of reticulin fibres within the bone marrow. Analysis of the bone marrow biopsy data collected in the EXTEND (TRA105325) study (302 patients with chronic ITP who received

eltrombopag treatment and were followed for up to 72 months or longer) did not suggest that REVOLADE is associated with clinically relevant increases in bone marrow reticulin or collagen fibres. Analysis of the bone marrow biopsy data collected from 159 patients in study TRA112940 (a longitudinal 2 year bone marrow study of eltrombopag in adults with chronic ITP) suggests that, for most chronic ITP patients, treatment with REVOLADE is not associated with clinically significant increases in bone marrow reticulin or collagen. Four patients in the TRA112940 study had bone marrow biopsies performed at > 14 days after the last dose of study medication to assess the reversibility in fibrosis after stopping REVOLADE. The bone marrow biopsies from half of them demonstrated a lower reticulin fibrosis grade when compared with prior biopsy results.

Prior to initiation of REVOLADE, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of REVOLADE, perform FBC with white blood cell count (WBC) differential monthly. If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with REVOLADE and consider a bone marrow biopsy, including staining for fibrosis. Cytogenetic analysis of the bone marrow sample for clonal abnormality should also be considered.

Biennial bone marrow examinations are recommended while patients are receiving eltrombopag treatment until the clinical significance of such findings can be elucidated.

This risk has not been well characterised in children.

Cytogenetic abnormalities

In study ELT112523, bone marrow aspirates were tested for cytogenetic abnormalities by the North American National Institute of Health (NIH). Consistent with the known occurrence of cytogenetic abnormalities in SAA, three out of forty-three patients had a cytogenetic abnormality present at baseline (7%).

At the Primary Response Assessment, twelve to sixteen weeks after initiating REVOLADE treatment, eight patients (19%) had a new cytogenetic abnormality detected after treatment. Of these eight patients, five patients (all non-responders) had cytogenetic abnormalities affecting the structure or number of chromosome 7. One patient subsequently developed fatal hypocellular MDS.

Malignancies and progression of malignancies

There is a theoretical concern that thrombopoietin-receptor (TPO-R) agonists may stimulate the progression of existing haematological malignancies such as MDS (see section 5.3 - Preclinical safety data - Carcinogenicity).

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

There have been post-marketing cases describing appearance or progression of MDS in patients receiving REVOLADE. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal relationship between treatment with REVOLADE and the appearance or worsening of MDS.

Cataracts

Treatment related cataracts were detected in rodents; an effect that was both dose- and time-

dependent. Cataract formation was observed after 6 weeks of treatment at systemic exposure ³ 6 times and 3 times that anticipated in humans in ITP at 75 mg/day and HCV patients at 100 mg/day, respectively (based on plasma AUC). This effect was also evident during long-term (2 years) treatment at systemic exposure 2-5 times the anticipated clinical exposure, with the no-effect-dose level being similar to or below the anticipated clinical exposure level. Cataract formation progressed even after the cessation of treatment. Cataracts have not been observed in dogs after 52 weeks of dosing at 3 times the anticipated clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on plasma AUC.

In the three controlled ITP clinical studies, cataracts developed or worsened in 15 (7%) of patients who received 50 mg REVOLADE daily and 8 (7%) placebo-group patients. Perform a baseline ocular examination prior to administration of REVOLADE and, during therapy with REVOLADE, regularly monitor patients for signs and symptoms of cataracts.

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

Routine monitoring of patients for cataracts is recommended.

Interference with serological testing

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

Photosensitivity

Eltrombopag is phototoxic and photoclastogenic *in vitro*. *In vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic (≥ 15 µg/mL) in the presence of high ultraviolet (UV) light exposures (700 mJ/cm^2). There was no evidence of *in vivo* cutaneous phototoxicity in mice (10 times the human clinical exposure in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day based on AUC) or photo-ocular toxicity in mice or rats (up to 10 and 6 times the human clinical exposure in ITP patients at 75 mg/day and 5 and 3 times the human clinical exposure in HCV patients at 100 mg/day based on AUC). Furthermore, a clinical pharmacology study in 36 patients showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg once daily for six days. 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.

Use in hepatic impairment

REVOLADE 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, caution should be exercised when administering REVOLADE to patients with hepatic impairment (see section 4.2 Dose and method of administration and section 4.8 Adverse effects (Undesirable effects)).

Use in renal impairment

Patients with impaired renal function should use REVOLADE with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2 Pharmacokinetic properties - Special Patient Populations).

Use in the elderly

Refer to sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties for information on elderly patients.

Paediatric use

Refer to sections 4.2 Dose and Method of Administration, 4.4 Special warnings and precautions for use, 4.8 Adverse effects (undesirable effects) and 5.2 Pharmacokinetic properties for information on paediatric patients.

Effects on laboratory tests

Refer to section 4.2 Dose and Method of Administration and 4.4 Special warnings and precautions for use for information on effects on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

***In vitro* evaluation of drug interaction potential**

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. *In vitro* studies demonstrate that eltrombopag is an inhibitor of UGT1A1 UGT1A3 UGT1A4 UGT1A6 UGT1A9 UGT2B7 and UGT2B15 (IC_{50} values 3-33 μM; 1.3-14.6 μg/mL). Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag and potential co-medications.

Based on a human study with radiolabelled 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. *In vitro* eltrombopag was an inhibitor of CYP2C8 and CYP2C9 (IC_{50} 20-25 μM; 8.9-11 μg/mL), but eltrombopag did not inhibit or induce the metabolism of the CYP2C9 probe substrate flurbiprofen in a clinical drug interaction study when eltrombopag was administered as 75 mg once daily for 7 days to 24 healthy adult patients. In the same study, eltrombopag also did not inhibit or induce the metabolism of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole) or CYP3A3 (midazolam). No clinically significant interactions are expected when eltrombopag and CYP450 substrates, inducers, or inhibitors are co-administered.

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter with an IC_{50} value of 2.7 μM (1.2 μg/mL). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor with an IC_{50} value of 2.7 μM (1.2 μg/mL).

Effects of other drugs on REVOLADE and effects of REVOLADE on other drugs

Rosuvastatin

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 patients increased plasma rosuvastatin C_{max} 103% (90% CI: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). When co-administered with eltrombopag, a

reduced dose of rosuvastatin should be considered and careful monitoring should be undertaken. In clinical studies with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for co-administration of rosuvastatin and eltrombopag. Concomitant administration of eltrombopag and other OATP1B1 and BCRP substrates should be undertaken with caution.

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, of which 23 (58%) were women and 30 (75%) were of White/Caucasian/European, 9 (23%) of African American/African, and 1 (3%) of Central/South Asian heritage, showed that the co-administration of a single dose of REVOLADE 100 mg with repeat dose LPV 400 mg/RTV 100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of eltrombopag when LPV/RTV therapy is initiated or discontinued.

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). REVOLADE should be taken at least two hours before or four hours after any products such as antacids, dairy products and other products containing polyvalent cations to avoid significant reduction in eltrombopag absorption (see section 4.2 Dose and method of administration*)*.

Calcium interaction

Administration of a single 50 mg-dose of REVOLADE tablet with a standard high-calorie, high-fat breakfast that included dairy products, reduced plasma eltrombopag $AUC_{0-\infty}$ by 59% and C_{max} by 65% (see section 5.2 Pharmacokinetic properties – Pharmacokinetics: Absorption and bioavailability, and section 4.2 Dose and method of administration).

Ciclosporin

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 ciclosporin (a BCRP inhibitor). Administration of a single dose of eltrombopag 50 mg with 200 mg ciclosporin (a BCRP inhibitor) decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 25% (90% CI: 15%, 35%) and 18% (90% CI: 8%, 28%), respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 39% (90% CI: 30%, 47%) and 24% (90% CI: 14%, 32%), respectively. 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 section 4.2 Dose and method of administration). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Eltrombopag did not affect female or male fertility in rats at doses 2-4 or 1-2 times the human clinical exposure (based on AUC) in ITP patients at 75 mg/day and in HCV patients at 100 mg/day, respectively. However, due to differences in TPO receptor specificity, data from nonclinical species do not fully model effects in humans.

Use in pregnancy – Pregnancy Category B3

Eltrombopag was not teratogenic in rats or rabbits at doses up to 20 mg/kg/day and 150 mg/kg/day respectively. The doses resulted in exposures 2 and 0.5 fold the expected clinical AUC in ITP patients at 75 mg/day and subclinical exposures in HCV patients at 100 mg/day. At the maternally toxic dose of 60 mg/kg/day in rats, foetal weights were significantly reduced and there was an increase in foetal variation, cervical rib, when administered during the period of organogenesis. Eltrombopag treatment during early embryogenesis was associated with an increase in pre-and post-implantation loss (or embryonic death). Due to the fact that eltrombopag is not pharmacologically active in rats or rabbits, the potential teratogenicity of eltrombopag may not have been fully revealed in the studies with these animal species.

There are no adequate and well-controlled studies of REVOLADE in pregnant woman. The effect of REVOLADE on human pregnancy is unknown. REVOLADE should not be used during pregnancy unless the expected benefit clearly out-weighs the potential risk to the foetus.

Use in lactation.

It is not known whether REVOLADE is excreted in human milk. Eltrombopag was detected in the pups of lactating rats 10 days post-partum suggesting the potential for transfer during lactation. REVOLADE is not recommended for nursing mothers unless the expected benefit justifies the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of REVOLADE on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of REVOLADE. The clinical status of the patient and the adverse event profile of REVOLADE should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills. The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Chronic ITP Studies in adult and paediatric patients

Adults

The safety and efficacy of REVOLADE was assessed in adult patients using pooled double-blind, placebo controlled studies (TRA102537 RAISE and TRA100773A and B), and TRA113765 in which 403 patients were exposed to REVOLADE and 179 to placebo, in addition to data from completed open label studies TRA108057 (REPEAT), TRA105325 (EXTEND), and TRA112940. Patients received study

medication for up to 8 years (in EXTEND).

The most common adverse drug reactions (≥10%) for REVOLADE were diarrhoea, nausea, increased alanine aminotransferase and back pain.

Adverse drug reactions for the adult ITP study population are shown in Table 8.

Paediatrics

The safety and efficacy of REVOLADE in paediatric patients (aged 1 to 17 years) with previously treated chronic ITP have been demonstrated in two studies. PETIT 2 (TRA115450) was a two-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 1 (TRA108062) was a three-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. Adverse drug reactions in the adult ITP study population (Table 8) may also occur in the paediatric ITP population.

The most common additional adverse drug reactions (≥10%) for REVOLADE were upper respiratory tract infection, pyrexia, abdominal pain, nasopharyngitis and cough. Additional adverse drug reactions occurring in the paediatric adult ITP study population are shown in Table 9.

Thrombocytopenia in patients with HCV infection in adult patients

The safety of REVOLADE was assessed in adult patients, in two controlled studies, including data from patients who initially received REVOLADE in the pre-antiviral treatment phase and were later randomised to the placebo arm. ENABLE 1 (TPL103922, n=716) and ENABLE 2 (TPL108390, n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of REVOLADE in thrombocytopenic subjects with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies, the safety population consisted of all randomised subjects who received double-blind study drug during Part 2 of ENABLE 1 (REVOLADE treatment n = 449, placebo n = 232) and ENABLE 2 (REVOLADE treatment n = 506, placebo n = 252). Subjects are analysed according to the treatment received (total safety double-blind population, REVOLADE n = 955 and placebo n = 484).

The most common adverse drug reactions (≥10%) for REVOLADE were anaemia, pyrexia, fatigue, headache, nausea, influenza like illness, diarrhoea, decreased appetite, asthenia, pruritus, cough, chills, and myalgia.
The adverse reactions identified in the HCV study populations are presented in Table 10.

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 ciclosporin 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 section 5.1 Pharmacodynamic Properties - 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 ciclosporin were initiated concurrently at the recommended dose and schedule (the trial's 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 ciclosporin for 6 months, followed by low dose of ciclosporin (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. A

summary of the safety profile is provided below (see section - Definitive immunosuppressive therapy-naïve SAA population).

The most common adverse drug reactions (≥10%) for REVOLADE were alanine aminotransferase increased, aspartate aminotransferase increased and blood bilirubin increased (including ocular icterus).

Refractory severe aplastic anaemia in adult patients

The safety of REVOLADE in refractory severe aplastic anaemia was assessed in a single-arm, open-label study (n = 43) in which 12 patients (28%) were treated for > 6 months and 9 patients (21%) were treated for > 1 year. The adverse reactions identified in the SAA study population are presented in Table 11 and Table 12.

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

The most undesirable reactions associated with REVOLADE in ITP, HCV and SAA were mild to moderate in severity, early in onset and rarely treatment limiting.

Tabulated summary of reactions from clinical studies

Adverse reactions from clinical studies are listed below by MedDRA body system organ class and by frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1 in 10,000 and < 1 in 1,000

TRA102537 (RAISE)

In the RAISE study, 197 patients were randomised 2:1, REVOLADE (n=135) to placebo (n=62). Patients received study medication for up to 6 months. See Table 7.

TRA100773B

In this study, 114 patients were randomised and treated for up to 42 days with either placebo (n = 38) or REVOLADE (n = 76).

Table 7 **On-therapy Adverse Events reported by 5% or More of Patients in Either Treatment Group in RAISE**

AE Preferred Term	Treatment Group, n (%)	
	Placebo n = 61	REVOLADE n = 135
Patients with Any AE	56 (92)	118 (87)
Diarrhoea	6 (10)	17 (13)
Nausea	4 (7)	16 (12)
Vomiting	1 (2)	10 (7)
Pharyngolaryngeal pain	3 (5)	9 (7)
Myalgia	2 (3)	8 (6)
Pharyngitis	1 (2)	8 (6)
AST increased	2 (3)	7 (5)

Table 8 Adult ITP study population adverse events

Body system/ organ class/ frequency	Adverse reactions
Infections and infestations	
Common	Pharyngitis
Uncommon	Urinary tract infection, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection
Gastrointestinal disorders	
Very common	Diarrhoea, nausea
Common	Vomiting
Uncommon	Dry mouth, abdominal pain, glossodynia, mouth haemorrhage, abdominal tenderness, faeces discoloured, flatulence, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Eye disorders	
Common	Dry eye, cataract
Uncommon	Vision blurred, lenticular opacities, astigmatism, eye pain, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy, visual acuity reduced, visual impairment, visual acuity tests abnormal, blepharitis and keratoconjunctivitis sicca
Hepatobiliary disorders	
Very common	Increased alanine aminotransferase
Common	Increased aspartate aminotransferase, hyperbilirubinaemia, hepatic function abnormal
Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	
Common	Alopecia, rash
Uncommon	Hyperhidrosis, pruritus generalised, urticaria, dermatosis, petechiae, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	
Very common	Back pain
Common	Musculoskeletal pain (including musculoskeletal chest pain), muscle spasm, myalgia, bone pain
Uncommon	Muscular weakness
Vascular disorders	
Common	Thromboembolic events, thrombotic microangiopathy with acute renal failure

Uncommon	Deep vein thrombosis, embolism, hot flush, thrombophlebitis superficial, flushing, haematoma

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon	Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon	Anaemia, anisocytosis, eosinophilia, haemolytic anaemia, leukocytosis, myelocytosis, thrombocytopenia, haemoglobin increased, band neutrophil count increased, haemoglobin decreased, myelocyte present, platelet count increased, white blood cell count decreased

Immune system disorders

Uncommon	Hypersensitivity

Metabolism and nutrition disorders

Uncommon	Anorexia, hypokalaemia, decreased appetite, gout, hypocalcaemia, blood uric acid increased

Psychiatric disorders

Uncommon	Sleep disorder, depression, apathy, mood altered, tearfulness

Nervous systems disorders

Common	Paraesthesia
Uncommon	Hypoaesthesia, somnolence, migraine, tremor, balance disorder, dysaesthesia, hemiparesis, migraine (with aura), neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache

Ear and labyrinth disorders

Uncommon	Ear pain, vertigo

Cardiac disorders

Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged

Respiratory, thoracic and mediastinal disorders

Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, oropharyngeal pain, sinus disorder, sleep apnoea syndrome

Renal and urinary disorders

Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, proteinuria, blood urea increased, blood creatinine increased, urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common	Menorrhagia

General disorders and administration site conditions

Uncommon	Chest pain, feeling hot, vessel puncture site haemorrhage, asthenia, feeling jittery, inflammation of wound, malaise, pyrexia, sensation of foreign body

Investigations

Uncommon	Blood albumin increased, blood alkaline phosphatase increased, protein total increased, blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon	Sunburn.

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving REVOLADE (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see section 4.4 Special warnings and precautions for use).

Table 9 Additional adverse events observed in paediatric ITP patients

Body system organ class/ frequency	Adverse reactions
Infections and infestations	
Very Common	Nasopharyngitis, upper respiratory tract infection
Common	Rhinitis
Respiratory, thoracic and mediastinal disorders	
Very Common	Cough
Common	Oropharyngeal pain, rhinorrhoea
Gastrointestinal disorders	
Very common	Abdominal pain
Common	Toothache
General disorders and administrative conditions	
Very Common	Pyrexia

Table 10 Adverse events in HCV study population (REVOLADE in combination with antiviral interferon and ribavirin therapy)

Blood and lymphatic system disorders

Very Common	Anaemia
Common	Lymphopenia, haemolytic anaemia

Metabolism and nutrition disorders

Very Common	Decreased appetite
Common	Hyperglycaemia, abnormal loss of weight

Nervous systems 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

Respiratory, thoracic and mediastinal disorders

Very Common	Cough
Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough

Gastrointestinal disorders

Very Common	Diarrhoea, nausea
Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophageal reflux disease, haemorrhoids, abdominal discomfort, gastritis, varices oesophageal, aphthous stomatitis, oesophageal varices haemorrhage

Hepatobiliary disorders

Very Common	Hyperbilirubinaemia
Common	Hepatic failure, drug-induced liver injury, jaundice, portal vein thrombosis

Skin and subcutaneous tissue disorders

Very Common	Pruritus, alopecia
Common	Rash, dry skin, eczema, rash pruritic, erythema, hyperhidrosis, pruritus generalised, night sweats, skin lesion

Musculoskeletal and connective tissue disorders

Very Common	Myalgia
Common	Arthralgia, muscle spasms, back pain (including musculoskeletal chest pain), pain in extremity, musculoskeletal pain, bone pain

General disorders and administrative conditions

Very Common	Fatigue, pyrexia, chills, asthenia, oedema peripheral, influenza like illness
Common	Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, injection site rash, chest discomfort, injection site pruritus

Vascular disorders

Common	Thromboembolic events (including portal vein thrombosis)

Infections and infestations

Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes, gastroenteritis, pharyngitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Common	Hepatic neoplasm malignant

Psychiatric disorders

Very Common	Insomnia
Common	Depression, anxiety, sleep disorder, confusional state, agitation

Ear and labyrinth disorders

Common	Vertigo

Cardiac disorders

Common	Palpitations

Renal and urinary disorders

Uncommon	Dysuria

Investigations

Common	Weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio (INR) increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased, electrocardiogram QT prolonged

Table 11 Adverse events in the refractory SAA study population

Nervous systems disorders

Very Common	Headache, dizziness
Common	Syncope

Eye disorders

Common	Cataract, dry eye, eye pruritus, ocular icterus, vision blurred, visual impairment, vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very Common	Oropharyngeal pain, cough, dyspnoea, rhinorrhoea
Common	Epitaxis

Gastrointestinal disorders

Very Common	Nausea, diarrhoea, abdominal pain
Common	Gingival bleeding, oral mucosal blistering, oral pain, vomiting, abdominal discomfort, abdominal pain, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence

Hepatobiliary disorders

Very Common	Transaminases increased
Common	Blood bilirubin increased (hyperbilirubinemia), jaundice

Skin and subcutaneous tissue disorders

Very Common	Ecchymosis
Common	Rash, petechiae, pruritus, urticaria, skin lesion, rash macular

Musculoskeletal and connective tissue disorders

Very Common	Arthralgia, pain in extremity, muscle spasms
Common	Back pain, myalgia, bone pain

General disorders and administrative conditions

Very Common	Fatigue, dizziness, pyrexia febrile neutropenia,
Common	Asthenia, oedema peripheral, chills, malaise

Blood and lymphatic system disorders

Common	Neutropenia, splenic infarction

Psychiatric disorders

Very common	Insomnia
Common	Anxiety, depression

Renal and urinary disorders

Common	Chromaturia

Metabolism and nutrition disorders

Common	Iron overload, decreased appetite, hypoglycaemia, increased appetite

Investigations

Common	Blood creatine phosphokinase increased

In the single-arm, open-label study in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7 (see section 4.4 Special warnings and precautions for use).

Definitive immunosuppressive therapy-naïve SAA population

The adverse drug reaction associated with REVOLADE reported in the definitive immunosuppressive therapy-naïve SAA patients are summarised in Table 12. In definitive immunosuppressive therapy-naïve SAA patients, blood bilirubin increase (very common) was reported more frequently than in the refractory SAA study population (common, see Table 11).

Table 12 Adverse events in the definitive immunosuppressive therapy-naïve SAA study population (first line SAA)

REVOLADE in combination with standard immunosuppressive therapy.

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)

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 the 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. The safety profile in paediatric patients was consistent with the safety profile observed in the overall population.

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 anaemia; 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 out of 92 (7.6%) 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.

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 (see Table 13). 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 categorised 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

Vascular disorders	
Rare	Thrombotic microangiopathy with acute renal failure
Skin and subcutaneous tissue disorders	
Not known	Skin discolouration *

** In patients taking REVOLADE reversible skin discolouration including hyperpigmentation and skin yellowing was observed at eltrombopag 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.*

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and Signs

In the clinical studies, there was one report of overdose where the patient ingested 5000 mg of REVOLADE. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Liver enzymes measured between Days 2 and 18 after ingestion peaked at 1.6 x ULN in AST, 3.9 x ULN in ALT, and 2.4 x ULN in total bilirubin. The platelet counts were 672 x 10^9/L on day 18 after ingestion and the maximum platelet count was 929 x 10^9/L. All events resolved without sequelae following treatment.

Treatment

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with REVOLADE in accordance with dosing and administration recommendations (see section 4.2 Dose and method of administration).

Because REVOLADE 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, eltrombopag treatment of normal human platelets does not enhance adenosine diphosphate (ADP)-induced aggregation or induce P-selectin expression. Eltrombopag does not antagonise platelet aggregation induced by ADP or collagen.

Mechanism of action

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

Clinical trials

Pharmacotherapeutic group: antihaemorrhagics; ATC code: B02BX 05

Chronic immune thrombocytopaenia (ITP) studies

Adults

The safety and efficacy of REVOLADE have been demonstrated in two, randomised, double-blind, placebo-controlled studies (TRA102537 RAISE and TRA100773B) and one open label study (EXTEND TRA105325) in adult patients with previously treated chronic ITP. The single-arm phase II study TAPER (CETB115J2411) evaluated the safety and efficacy of REVOLADE 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 (TRA102537)

The primary efficacy endpoint was the odds of achieving a platelet count $\geq 50 \times 10^9$/L and $\leq 400 \times 10^9$/L, during the 6 month treatment period, for patients receiving REVOLADE relative to placebo. One hundred and ninety seven patients were randomised 2:1, REVOLADE (n=135) to placebo (n=62), and were stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. Patients received study medication for up to 6 months, during which time the dose of REVOLADE could be adjusted based on individual platelet counts. In addition, patients could have tapered off concomitant ITP medications and received rescue treatments as dictated by local standard of care.

The odds of achieving a platelet count between 50×10^9/L and 400×10^9/L during the 6 month treatment period were 8 times higher for REVOLADE treated patients than for placebo-treated patients (Odds Ratio: 8.2 [99% CI: 3.59, 18.73] p = < 0.001). Median platelet counts were maintained above 50×10^9/L at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below 30×10^9/L throughout the study.

At baseline, 77% of patients in the placebo group and 73% of patients in the REVOLADE group reported any bleeding (WHO Grades 1-4); clinically significant bleeding (WHO Grades 2-4) at baseline was reported in 28% and 22% of patients in the placebo and REVOLADE groups, respectively. The proportion of patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% throughout the 6 month treatment period in REVOLADE-treated patients. When compared to the placebo group, the odds of any bleeding (Grades 1-4) and the odds of clinically significant bleeding (Grades 2-4) were 76% and 65% lower in the REVOLADE-treated patients compared to the placebo-treated patients ($p < 0.001$).

REVOLADE therapy allowed significantly more patients to reduce or discontinue baseline ITP therapies compared to placebo (59% vs. 32%; $p < 0.016$).

Significantly fewer REVOLADE-treated patients required rescue treatment compared to placebo-treated patients [18% vs. 40%; $p = 0.001$].

Four placebo and 14 REVOLADE patients had at least 1 haemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. Fewer REVOLADE-treated patients (29%) required rescue treatment to manage their haemostatic challenge, compared to placebo-treated patients (50%).

In terms of improvements in health related quality of life, statistically significant improvements from baseline were observed in the REVOLADE group in fatigue, including severity and impact on thrombocytopenia-impacted daily activities and concerns [as measured by the vitality subscale of the SF36, the motivation and energy inventory, and the 6-item extract from the thrombocytopenia subscale of the FACIT-Th]. Comparing the REVOLADE group to the placebo group, statistically significant improvements were observed with thrombocytopenia impacted activities and concerns specifically regarding motivation, energy and fatigue, as well as physical and emotional role and overall mental health. The odds of meaningful improvement in health related quality of life while on therapy were significantly greater among patients treated with REVOLADE than placebo.

TRA100773B

In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to $\geq 50 \times 10^9$/L at Day 43 from a baseline $< 30 \times 10^9$/L; patients who withdrew prematurely due to a platelet count $> 200 \times 10^9$/L were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1, with 76 randomised to REVOLADE and 38 randomised to placebo.

Fifty-nine percent of patients on REVOLADE responded, compared to 16% of patients on placebo. The odds of responding were 9 times higher for REVOLADE treated patients compared to placebo (Odds Ratio: 9.6 [95% Cl: 3.31, 27.86] $p < 0.001$). At baseline, 61% of patients in the REVOLADE group and 66% of patients in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39% of patients in the REVOLADE treatment group had bleeding compared with 60% in the placebo group. Analysis over the treatment period using a repeated measures model for binary data confirmed that a lower proportion of REVOLADE patients had bleeding (Grade 1-4) at any point in time over the course of their treatment (Day 8 up to Day 43) compared to patients in the placebo group (OR=0.49, 95% CI=[0.26,0.89], $p = 0.021$). Two placebo and one REVOLADE patient had at least one haemostatic challenge during the study.

In both RAISE (TRA102537) and TRA100773B, the response to REVOLADE relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count ($\leq 15 \times 10^9$/L, $> 15 \times 10^9$/L) at randomisation.

Open Label (Non-Controlled) Studies

EXTEND (TRA105325)

EXTEND is an open label extension study which has evaluated the safety and efficacy of REVOLADE in patients with chronic ITP who were previously enrolled in a REVOLADE study. In this study, patients were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

REVOLADE was administered to 207 ITP patients; 104 completed 3 months of treatment, 74 completed 6 months, and 27 completed 1 year of therapy. The median baseline platelet count was 18×10^9/L prior to REVOLADE administration. REVOLADE increased median platelet counts to $\geq 50 \times 10^9$/L at the majority of the post-baseline visits on the study. The median platelet count post-baseline increased

to ≥ 50 x 10^9/L beginning at the second week on study and remained elevated until the end of the observation period presented (i.e. 55 weeks), with the exception of weeks 29, 33, and 45, where the median platelet counts was 44 x 10^9/L, 43 x 10^9/L, and 42 x 10^9/L respectively. Just over half of the patients (51%) experienced ≥ 4 weeks of continuous elevation of platelets ≥ 50 x 10^9/L and 2 x baseline while receiving REVOLADE.

At baseline, 59% of patients had any bleeding (WHO Bleeding Grades 1–4) and 18% had clinically significant bleeding (WHO Bleeding Grades 2 indicating clinically significant bleeding). By weeks 24, 36 and 48, 26%, 8% and 33% of patients, respectively, had any bleeding and 9%, 4% and 25% of patients, respectively, had clinically significant bleeding. The apparent increase in proportion of patients with clinically significant bleeding at week 48 in comparison to baseline may be due to few patients having assessments by week 48.

Seventy percent of patients who reduced a baseline medication permanently discontinued or had a sustained reduction of their baseline ITP medication and did not require any subsequent rescue treatment. Sixty-five percent of these patients maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of patients completely discontinued at least one baseline ITP medication, and 55% of patients permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

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

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 until Month 12

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. After the daily dose was reduced to 25 mg for 2 weeks, the dose of 25 mg was administered on alternate days for 2 weeks until treatment discontinuation.

The duration of tapering was individualised 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.

Eighty-nine patients (84.8%) achieved a complete response (platelet count ≥100 000/µL) (Step 1, Table 14) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts below 70 000/µL (Step 2, Table 14). Forty-four patients (41.9%) were able to be tapered off

REVOLADE until treatment discontinuation while maintaining platelet counts ≥30 000/µL in the absence of bleeding events or the use of rescue therapy (Step 3, Table 14).

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 of the 105 enrolled patients (30.5%; p<0.0001; 95% CI: 21.9, 40.2) (Step 4, Table 14). By Month 24, 20 of the 105 enrolled patients (19.0%; 95% CI: 12.0, 27.9) maintained sustained response off treatment in the absence of bleeding events or the use of rescue therapy (Step 5, Table 14).

The median duration of sustained response after treatment discontinuation to Month 12 was 33.3 weeks (min-max: 4-51), and the median duration of sustained response after treatment discontinuation to Month 24 was 88.6 weeks (min-max: 57-107).

After tapering off and discontinuation of REVOLADE treatment, 12 patients had a loss of response, 8 of them re-started REVOLADE and 7 had a recovery response.

During the 2-year follow-up, 6 out of 105 patients (5.7%) experienced thromboembolic events, of which 3 patients (2.9%) experienced deep vein thrombosis, 1 patient (1.0%) experienced superficial vein thrombosis, 1 patient (1.0%) experienced cavernous sinus thrombosis, 1 patient (1.0%) experienced cerebrovascular accident and 1 patient (1.0%) experienced pulmonary embolism. Of the 6 patients, 4 patients experienced thromboembolic events that were reported at or greater than Grade 3, and 4 patients experienced thromboembolic event that were reported as serious. No fatal cases were reported.

Twenty out of 105 patients (19.0%) experienced mild to severe haemorrhage events on treatment before tapering started. Five out of 65 patients (7.7%) who started tapering experienced mild to moderate haemorrhage events during tapering. No severe haemorrhage event occurred during tapering. Two out of 44 patients (4.5%) who tapered off and discontinued REVOLADE treatment experienced mild to moderate haemorrhage events after treatment discontinuation until Month 12. No severe haemorrhage event occurred during this period. None of the patients who discontinued REVOLADE and entered the second year follow-up experienced haemorrhage event during the second year. Two fatal intracranial haemorrhage events were reported during the 2-year follow-up. Both events occurred on treatment, not in the context of tapering. The events were not considered to be related to study treatment.

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 14 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)		

		All patients N=105		Hypothesis Testing	
		n (%)	95% CI	p-value	Reject H0
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
Step 5:	Patients with sustained response off-treatment from Month 12 to Month 24. Maintaining platelet count ≥30,000/µL in the absence of bleeding events of use of any rescue therapy	20 (19.0)	(12.0, 27.9)		

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 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.

Paediatric patients (aged 1 to 17 years)

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

Double-Blind Placebo-Controlled Studies

TRA115450 (PETIT 2)

The primary endpoint was a sustained response, defined as the proportion of patients receiving eltrombopag, compared to placebo, achieving platelet counts ≥ 50 x 10^9/L for at least 6 out of 8 weeks (in the absence of rescue therapy), between Weeks 5 to 12 during the double-blind randomised period. Patients were refractory or relapsed to at least one prior ITP therapy, or unable to continue other ITP treatments for a medical reason, and had platelet count < 30 x 10^9/L. Ninety-two patients 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 patients (40%) compared with placebo patients (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 15).

Table 15 Sustained platelet response rates by age in paediatric patients with chronic ITP

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

A significantly greater proportion of patients treated with eltrombopag (75%) compared with placebo (21%) had a platelet response (at least one platelet count > 50 x 10^9/L during the first 12 weeks of randomised treatment in absence of rescue therapy) (Odds Ratio: 11.7, [95% CI: 4.0, 34.5], p < 0.001).

Baseline platelet count was evaluated for effect on the primary endpoint. The majority of patients in the study population (57/91, 62.6%) had a baseline platelet count ≤ 15 x 10^9/L. In subgroups defined by baseline platelet count ≤ 15 x 10^9/L and >15 x 10^9/L, response rates were 29% (11/38) and 54% (13/24) respectively in the eltrombopag treatment group.

The proportion of patients who responded to eltrombopag in the open-label 24-week period (80%) was similar to that observed during the randomised portion of the study.

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

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

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

TRA108062 (PETIT)

The primary endpoint was the proportion of patients achieving platelet counts ≥ 50 x 10^9/L at least once between Weeks 1 and 6 of the randomised period. Patients were refractory or relapsed to at least one prior ITP therapy with a platelet count <30 x 10^9/L (n = 67). During the randomised period of the study, patients 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 patients (62%) compared with placebo patients (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p = 0.011). Table 16 shows platelet response across the three age cohorts.

Table 16 Platelet response rates in paediatric patients with chronic ITP

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

A significantly greater proportion of patients treated with eltrombopag (36%) compared with placebo (0%) had a platelet response (platelet counts > 50 x 10^9/L for at least 60% of assessments between Weeks 2 and 6) (Odds Ratio: 5.8, [95% CI: 1.2, 28.9], p = 0.002).

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

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

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

Long-term use (greater than nine months) of REVOLADE has not been studied in paediatric patients.

Chronic hepatitis C associated thrombocytopenia studies

Double-Blind Placebo-Controlled Studies

The efficacy and safety of REVOLADE for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled, multicentre studies (TPL103922 ENABLE 1 and TPL108390 ENABLE 2).

ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. In both studies, patients with a platelet count of < 75 x 10^9/L were enrolled and stratified by platelet count (< 50 x 10^9/L and ≥ 50 x 10^9/L to < 75 x 10^9/L), screening HCV RNA (< 8 x 10^5 IU/mL and ≥ 8 x 10^5 IU/mL), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The studies consisted of two phases: a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label REVOLADE to increase the platelet count to ≥ 90 x 10^9/L for ENABLE 1 and ≥ 100 x 10^9/L for ENABLE 2. REVOLADE was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25 mg increments over 2 to 3 week periods to achieve the required platelet count for phase 2 of the study. The maximal time patients could receive open-label REVOLADE was 9 weeks. If sufficient platelet counts were achieved, patients were randomised (2:1) to the same dose of REVOLADE at the end of the pre-treatment phase or to placebo. REVOLADE was administered in combination with antiviral treatment per their respective product information for up to 48 weeks.

The primary efficacy endpoint for both studies was sustained virological response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70% of patients were genotype 1/4/6 and 30% were genotype 2/3. Approximately 30% of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately 60 x 10^9/L) were similar among all treatment groups. The median time to achieve the target platelet count ≥ 90 x 10^9/L was 2 weeks. The median time to achieve the target platelet count ≥ 90 x 10^9/L (ENABLE 1) or ≥ 100 x 10^9/L (ENABLE 2) was 2 weeks.

In both HCV studies, a significantly greater proportion of patients treated with REVOLADE achieved SVR compared to those treated with placebo (see Table 16). Significantly fewer patients treated with REVOLADE had any antiviral dose reductions compared to placebo. The proportion of patients with no antiviral dose reductions was 45% for REVOLADE compared to 27% for placebo. Significantly fewer patients treated with REVOLADE prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, $p < 0.0001$). The majority of patients treated with REVOLADE (76%) had minimum platelet counts that were ≥ 50 x 10^9/L compared to 19% for placebo. A greater proportion of patients in the placebo group (20%) had minimum platelet counts fall below 25 x 10^9/L during antiviral treatment compared to the REVOLADE group (3%). In the REVOLADE group, SVR rates in patients with high viral loads (> 8 x 10^5 IU/mL) were 18% as compared to 8% in the placebo group. Significantly more patients reached the 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 REVOLADE.

Table 17 ENABLE 1 and ENABLE 2 virological response in HCV patients with thrombocytopenia

	ENABLE 1[a] (TPL103922)		**ENABLE 2[b] (TPL108390)**	
Pre-antiviral Treatment Phase	N = 715		N = 805	
% Achieving target platelet counts and initiating antiviral therapy[c]	95%		94%	
	REVOLADE	**Placebo**	**REVOLADE**	**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] REVOLADE given in combination with peginterferon alfa-2a (180 µg 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] REVOLADE given in combination with peginterferon alfa-2b (1.5 µg/kg once weekly for 48 weeks for genotype 1; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1400 mg orally)

[c] Target platelet count was $\geq$ 90 x 10^9/L for HCV Study 1 and $\geq$ 100 x 10^9/L for HCV Study 2.

[d] *P* value < 0.05 for REVOLADE versus placebo

Definitive immunosuppressive therapy-naive severe aplastic anaemia study

CETB115AUS01T

REVOLADE in combination with horse antithymocyte globulin (h-ATG) and ciclosporin was investigated in a single-arm, single-centre, open-label, sequential cohort study in patients with severe aplastic anaemia 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 REVOLADE treatment and the initiation of low dose of ciclosporin (maintenance dose) for patients who achieved a haematologic response at 6 months. A total of 153 patients received REVOLADE in sequential cohorts:

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

The starting dose of REVOLADE for adults and paediatric patients aged 12 to 17 years was 150 mg once daily (a reduced dose of 75 mg was administered for East and Southeast Asians), 75 mg once daily for patients aged 6 to 11 years (a reduced dose of 37.5 mg was administered for East and 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 and Southeast Asians). The dose of REVOLADE was reduced if the platelet count exceeded 200 x 10^9/L and interrupted and reduced if it exceeded 400 x 10^9/L.

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 ciclosporin 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 ciclosporin was administered for an additional 18 months to 15 patients who achieved a haematologic response at 6 months in the REVOLADE D14-M3 cohort and all patients who achieved a haematologic response at 6 months in the REVOLADE D1-M6 cohort.

Data from the recommended schedule of REVOLADE on Day 1 to Month 6 (D1-M6) in combination with h-ATG and ciclosporin (Cohort 3 regimen) are presented below. This cohort had the highest complete response rates.

In the REVOLADE D1-M6 cohort, the median age was 28.0 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 REVOLADE in combination with h-ATG and ciclosporin was established on the basis of complete haematological response at 6 months. A complete response was defined as haematological 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 x 10^9/L, platelet count >100 x 10^9/L and haemoglobin >10 /L. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anaemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC > 0.5 x 10^9/L, platelet count > 20 x 10^9/L, or reticulocyte count > 60 x 10^9/L.

Table 18 Efficacy results in definitive immunosuppressive therapy-naive SAA patients

	REVOLADE D1-M6 + h-ATG + ciclosporin 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 haematological 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.

Paediatric patients

Thirty-seven patients aged 2 to 17 years were enrolled in the single-arm, sequential-cohort study. 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 REVOLADE D1-M6 cohort, the complete response rate at 6 months was 28.0% (7/25) and the overall response rate at 6 months was 68.0% (17/25).

Refractory Severe Aplastic Anaemia

CETB115AUS28T

REVOLADE was studied in a single-arm, single-centre open-label study (ELT112523) in 43 patients with severe aplastic anaemia who had an insufficient response to at least one prior immunosuppressive therapy, and had a platelet count ≤ 30 x 10^9/L (see Table 18). REVOLADE 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 REVOLADE treatment.

Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20 x 10^9/L above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 15 g/L, or a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks, compared to the number of transfusions in the 8 weeks pre-treatment; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase > 0.5 x 10^9/L.

Table 19 Summary of SAA disease characteristics at screening

	Eltrombopag Total (N=43)
Time Since Diagnosis (Months)	
Median (min-max)	30.9 (10-190)
Transfused at Referral - Platelets, n (%)	
Yes	39 (91)
Number of Platelet Transfusions per Month at Referral, n (%)	
N	39
Median (min-max)	4.0 (1-9)
Transfused at Referral - RBC, n (%)	
Yes	37 (86)
Number of RBC Transfusions per 8 Weeks at Referral	
N	37
Median (min-max)	4.0 (1-17)
Karyotype, n (%)	
Normal	38 (88)
Abnormal	3 (7)
Insufficient metaphases	1 (2)
Baseline Labs, median (range)	
Platelet Count/L	20 (6-90) x 10^9
Neutrophils/L	0.58 (0.07-2.81) x 10^9
Hemoglobin, g/L	84 (66-138)

	Eltrombopag Total (N=43)
Reticulocytes/L	24.3 (1.7-96.9) x 10^9
Severe Cytopenias	
Neutropenia <0.5 x 10^9/L	18 (42)
Thrombocytopenia <20 x 10^9/L	18 (42)
Anaemia <100 g/L	35 (81)
Number of prior immunosuppressive therapies, n (%)	
≥ 1	43 (100)
≥ 2	36 (84)
≥ 3	14 (33)
≥ 4	3 (7)

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

The treated population had a median age of 45 years (range 17 to 77 years) and 56% of patients were male. At baseline the median platelet count was 20 x 10^9/L, haemoglobin was 84 g/L, and ANC was 0.58 x 10^9/L. The prior immunosuppressive history of these patients is given in Table 13 (see section 5.1 Pharmacodynamic properties – Clinical trials). The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline (see section 4.4 Special warnings and precautions for use – cytogenetic abnormalities).

At baseline, 91% (39/43) and 86% (37/43) of patients were platelet and RBC transfusion dependent respectively. Of these, 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion) while being treated with REVOLADE.

The haematological response rate was 40% (17/43 patients; 95% CI 25, 56). In the 17 responders, the platelet transfusion-free period ranged from 8 to 1,190 days with a median of 287 days, and the RBC transfusion-free period ranged from 15 to 1,190 days with a median of 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).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic (PK) parameters of eltrombopag after administration of eltrombopag to adult patients with ITP are shown in Table 19. Plasma eltrombopag concentration-time data collected in 590 patients with HCV enrolled in Phase III studies TPL103922/ ENABLE 1 and TPL108390/ ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult patients in a population PK analysis.

Table 20 Geometric mean (95% CI) steady-state eltrombopag plasma pharmacokinetic parameters in adults with ITP

REVOLADE regimen	C_{max} (μg/mL)	$AUC_{(0-\tau)}$ (μg.hr/mL)
50 mg once daily (n=34)	8.01 (6.73, 9.53)	108 (88, 134)
75 mg once daily (n=26)	12.7 (11.0, 14.5)	168 (143, 198)

Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in Phase III studies TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2) are presented for each dose studied in Table 21. A higher eltrombopag exposure was observed in patients with HCV at a given eltrombopag dose.

Table 21 Geometric mean (95% CI) steady-state eltrombopag plasma pharmacokinetic parameters in adults with chronic HCV

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

$AUC_{(0-\tau)}$ and C_{max} shown in Table 20 are derived from *post-hoc* estimates of the population PK model.

The pharmacokinetic parameters of eltrombopag after administration of REVOLADE 150 mg once daily 45 patients with definitive immunosuppressive therapy-naïve severe aplastic anaemia are shown in Table 22.

Table 22 Steady-state plasma eltrombopag pharmacokinetic parameters in patients with definitive immunosuppressive therapy-naïve severe aplastic anaemia

Regimen of eltrombopag	C_{max} (μg/mL)	$AUC_{(0-\tau)}$ (μg.h/mL)
150 mg once daily (n = 45)	40.1 (44.9%)	772 (47.2%)

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

Special Patient Populations

Renal Impairment

The PK of eltrombopag has been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was decreased by 32% (90% CI: 63% decrease, 26% increase) in patients with mild renal impairment, 36% (90% CI: 66% decrease, 19% increase) in patients with moderate renal impairment, and 60% (90% CI: 18% decrease, 80% decrease) in patients with severe renal impairment compared with healthy

volunteers. There was a trend for reduced plasma eltrombopag exposure in patients with renal impairment, but there was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Patients with impaired renal function should use eltrombopag with caution and close monitoring (see section 4.4 Special warnings and precautions for use).

Hepatic Impairment

The PK of eltrombopag has been studied after administration of eltrombopag to adult patients with liver cirrhosis (hepatic impairment). Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was increased by 41% (90% CI: 13% decrease, 128% increase) in patients with mild hepatic impairment, 93% (90% CI: 19%, 213%) in patients with moderate hepatic impairment, and 80% (90% CI: 11%, 192%) in patients with severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers.

ITP patients with liver cirrhosis (hepatic impairment) (Child-Pugh score ≥ 5), should use eltrombopag with caution and close monitoring (see section 4.4 Special warnings and precautions for use). For patients with chronic ITP and with mild, moderate and severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily (see section 4.2 Dose and method of administration).

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

A similar analysis was also conducted in 28 healthy adults and 635 patients with HCV. A majority of patients had Child-Pugh score of 5-6. Based on estimates from the population pharmacokinetic analysis, patients with HCV had higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to healthy patients, and $AUC_{(0-\tau)}$ increased with increasing Child-Pugh score, HCV patients with mild hepatic impairment had approximately 100-144% higher plasma eltrombopag $AUC_{(0-\tau)}$ compared with healthy patients. For patients with HCV initiate REVOLADE at a dose of 25 mg once daily (see section 4.2 Dose and method of administration).

Race

Immune thrombocytopaenia (ITP): The influence of East-Asian ethnicity on the PK of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East-Asians) and 88 patients with ITP (18 East-Asians). Based on estimates from the population pharmacokinetic analysis, East-Asian ITP patients 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 section 4.2 Dose and method of administration).

HCV-associated thrombocytopenia: The influence of East-/Southeast-Asian ethnicity on the PK of eltrombopag was also evaluated using a population pharmacokinetic analysis in 635 patients with HCV (214 East-/Southeast-Asians). On average, East-/Southeast-Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2 Dose and method of administration).

Gender

The influence of gender on the PK of eltrombopag was evaluated using a population pharmacokinetic

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

The influence of gender on eltrombopag PK was evaluated also using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimates, female HCV patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Elderly Population

The age difference of eltrombopag PK was evaluated using population PK analysis in 28 healthy patients and 635 patients with HCV ranging from 19 to 74 years old. Based on model estimates, elderly (> 60 years) patients had approximately 36% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2 Dose and method of administration).

Paediatric population (patients aged 1 to 17 years)

The PK of eltrombopag have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Patients aged 1 to 5 years received the eltrombopag powder for oral suspension. Patients aged 6 to 17 years received the eltrombopag tablet. The PK parameters of eltrombopag in paediatric patients with ITP are shown in Table 23. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Approximately 43% higher plasma eltrombopag AUC(o-τ) was observed in patients of East-/Southeast-Asian descent and 25% higher AUC(o-τ) was observed in female patients. The bioavailability of the powder for oral suspension in children was estimated as 29% lower than the tablet. Age and/or formulation may be confounding factors in the analysis.

Table 23 Geometric Mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric patients with ITP derived from the population PK model for a dose of 50 mg once daily dosing regimen.

Age	C_{max} (µg/mL)	$AUC_{(0-\tau)}$ (µg.hr/mL)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n =68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

The parameters AUC(0-τ) and C_{max} in Table 22 are derived from the *post-hoc* estimates of the population PK model for a theoretical dose of 50 mg once daily (as powder for oral suspension for age group 1 to 5 years and as tablets for age groups 6 to 11 years and 12 to 17 years)

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral 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%.

In a relative bioavailability study in healthy adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the tablet formulation. In a pooled analysis of data from paediatric ITP patients aged 1 to 17 years, the bioavailability of the powder for oral suspension in children was estimated as 29% lower than the tablet. Patients aged 1-5 years received the powder for oral suspension and patients aged 6-17 years received the tablets, so age may be a confounding factor in this analysis.

Food & Chelation

Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2 Dose and method of administration, and section 4.5 Interactions with other medicines and other forms of interactions – Polyvalent Cations (Chelation)).

The effect of food on the pharmacokinetics of eltrombopag was studied in adults. Administration of a single 50 mg-dose of REVOLADE tablet with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ by 59% (90% CI: 54%, 64%) and Cmax by 65% (90% CI: 59%, 70%).

The administration of a single 25 mg dose of REVOLADE powder for oral suspension with a high-calcium, moderate fat and calorie meal reduced plasma eltrombopag AUC by 75% (90% CI: 71%, 88%) and Cmax by 79% (90% CI: 76%, 82%).

The administration of a single 25 mg dose of REVOLADE powder for oral suspension 2 hours after the high-calcium meal reduced plasma eltrombopag AUC by 47% (90% CI: 40%, 53%) and Cmax by 48% (90% CI: 40%, 54%).

The administration of a single 25 mg-dose of eltrombopag powder for oral suspension 2 hours before a high-calcium meal attenuated the effect, where plasma eltrombopag AUC(0-∞) was decreased by 20% (90% CI: 9%, 29%) and Cmax by 14% (90% CI: 2%, 25%).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.

REVOLADE should be taken at a time away from food containing polyvalent cations, and preferably at the same time in relation to food (see section 4.2 Dose and method of administration).

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%). 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 $AUC_{0-\infty}$. Minor metabolites, each accounting for < 10% of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20% of a dose is metabolised by oxidation. *In vitro* studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

Excretion

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 in healthy patients, and 26-35 hours in ITP patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Eltrombopag was not mutagenic in a bacterial mutation assay or clastogenic in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 8 times the human clinical exposure based on $C_{max,}$ in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). The clinical significance of the in vitro finding remains unclear.

Carcinogenicity

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 greater than 3 times the anticipated clinical exposure based on plasma AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV at 100 mg/day). Eltrombopag activates TPO receptors on the surface of haematopoietic cells and has been shown to stimulate the proliferation of megakaryocytic leukaemia cells *in vitro.* There is therefore a theoretical possibility that eltrombopag may increase the risk for haematologic malignancies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet also contains magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycollate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80 (12.5 mg tablet and 25 mg tablet only), iron oxide red CI77491 (50 mg tablet and 75 mg tablets only), iron oxide yellow CI77492 (50 mg tablet only) and iron oxide black CI77499 (75 mg tablet only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Film-coated tablets

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

REVOLADE 25 mg and 50 mg film coated tablets are supplied in blister packs containing 28 tablets. Other packs sizes and tablet strengths are not supplied in Australia.

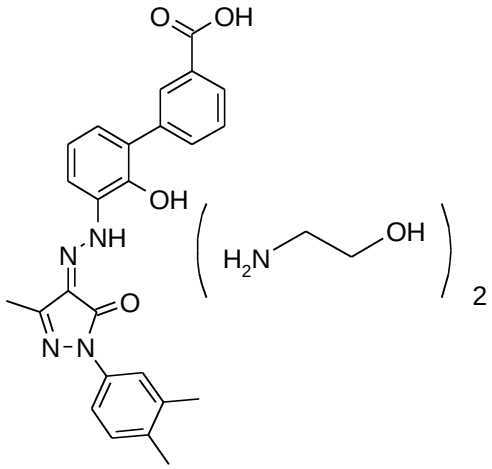
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: 3'-{(2Z)-2-[1-(3,4-dimethyl-phenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenyl carboxylic acid-2-amino ethanol (1:2)

Chemical structure



Molecular formula: C25 H22 N4 O4. 2 (C2H7NO)

Molecular weight: **564.65**

CAS number

496775-62-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

25 mg, 50 mg, and 75 mg film coated tablets (AUST R 158419, 158356, and 200121): 16 July 2010.

12.5 mg film coated tablets (AUST R 236115): 30 March 2016.

10 DATE OF REVISION

12 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

4.1	Extension of indication for the treatment of ITP in adult patients enabling access for patients with condition lasting less than 6 months from initial ITP diagnosis.
5.1	Efficacy update based on 12-month primary analysis and 6-month ad-hoc analysis (TAPER study) to include information on ITP patients who taper off treatment to maintain response.
All	Editorial updates to table numbers and localised spelling.

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