REVOLADE®

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

REVOLADE 25 mg film coated tablet
REVOLADE 50 mg film coated tablet
REVOLADE 75 mg film coated tablet*

* *This strength is not available in New Zealand*.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REVOLADE 25 mg film coated tablet
Each film coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

REVOLADE 50 mg film coated tablet
Each film coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

REVOLADE 75 mg film coated tablet*
Each film coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

REVOLADE 25 mg film-coated tablet
Round, biconvex, white tablet (approximately 10.3 mm diameter), and debossed with 'GS NX3' and '25' on one side.

REVOLADE 50 mg film-coated tablet
Round, biconvex, brown tablet (approximately 10.3 mm diameter), and debossed with 'GS UFU' and '50' on one side.

REVOLADE 75 mg film-coated tablet*
Round, biconvex, pink tablet (approximately 10.3 mm diameter), and debossed with 'GS FSS' and '75' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REVOLADE is indicated for the treatment of:

- Adult patients with immune thrombocytopenia (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins; or
- Thrombocytopenia in adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy; or
- Severe aplastic anaemia (SAA) in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older; or

- Adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy (refractory SAA).

4.2 Dose and method of administration

Dose (adults)

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).

REVOLADE should be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium (see below), iron, magnesium, selenium and zinc) (see section 4.5 and section 5.2).

REVOLADE may be taken with food containing little (< 50 mg) or preferably no calcium (see section 4.5 and section 5.2).

Immune thrombocytopenia (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

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

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

Platelet monitoring and dose adjustment

After initiating REVOLADE, adjust the dose to achieve and maintain a platelet count ≥ 50 x 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, complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥ 50 x 10^9/L for at least 4 weeks) has been achieved. CBCs 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.

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 and section 4.4).

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 a dose of 25 mg once every other day.
> 400 x 10^9/L	Discontinue 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 every other day, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

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 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 any liver cirrhosis (i.e. hepatic impairment), wait three weeks before increasing the dose (see Special Populations (All Indications), and section 4.4).

Discontinuation

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 (HCV) associated thrombocytopenia

When REVOLADE is administered in combination with antiviral therapies, reference should be made to the full Data Sheet(s) of the respective coadministered 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 to 2 weeks after starting REVOLADE.

Initial Dose Regimen

Initiate REVOLADE in adults at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry, or with hepatic impairment (see section 5.2).

Monitoring and dose adjustment

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.

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

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 100 mg/day.
≥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 reinitiating dosing at 25 mg every other day.
>400 x 10^9/L	Discontinue 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 reinitiating dosing at 25 mg every other day.

During antiviral therapy, adjust the dose of REVOLADE as necessary to avoid dose reduction of peg-interferon. Monitor platelet counts weekly during antiviral therapy until a stable platelet count is achieved. FBC's, 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 peg-interferon alfa or ribavirin, refer to their respective Data Sheet.

Discontinuation

In adult 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).

First-line severe aplastic anaemia (SAA)

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.
Cyclosporin* (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.

Agent	Dose administered in the pivotal study
Cyclosporin (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 cyclosporin may need to be adjusted to achieve the above recommended target trough levels when cyclosporin is used concomitantly with other therapies; refer to the appropriate cyclosporin product information.*

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

Monitoring and dose adjustment for eltrombopag

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 in first-line SAA patients

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.

Event	Recommendation
	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, pulmonary embolus, transient ischaemic attack (TIA) or stroke, myocardial infarction at any time while on REVOLADE:** Discontinue REVOLADE but remain on h-ATG and cyclosporin. 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 (SAA)

Initial Dose Regimen

Initiate REVOLADE in adults 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 Special Populations (All Indications) and section 5.1)).

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting REVOLADE (see section 5.1). 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 severe aplastic anaemia patients

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	Discontinue 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

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 ADVERSE EFFECTS). Excessive platelet count responses (as outlined in Table 6) or important liver test abnormalities also necessitate discontinuation of REVOLADE (see section 4.4).

Special populations (all indications)

Paediatric population

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 younger than 2 years of age (see section 4.8 Adverse effects (Undesirable effects) and section 5.1 Pharmacodynamic properties – Clinical trials).

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 5.1).

Hepatic impairment
Exercise caution when administering REVOLADE to ITP patients with liver cirrhosis (hepatic impairment, Child-Pugh score ≥ 5) (see section 4.4 and section 5.1). 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.

Thrombocytopenic patients with chronic HCV with hepatic impairment and severe aplastic anaemia should initiate REVOLADE at a dose of 25 mg once daily (see PHARMACOLOGY - Special Patient Populations). After initiating the dose of REVOLADE in patients with hepatic impairment, wait 3 weeks before increasing the dose.

REVOLADE should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) unless the expected benefit outweighs the identified risk of portal venous thrombosis.

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).

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 5.1).

East-/Southeast-Asian patients
For ITP, HCV-associated thrombocytopenia and refractory SAA patients of East-/Southeast-Asian ancestry, REVOLADE should be initiated at a dose of 25mg once daily (see section 5.1). For the treatment of patients with first-line SAA refer to section 4.2 Dose and Method of Administration, Initial dose regimen.

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

For ITP or HCV patients of East-/Southeast-Asian ancestry with hepatic impairment initiate REVOLADE at a dose of 25 mg once daily (see section 5.1).

Method of administration
Swallow REVOLADE tablets 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 5.1– Absorption, and section 4.5).

REVOLADE may be taken with food containing little (< 50 mg) or preferably no calcium (see section 4.5, and section 5.2).

4.3 Contraindications

REVOLADE is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or Model for End-Stage Liver Disease (MELD) score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. 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. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required. See section 4.2.

Hepatotoxicity

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

Clinical data

In clinical studies in chronic ITP studies with REVOLADE, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect (unconjugated) bilirubin were observed (see section 4.8).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 the two controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST ≥ 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 cyclosporin, 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

Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. In patients with ITP, HCV and refractory SAA, monitor serum ALT, AST and bilirubin:

- prior to initiation of REVOLADE,
- every 2 weeks during the dose adjustment phase, and
- monthly following establishment of a stable dose.

If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests until the abnormality(ies) resolve, stabilise, or return to baseline levels. Discontinue REVOLADE if ALT levels increase to 3 x the upper limit of normal [ULN] in patients with normal liver function or ≥ 3 x baseline (or > 5 x ULN, whichever is the lower) in patients with elevations in transaminases before treatment and that are:

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

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.

Exercise caution when administering REVOLADE to patients with hepatic disease. In ITP and refractory SAA patients, use a lower starting dose of REVOLADE 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 occurred approximately three months after initiation of REVOLADE and improved or resolved following REVOLADE interruption or discontinuation. No cases of severe liver injury related to REVOLADE were identified from clinical studies in patients with definitive immunosuppressive therapy-naiive 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 alpha interferon therapy. In the two controlled clinical studies in thrombocytopenic patients with HCV, where REVOLADE was used as necessary to achieve the target platelet count required to enable antiviral therapy, safety findings suggestive of hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) were reported more frequently in the REVOLADE arm (13 %) than in the placebo arm (7 %). In patients with low albumin levels (≤ 35 g/L) or 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. Refer to the respective interferon Data Sheet for discontinuation criteria. REVOLADE should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Renal impairment

Patients with impaired renal function should use REVOLADE with caution and close monitoring (see section 4.2), for example by testing serum creatinine and/or performing urine analysis (see section 5.1).

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, exercise caution when administering REVOLADE to patients with hepatic impairment (see sections 4.2 and 4.8).

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.

Use caution 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).

In adult ITP studies, thromboembolic/thrombotic events (TEEs) were observed in 42 out of 763 patients (5.5 %). The TEEs included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, 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 from 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 venous 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 eltrombopag experienced thromboembolic events (all of the portal venous system) and two out of 145 (1 %) patients in the placebo group experienced thromboembolic events (one in the portal venous system and one myocardial infarction). Five eltrombopag-treated patients with a TEE experienced the event within 14 days of completing eltrombopag 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), 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.

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 myelodysplastic syndrome (MDS) (see Carcinogenicity in section 5.3).

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. The effectiveness and safety of REVOLADE have 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.

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

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 ≥ 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 50mg 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 (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.

Photosensitivity

Eltrombopag is phototoxic and photoclastogenic *in vitro*. However *in vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic (≥15 µg/mL) in the presence of high ultraviolet (UV) light intensity (30 times the minimal erythematous dose). 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 11 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.

Interference with serological testing
Eltrombopag is highly coloured and has the potential to interfere with some laboratory tests. Serum discolouration 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.

4.5 Interaction with other medicines and other forms of interaction

In vitro evaluation of drug interaction potential

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of REVOLADE. 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 enzymes (IC50 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 REVOLADE 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 75mg 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.

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

Rosuvastatin
In vitro studies demonstrated that REVOLADE is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter with an IC50 value of 2.7μM (1.2μg/mL). *In vitro* studies also demonstrated that REVOLADE is a breast cancer resistance protein (BCRP) substrate and inhibitor with an IC_{50} value of 2.7μM (1.2 μg/mL). 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 REVOLADE, a reduced dose of rosuvastatin should be considered and careful monitoring should be undertaken. In clinical studies with REVOLADE, a dose reduction of rosuvastatin by 50 % was recommended for co-administration of rosuvastatin and REVOLADE. Concomitant administration of REVOLADE and other OATP1B1 and BCRP substrates should be undertaken with caution.

Lopinavir/ritonavir
Co-administration of REVOLADE with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17 % (90 % CI: 6.6 %, 26.6 %). Therefore, caution should be used when co-administration of REVOLADE 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 REVOLADE when lopinavir/ritonavir therapy is initiated or discontinued.

Polyvalent Cations (Chelation)
REVOLADE 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 %) (see DOSAGE AND ADMINISTRATION, and PHARMACOLOGY). Antacids, dairy products and other products containing polyvalent cations such as mineral supplements should be administered at least two hours before or four hours after REVOLADE dosing to avoid significant reduction in REVOLADE absorption (see section 4.2).

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 sections 5.2 and 4.2).

Cyclosporin
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 cyclosporin (a BCRP inhibitor). Administration of a single dose of eltrombopag 50 mg with 200 mg cyclosporin (a BCRP inhibitor) decreased the Cmax 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 cyclosporin 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). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with cyclosporin. The REVOLADE dose may need to be increased based on these platelet counts.

4.6 Fertility, pregnancy and lactation

Fertility
Eltrombopag did not affect female or male fertility in rats at doses 2 to 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.

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 equivalent to the human clinical subclinical exposures in HCV patients at 100 mg/day. Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day based on AUC). However, at the maternally toxic dose of eltrombopag 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, fetal weights were significantly reduced and there was an increase in fetal 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 fetus.

Breastfeeding

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.

4.8 Undesirable effects

Summary of the safety profile

ITP Studies in adult patients

The safety of REVOLADE was assessed in adult patients with previously treated chronic ITP using data from pooled double blind, placebo controlled studies (N=763) (TRA102537 RAISE and TRA100773B). Adverse drug reactions occurring in the adult ITP population are shown in Table 7. The most common adverse drug reactions (≥10%) for REVOLADE were diarrhoea, nausea, increased alanine aminotransferase and back pain.

Thrombocytopenia with HCV infection in adult patients

The safety of REVOLADE was assessed in adult patients treated with REVOLADE using 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 (N=1520). 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 patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies, the safety population consisted of all randomised patients who received double-blind study drug during Part 2 of ENABLE 1 (REVOLADE treatment n=449, placebo n=232) and ENABLE 2 (REVOLADE treatment n=506, placebo treatment n=252). Patients were analysed according to the treatment received (total safety double blind population, REVOLADE n=955 and placebo n=484). Adverse drug reactions occurring in the HCV study population are shown in Table 8.
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.

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 cyclosporin 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 cyclosporin were initiated concurrently at the recommended dose and schedule (Cohort 3 regimen): REVOLADE up to 150 mg once daily on Day 1 to Month 6 (D1-M6) in combination with h-ATG on Days 1 to 4 and cyclosporin for 6 months, followed by low dose of cyclosporin (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. Adverse drug reactions for the refractory SAA study population (N=43) are shown in Table 9.

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 considered are listed in the following tables by MedDRA body system organ class and by frequency with the most frequent reactions first. The corresponding frequency categories for the adverse drug reactions are 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

Table 7 Adverse drug reactions in the adult ITP study population (N=763)

Body system/ organ class/ frequency	**Adverse reactions**
Infections and infestations	
Common	Pharyngitis
Gastrointestinal disorders	
Very common	Nausea, diarrhoea
Common	Vomiting
Uncommon	Dry mouth
Eye disorders	
Common	Cataract
Hepatobiliary disorders	
Very common	Increased alanine aminotransferase
Common	Hyperbilirubinaemia, increased aspartate aminotransferase
Uncommon	Drug-induced liver injury
Skin and subcutaneous tissue disorders	
Common	Alopecia, rash
Musculoskeletal and connective tissue disorders	
Very common	Back pain
Common	Musculoskeletal pain (including musculoskeletal chest pain), myalgia
Vascular disorders	
Common	Thromboembolic events, thrombotic microangiopathy with acute renal failure

Table 8 Adverse drug reactions in the HCV study population (REVOLADE in combination with antiviral interferon and ribavirin therapy) (N=1520)

Body system/ organ class/ frequency	Adverse reactions
Blood and lymphatic system disorders	
Very Common	Anaemia
Metabolism and nutrition disorders	
Very Common	Decreased appetite
Nervous systems disorders	
Very Common	Headache
Eye disorders	
Common	Cataracts
Vascular disorders	
Common	Thromboembolic events (including portal vein thrombosis)
Respiratory, thoracic and mediastinal disorders	
Very Common	Cough
Gastrointestinal disorders	
Very Common	Nausea, diarrhoea
Hepatobiliary disorders	
Common	Hyperbilirubinaemia, hepatic failure, drug-induced liver injury
Skin and subcutaneous tissue disorders	
Very Common	Pruritus
Common	Rash, alopecia
Musculoskeletal and connective tissue disorders	
Very Common	Myalgia
General disorders and administrative conditions	
Very Common	Fatigue, pyrexia, chills, asthenia, oedema, influenza like illness

Table 9 Adverse drug reactions in the refractory SAA study population (N=43)

Body system/ organ class/ frequency	Adverse reactions
Nervous systems disorders	
Very Common	Headache, dizziness

Eye disorders
Common Cataract

Respiratory, thoracic and mediastinal disorders
Very Common Cough, oropharyngeal pain, rhinorrhoea

Gastrointestinal disorders
Very Common Abdominal pain, diarrhoea, nausea

Hepatobiliary disorders
Very Common Transaminases increased
Common Hyperbilirubinemia

Skin and subcutaneous tissue disorders
Common Rash

Musculoskeletal and connective tissue disorders
Very Common Arthralgia, pain in extremity, muscle spasms

General disorders and administrative conditions
Very Common Fatigue, pyrexia

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).

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 10. 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 9).

Table 10 Adverse events in the definitive immunosuppressive therapy-naïve SAA (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 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; occuring 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 reaction has been reported during post-approval use of REVOLADE. This includes 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 11 Adverse drug reactions identified during post-approval use

Skin and subcutaneous tissue disorders
Skin discolouration*

** In patients taking eltrombopag, 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 eltrombopag for indications that require administration of high doses of eltrombopag including severe aplastic anaemia.*

Reporting of suspected adverse reactions

The reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: https//nzphvc.otago.ac.nz/reporting/.

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-fold ULN in AST, 3.9-fold ULN in ALT, and 2.4-fold 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. Further management should be as clinically indicated. For advice on the management of overdose please contact the National Poisons Centre (telephone 0800 POISON or 0800 764 766).

5. PHARMACOLOGY

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics; ATC code: B02BX05

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 signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes and bone marrow progenitor cells.

Pharmacodynamic Effects

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.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

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.

Double-Blind Placebo-Controlled Studies

RAISE (TRA102537)

In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count ≥ 50 x 10^9/L and ≤ 400 x 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 x 10^9/L and 400 x 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 50,000/µL 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 x 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 was 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 $\geq 50 \times 10^9/\mu L$ at Day 43 from a baseline $<30 \times 10^9/L$; patients who withdrew prematurely due to a platelet count $> 200 \times 10^9/\mu L$ 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 % CI: 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 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 Studies

EXTEND (TRA105325)

EXTEND was 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 302 ITP patients; 218 completed 1 year of treatment, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years of therapy. The median baseline platelet count was $19 \times 10^9/L$ 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 count post-baseline increased to $\geq 50 \times 10^9/L$ beginning at the second week on study and were $85 \times 10^9/L$, $85 \times 10^9/L$, $105 \times 10^9/L$, $64 \times 10^9/L$, $75 \times 10^9/L$, $119 \times 10^9/L$, and $76 \times 10^9/L$ respectively at 1, 2, 3, 4, 5, 6 and 7 years on study.

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.

Chronic hepatitis C (HCV) 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 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 Data Sheets 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 12). 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 12 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 administered in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1 or 4; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

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

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

[d] p value < 0.05 for REVOLADE versus placebo

Definitive immunosuppressive therapy-naiive severe aplastic anaemia study

CETB115AUS01T

REVOLADE in combination with horse antithymocyte globulin (h-ATG) and cyclosporin 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 cyclosporin (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 cyclosporin (Cohort 1 regimen, n=30).
- REVOLADE on Day 14 to Month 3 (D14-M3) plus h-ATG and cyclosporin (Cohort 2 regimen, n=31), with half of the patients eligible to receive low dose of cyclosporin (maintenance dose) if they achieved a haematologic response at 6 months.
- REVOLADE on Day 1 to Month 6 (D1-M6) plus h-ATG and cyclosporin (Cohort 3 regimen, n=92), with all patients eligible to receive low dose of cyclosporin (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 cyclosporin 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 cyclosporin 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 cyclosporin (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 cyclosporin 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 13 Efficacy results in definitive immunosuppressive therapy-naiive SAA patients

	REVOLADE D1-M6 + h-ATG + cyclosporin 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

Open Label Studies

CETB115AUS28T

REVOLADE was studied in a single-arm, single-centre open-label study (ELT112523) in 43 adult 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 14). 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 14 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
Haemoglobin, g/L	84 (66-138)
Reticulocytes/L	24.3 (1.7-96.9) x 10^9
Severe Cytopenias	

	Eltrombopag Total (N=43)
Neutropenia <0.5 x 10^9/L	18 (42)
Thrombocytopenia <20 x 10^9/L	18 (42)
Anemia <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 14. 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 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 15 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. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase III studies are presented for each dose studied in Table 16. A higher eltrombopag exposure was observed in patients with HCV at a given eltrombopag dose. The pharmacokinetic parameters of eltrombopag after administration of REVOLADE 150 mg once daily to 45 patients with definitive immunosuppressive therapy-naïve severe aplastic anaemia are shown in Table 17.

Table 15 steady-state eltrombopag plasma PK parameters in adults with ITP, geometric mean (95% CI)

Regimen of eltrombopag	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)

Table 16 Steady-state plasma eltrombopag PK parameters in adult patients with chronic HCV, geometric mean (95 % CI)

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)

Table 17 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)		

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 %.

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).

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-∞) by 59 % (90 % CI: 54 %, 64 %) and Cmax by 65 % (90 % CI: 59 %, 70 %).

Food low in calcium (<50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

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).

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.

Biotransformation

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.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours in healthy patients and 26-35 hours in ITP patients.

Pharmacokinetics in 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).

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). 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).

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).

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).

HCV-associated thrombocytopaenia: 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).

Gender

The influence of gender on the PK of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic 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 using population PK 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).

5.3 Preclinical Safety Data

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 up to 4-5 times the human 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.

Genotoxicity
Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or clastogenic in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on Cmax, in ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day). In the in vitro mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). The clinical significance of the in vitro and in vivo findings suggest that REVOLADE does not pose a genotoxic risk to humans.

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 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
Not applicable.

6.3 Shelf life
3 years when stored at or below 30°C.

6.4 Special precautions for storage
REVOLADE does not require any special storage conditions.

6.5 Nature and Contents of Container
Aluminium-aluminium foil blister packs.

6.6 Special precautions for disposal

Any unused medicine should be returned to a pharmacist for safe disposal.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102, Newmarket. Auckland 1149, New Zealand
Telephone: 0800 354 335 (free telephone call within New Zealand)
Fax number: (09) 361 8181
E-mail: medinfo.phauno@novartis.com
® = registered trademark

9. DATE OF FIRST APPROVAL

The date of publication in the New Zealand Gazette of consent to distribute the medicine: 24 February 2011.

10. DATE OF REVISION OF THE TEXT

13 July 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Updates in relation to the addition of first line SAA indication.
All	Editorial amendments to table numbers, localised spelling, corrections to section references, alignment with Medsafe DS template and the Australian Product Information.

Internal Document Code
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