

# 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 patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy; or
- Severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy (refractory SAA).

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### 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  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding (see Table 1).

*Do not exceed a dose of 75 mg daily.*

Monitor clinical haematology and liver function tests regularly throughout therapy with REVOLADE and the dose of REVOLADE modified based on platelet counts as outlined in Table 7. During therapy with REVOLADE, complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ( $\geq 50 \times 10^9/L$  for at least 4 weeks) has been achieved. 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).

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**Table 1 Dose adjustments for REVOLADE in chronic ITP patients**

<b>Platelet count</b>	<b>Dose adjustment or response</b>
<50 x 10 <sup>9</sup> /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 <sup>9</sup> /L to ≤400 x 10 <sup>9</sup> /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 <sup>9</sup> /L	Discontinue REVOLADE. Increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10 <sup>9</sup> /L, reinstitute 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 normalize platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting REVOLADE.

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### *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**

<b>Platelet count</b>	<b>Dose adjustment or response</b>
<50 x 10 <sup>9</sup> /L following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥200 x 10 <sup>9</sup> /L to ≤400 x 10 <sup>9</sup> /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 <sup>9</sup> /L	Discontinue REVOLADE; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10 <sup>9</sup> /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 10 or important liver test abnormalities may also necessitate discontinuation of REVOLADE (see section 4.4).

### 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).

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### *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  $\geq 50 \times 10^9/L$ .

### ***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 3.

**Table 3 Dose adjustments of REVOLADE in refractory severe aplastic anaemia patients**

<b>Platelet Count Result</b>	<b>Dose Adjustment or Response</b>
$<50 \times 10^9/L$ 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.
$\geq 200 \times 10^9/L$ to $\leq 400 \times 10^9/L$ at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$>400 \times 10^9/L$	Discontinue REVOLADE for at least one week. Once the platelet count is $< 150 \times 10^9/L$ , reinitiate therapy at a dose reduced by 50 mg.
$>400 \times 10^9/L$ 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  $>50 \times 10^9/L$ , haemoglobin  $>100$  g/L in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC)  $>1 \times 10^9/L$  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  $< 30 \times 10^9/L$ , haemoglobin to  $<90$  g/L or ANC  $<0.5 \times 10^9/L$ , 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 11) or important liver test abnormalities also necessitate discontinuation of REVOLADE (see section 4.4).

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### Special populations (all indications)

#### *Paediatric population*

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

#### *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 at least 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  $\geq 5$ ) (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  $\geq 7$ ) 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).

#### *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).

Initiate REVOLADE at a dose of 25 mg once daily in thrombocytopenic patients of East-/Southeast-Asian ancestry with chronic HCV (see section 5.1).

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).

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### 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  $\leq 35$  g/L or Model for End-Stage Liver Disease (MELD) score  $\geq 10$ , 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  $\leq 35$  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.

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  $\geq 3$  x ULN were reported in 34 % and 38 % of the REVOLADE and placebo groups, respectively. REVOLADE administration in combination with peginterferon/ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin  $\geq 1.5$  x ULN was reported in 76 % and 50 % of the REVOLADE and placebo groups, respectively.

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

Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. Measure 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, stabilize, 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  $\geq 3$  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  $\geq 4$  weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

### 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. In all cases, the event resolved following REVOLADE. No cases were identified from clinical studies in refractory SAA, however the number of exposed patients in this indication was limited. As the highest authorized 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.

Exercise caution when administering REVOLADE to patients with hepatic disease. In ITP patients, use a lower starting dose of REVOLADE when administering to patients with hepatic impairment (see section 4.2).

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 ( $\leq 35$  g/L) or MELD score  $\geq 10$  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



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achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin  $\leq 35$  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  $\geq 5$ ) 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 clinical studies in refractory SAA, however the number of exposed patients in this indication was limited. As the highest authorized dose is administered to patients in 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.

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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 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  $200 \times 10^9/L$ .

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

### Bleeding following discontinuation of REVOLADE

Following discontinuation of REVOLADE, 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 randomized 1:1 and stratified by the International Prognostic Scoring System (IPSS): intermediate-1 (n = 64 [36 %]), intermediate-2 (n = 79 [44 %]), high-risk (n = 36 [20 %]) in the 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

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exposure  $\geq$  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 3 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 controlled 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 ( $\geq 15$   $\mu\text{g/mL}$ ) 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**

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 (IC<sub>50</sub> values 3-33  $\mu\text{M}$ ; 1.3-14.6  $\mu\text{g/mL}$ ). 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.

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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<sub>50</sub> 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.

### 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 IC<sub>50</sub> 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<sub>50</sub> 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<sub>max</sub> 103 % (90 % CI: 82 %, 126 %) and AUC<sub>0-∞</sub> 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<sub>(0-∞)</sub> 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<sub>0-∞</sub> by 70% (90% CI: 64%, 76 %) and C<sub>max</sub> 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,

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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  $C_{max}$  and the  $AUC_{0-\infty}$  of eltrombopag by 25 % (90 % CI: 15 %, 35 %) and 18 % (90 % CI: 8 %, 28 %), respectively. The co-administration of 600 mg 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

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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 adults 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 4.

The most common adverse drug reactions ( $\geq 10\%$ ) 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 randomized to the placebo arm (N=1520). ENABLE 1 (TPL103922, n=716) and ENABLE 2 (TPL108390, n=805) were randomized, 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 randomized 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 5.

The most common adverse drug reactions ( $\geq 10\%$ ) for REVOLADE were anaemia, pyrexia, fatigue, headache, nausea, influenza like illness, diarrhoea, decreased appetite, asthenia, pruritus, cough, chills, and myalgia.

#### Refractory severe aplastic anaemia in adult patients

The safety of REVOLADE in 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 6.

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

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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 4 Adverse drug reactions in the adult ITP study population (N=763)**

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

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**Table 5 Adverse drug reactions in the HCV study population (REVOLADE in combination with antiviral interferon and ribavirin therapy) (N=1520)**

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

**Table 6 Adverse drug reactions in the refractory SAA study population (N=43)**

<b>Body system/ organ class/ frequency</b>	<b>Adverse reactions</b>
<b>Nervous systems disorders</b>	
Very Common	Headache, dizziness
<b>Eye disorders</b>	
Common	Cataract
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very Common	Cough, oropharyngeal pain, rhinorrhoea



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### **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

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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).

### 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 categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

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### **Skin and subcutaneous tissue disorders**

Skin discolouration \*

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*\* 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 myelodysplastic syndrome and 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

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bilirubin. The platelet counts were  $672 \times 10^9/L$  on day 18 after ingestion and the maximum platelet count was  $929 \times 10^9/L$ . 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 DOSAGE AND 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: antihemorrhagics; 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)*

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In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count  $\geq 50 \times 10^9/L$  and  $\leq 400 \times 10^9/L$ , during the 6 month treatment period, for patients receiving REVOLADE relative to placebo. One hundred and ninety seven patients were randomized 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  $50 \times 10^9/L$  and  $400 \times 10^9/L$  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  $50,000/\mu L$  at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below  $30 \times 10^9/L$  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

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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 into the study, 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 randomization.

### *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.

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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 randomized, 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  $< 75 \times 10^9/L$  were enrolled and stratified by platelet count ( $< 50 \times 10^9/L$  and  $\geq 50 \times 10^9/L$  to  $< 75 \times 10^9/L$ ), screening HCV RNA ( $< 8 \times 10^5$  IU/mL and  $\geq 8 \times 10^5$  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  $\geq 90 \times 10^9/L$  for ENABLE 1 and  $\geq 100 \times 10^9/L$  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 randomized (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  $60 \times 10^9/L$ ) were similar among all treatment groups. The median time to achieve the target platelet count  $\geq 90 \times 10^9/L$  was 2 weeks. The median time to achieve the target platelet count  $\geq 90 \times 10^9/L$  (ENABLE 1) or  $\geq 100 \times 10^9/L$  (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 3). 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  $\geq 50 \times 10^9/L$  compared to 19 % for placebo. A greater proportion of patients in the placebo group (20 %) had minimum platelet counts fall below  $25 \times 10^9/L$  during antiviral treatment compared to the REVOLADE group (3 %). In the REVOLADE group, SVR rates in patients with high viral loads ( $> 8 \times 10^5$  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

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response (ETR) and sustained virologic response at 12-week follow-up (SVR12) when treated with REVOLADE.

**Table 7 ENABLE 1 and ENABLE 2 virological response in HCV patients with thrombocytopenia**

	<b>ENABLE 1<sup>a</sup></b> <b>(TPL103922)</b>	<b>ENABLE 2<sup>b</sup></b> <b>(TPL108390)</b>		
<b>Pre-antiviral Treatment Phase</b>	N = 715	N = 805		
% Achieving target platelet counts and initiating antiviral therapy <sup>c</sup>	95 %	94 %		
	<b>REVOLADE</b>	<b>Placebo</b>	<b>REVOLADE</b>	<b>Placebo</b>
Antiviral Treatment Phase	<b>n = 450</b>	<b>n = 232</b>	<b>n = 506</b>	<b>n = 253</b>
	<b>%</b>	<b>%</b>	<b>%</b>	<b>%</b>
<b>Overall SVR<sup>d</sup></b>	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7
<b>Overall EVR<sup>d</sup></b>	66	50	62	41
HCV Genotype 2,3	84	67	83	56
HCV Genotype 1,4,6	58	41	53	34

<sup>a</sup> 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)

<sup>b</sup> 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)

<sup>c</sup> Target platelet count was  $\geq 90 \times 10^9/L$  for HCV Study 1 and  $\geq 100 \times 10^9/L$  for HCV Study 2.

<sup>d</sup> p value < 0.05 for REVOLADE versus placebo

### 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  $\leq 30 \times 10^9/L$  (see Table 8). 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.

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Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to  $20 \times 10^9/L$  above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by  $> 15 \text{ g/L}$ , or a reduction in  $\geq 4$  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  $> 0.5 \times 10^9/L$ .

**Table 8 Summary of SAA disease characteristics at screening**

<b>Eltrombopag Total (N=43)</b>	
<b>Time Since Diagnosis (Months)</b>	
Median (min-max)	30.9 (10-190)
<b>Transfused at Referral - Platelets, n (%)</b>	
Yes	39 (91)
<b>Number of Platelet Transfusions per Month at Referral, n (%)</b>	
N	39
Median (min-max)	4.0 (1-9)
<b>Transfused at Referral - RBC, n (%)</b>	
Yes	37 (86)
<b>Number of RBC Transfusions per 8 Weeks at Referral</b>	
N	37
Median (min-max)	4.0 (1-17)
<b>Karyotype, n (%)</b>	
Normal	38 (88)
Abnormal	3 (7)
Insufficient metaphases	1 (2)
<b>Baseline Labs, median (range)</b>	
Platelet Count/L	$20 (6-90) \times 10^9$
Neutrophils/L	$0.58 (0.07-2.81) \times 10^9$
Hemoglobin, g/L	84 (66-138)
Reticulocytes/L	$24.3 (1.7-96.9) \times 10^9$
<b>Severe Cytopenias</b>	
Neutropenia $<0.5 \times 10^9/L$	18 (42)
Thrombocytopenia $<20 \times 10^9/L$	18 (42)
Anemia $<100 \text{ g/L}$	35 (81)
<b>Number of prior immunosuppressive therapies, n (%)</b>	
$\geq 1$	43 (100)
$\geq 2$	36 (84)
$\geq 3$	14 (33)
$\geq 4$	3 (7)

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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  $20 \times 10^9/L$ , haemoglobin was 84 g/L, and ANC was  $0.58 \times 10^9/L$ . The prior immunosuppressive history of these patients is given in Table 4. The majority of patients (84 %) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline (see PRECAUTIONS – 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 9. 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 10. A higher eltrombopag exposure was observed in patients with HCV at a given eltrombopag dose.

**Table 9 steady-state eltrombopag plasma PK parameters in adults with ITP, geometric mean (95% CI)**

Regimen of eltrombopag	$C_{max}$ ( $\mu\text{g/mL}$ )	$AUC_{(0-\tau)}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )
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 10 Steady-state plasma eltrombopag PK parameters in adult patients with chronic HCV, geometric mean (95 % CI)**

Regimen of eltrombopag	$C_{max}$ ( $\mu\text{g/mL}$ )	$AUC_{(0-\tau)}$ ( $\mu\text{g}\cdot\text{h/mL}$ )
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)



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Regimen of eltrombopag	C <sub>max</sub> (µg/mL)	AUC <sub>(0-τ)</sub> (µg.h/mL)
100 mg once daily (n=96)	19.19 (16.81, 21.91)	354 (304, 411)

### 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 C<sub>max</sub> 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 metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon AUC<sub>0-∞</sub>. 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.

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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  $\geq 5$ ), 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).

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### *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<sub>(0-τ)</sub> 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<sub>(0-τ)</sub> 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<sub>(0-τ)</sub> 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<sub>(0-τ)</sub> 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<sub>(0-τ)</sub> 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 C<sub>max</sub>, 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.

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### 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](mailto: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

30 October 2020

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### SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2, 5.2	Replaced the term “Asian” with “East-/Southeast-Asian” as appropriate and removed Asian population subsets e.g. Chinese, Japanese, Taiwanese, Korean or Thai.
4.2	Editorial – inclusion of text HCV- <i>associated thrombocytopenia</i> and refractory SAA
4.4	Precautions – Hepatotoxicity. Several editorial amendments to section including:  - Clarification of increases to indirect ( <b>unconjugated</b> ) bilirubin in clinical trials  - Clarification that the single-arm phase II monotherapy study in patients with refractory SAA, demonstrated concurrent ALT or AST > 3 x ULN with <b>total</b> bilirubin  Precautions - Thrombotic/Thromboembolic Complications:  - Statistical recalculations of Adverse Drug Reaction Frequency from Kaplan-Meier to Crude Incidence in adult ITP studies.
4.8	- Inclusion of verbiage for the most commonly reported adverse drug reactions added for clarity in each indication.  -Editorial amendments to section and table headers to align with approved indications and patient groups.
5.1	- Addition of clarification of ITP and HCV population groups in “Race” Section under Special Populations - Editorial to clarify the significant of WHO bleeding grades. - Addition of study sub-headings.

*Internal Document Code*

(rev021120iNZ is based on Novartis core data sheet dated 13 August 2020)