NOVARTIS

Regulatory Affairs

REVOLADE®

(eltrombopag olamine**)**

12.5 mg, 25 mg, 50 mg, 75 mg Film-coated tablets
12.5 mg, 25 mg Powder for oral suspension

International Package Leaflet

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Revolade®

Thrombopoietin-receptor agonist

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablets

The 12.5 mg tablets are white, round, biconvex, and film-coated, debossed with 'GS MZ1' and '12.5' on one side.

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

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

The 75 mg tablets are pink, round, biconvex, film-coated, debossed with 'GS FFS' and '75' on one side.

Powder for Oral Suspension

Each Revolade 12.5 mg powder for oral suspension sachet contains a reddish-brown to yellow powder.

Each Revolade 25 mg powder for oral suspension sachet contains a reddish-brown to yellow powder.

Active substance

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

Each 12.5 mg sachet delivers 16 mg of eltrombopag olamine equivalent to 12.5 mg of eltrombopag free acid.

Each 25 mg sachet delivers 32 mg of eltrombopag olamine equivalent to 25 mg of eltrombopag free acid.

Excipients

Film-coated tablets

Tablet core
Microcrystalline cellulose
Mannitol
Sodium starch glycolate
Magnesium stearate
Povidone

Tablet coating

Ingredient	Tablet Strength			
	12.5 mg	25 mg	50 mg	75 mg
Hypromellose (E464)	A, B, C	A, B, C	A, C	A, C
Macrogol (polyethylene glycol) (E1521)	A, B, C	A, B, C	A, C	A, C
Titanium dioxide (E171)	A, B, C	A, B, C	A, C	A, C
Polysorbate 80 (E433)	A, B, C	B, C	--	--
FD&C Yellow No. 6 aluminium lake (E110)	--	A	--	--
FD&C Blue No. 2 aluminium lake (E132)	--	--	A	--
Iron oxide red (E172)	--	--	C	A, C
Iron oxide yellow (E172)	--	--	C	--
Iron oxide black (E172)	--	--	--	A, C

A = ingredient in US tablet

B = ingredient in Japan tablet

C = ingredient in EU/ROW (excluding Japan) tablet

-- = ingredient not in this tablet strength in any region

Powder for Oral Suspension

Mannitol
Sucralose
Xanthan gum

Pharmaceutical formulations may vary between countries.

INDICATIONS

Revolade is indicated:

- for the treatment of previously treated adult and pediatric patients 1 year and older with immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis to increase platelet counts and reduce or prevent bleeding.
- in patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia to:
  - enable the initiation of interferon based therapy
  - optimize interferon based therapy
- for the treatment of cytopenias in patients with severe aplastic anemia (refractory SAA) who have had an insufficient response to immunosuppressive therapy.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Revolade dosing regimens must be individualized based on the patient's platelet counts.

General target population

Immune thrombocytopenia

The lowest dose of Revolade should be used to achieve and maintain a platelet count ≥50,000/microL. Dose adjustments are based upon the platelet count response. Revolade should not be used to normalize platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting Revolade and decreased within 1 to 2 weeks after discontinuation.

Initial dose regimen

Adults and pediatric patients aged 6 to 17 years

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

For adult and pediatric ITP patients aged 6 to 17 years of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), Revolade should be initiated at a dose of 25 mg once daily (see section CLINICAL PHARMACOLOGY, section SPECIAL POPULATIONS).

Pediatric patients aged 1 to 5 years

The recommended starting dose of Revolade is 25 mg once daily.

For pediatric ITP patients aged 1 to 5 years of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai), Revolade should be initiated at a dose of 25 mg once daily (see section CLINICAL PHARMACOLOGY, section SPECIAL POPULATIONS).

Monitoring and dose adjustment

Adults and pediatric patients aged 1 to 17 years

After initiating Revolade, the dose should be adjusted to achieve and maintain a platelet count ≥50,000/microL as necessary to reduce the risk for bleeding. A daily dose of 75 mg should not be exceeded.

Clinical hematology and liver function tests should be monitored regularly throughout therapy with Revolade and the dose of Revolade should be 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 (≥50,000/microL for at least 4 weeks) has been achieved. CBCs including platelet count and peripheral blood smears should be obtained monthly thereafter.

Table 1 Revolade dose adjustments in ITP patients

Platelet count	Dose adjustment or response
<50,000/microL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day#.
≥200,000/microL to ≤400,000/microL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments*.
>400,000/microL	Discontinue Revolade; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/microL, reinitiate therapy at a lower daily dose*.

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

* 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.

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

After any Revolade dose adjustment, platelet counts should be monitored at least weekly for 2 to 3 weeks. To see the effect of any dose adjustment on the patient's platelet response prior to considering another dose increase, one should wait for at least 2 weeks. In patients with any liver cirrhosis (i.e., hepatic impairment), one should wait 3 weeks before increasing the dose (see section DOSAGE REGIMEN AND ADMINISTRATION, SPECIAL POPULATIONS; section HEPATIC IMPAIRMENT).

When switching between the film-coated tablet and powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Discontinuation

Adults and pediatric patients aged 1 to 17 years

Treatment with Revolade should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at 75 mg once daily.

Chronic hepatitis C (HCV) associated thrombocytopenia

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

The lowest dose of Revolade to achieve and maintain a platelet count necessary to initiate and optimize antiviral therapy should be used. Dose adjustments should be based upon the platelet count response. Revolade should not be used to normalize platelet counts. In clinical studies, platelet counts generally increased within 1 week of starting Revolade.

Initial dose regimen

Adults

Revolade should be initiated at a dose of 25 mg once daily.

For chronic HCV patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), Revolade should be initiated at a dose of 25 mg once daily (see section CLINICAL PHARMACOLOGY and section SPECIAL POPULATIONS).

Monitoring and dose adjustment

The dose of Revolade should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy (see Table 2). Platelet counts should be monitored every week prior to starting antiviral therapy.

During antiviral therapy the dose of Revolade should be adjusted as necessary to avoid dose reduction of peginterferon. Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved. CBCs, including platelet counts and peripheral blood smears should be obtained monthly thereafter.

A dose of 100 mg Revolade once daily should not be exceeded.

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

Table 2 Revolade dose adjustments in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
<50,000/microL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥200,000/microL to ≤400,000/microL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments*.
>400,000/microL	Discontinue Revolade; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150,000/microL, reinitiate therapy at a lower daily dose*.

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

Discontinuation

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

Refractory severe aplastic anemia

Initial dose regimen

Adults

Revolade should be initiated at a dose of 50 mg once daily.

For SAA patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), Revolade should be initiated at a dose of 25 mg once daily (see section CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS).

Monitoring and dose adjustment

Hematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting Revolade (see section CLINICAL STUDIES). The dose of Revolade should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50,000/microL. A dose of 150 mg daily should not be exceeded. Clinical hematology and liver tests should be monitored regularly throughout therapy with Revolade and the dosage regimen of Revolade should be modified based on platelet counts as outlined in Table 3.

Table 3 Revolade dose adjustments in refractory SAA patients

Platelet Count Result	Dose Adjustment or Response
<50,000/microL following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients of Asian ancestry or those with hepatic impairment taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥200,000/microL to ≤400,000/microL at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000/microL	Discontinue Revolade for at least one week. Once the platelet count is <150,000/microL, reinitiate therapy at a dose reduced by 50 mg.
>400,000/microL after 2 weeks of therapy at lowest dose of Revolade	Discontinue Revolade.

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

Once platelet count is >50,000/microL, hemoglobin is >10 g/dL in the absence of red blood cell (RBC) transfusion, and absolute neutrophil count (ANC) is >1 x 109/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 Revolade should be discontinued and blood counts monitored. If platelet counts drop to <30,000/microL, hemoglobin drops to <9 g/dL or ANC to <0.5 x 109/L, Revolade may be reinitiated at the previous dose.

Discontinuation

If no hematological response has occurred after 16 weeks of therapy with Revolade, therapy should be discontinued. Discontinuation should be considered if new cytogenetic abnormalities are observed (see section ADVERSE DRUG REACTIONS). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of Revolade (see section WARNINGS AND PRECAUTIONS).

Special populations (all indications)

Renal impairment

No dose adjustment is necessary in patients with renal impairment. However, because of limited clinical experience, patients with impaired renal function should use Revolade with caution and close monitoring (see section CLINICAL PHARMACOLOGY and section SPECIAL POPULATIONS).

Hepatic impairment

ITP patients with liver cirrhosis (hepatic impairment, Child-Pugh score ≥5) should use Revolade with caution and close monitoring (see section WARNINGS AND PRECAUTIONS, section CLINICAL PHARMACOLOGY and section SPECIAL POPULATIONS).

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

Chronic HCV patients with hepatic impairment and refractory severe aplastic anemia patients with hepatic impairment should initiate Revolade at a dose of 25 mg once daily (see section CLINICAL PHARMACOLOGY and section SPECIAL POPULATIONS).

Pediatric patients (below 18 years)

The safety and efficacy of Revolade have not been established in pediatric patients with ITP younger than 1 year of age, chronic HCV and refractory SAA (see sections ADVERSE DRUG REACTIONS and CLINICAL STUDIES).

Geriatric patients (65 years of age or older)

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 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 CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS).

Method of administration

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, iron, magnesium, selenium, and zinc) (see section INTERACTIONS DRUG-FOOD/DRINK INTERACTIONS).

Revolade may be taken with food containing little (< 50 mg) or preferably no calcium (see section -INTERACTIONS, DRUG-FOOD/DRINK INTERACTIONS).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

Hepatotoxicity:

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

Clinical data

In clinical studies of adult and pediatric patients (aged 1 to 17 years) with ITP who received Revolade, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed (see section ADVERSE DRUG REACTIONS)

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. In two placebo-controlled studies in adults with ITP, adverse events of ALT increase were reported in 5.7% and 4.0% of Revolade and placebo-treated patients respectively. In two placebo-controlled studies in pediatric patients (aged 1 to 17 years) with ITP, ALT ≥ 3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the Revolade and placebo groups, respectively.

In 2 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 hyperbilirubinemia. Overall, total bilirubin ≥1.5 x ULN was reported in 76% and 50% of the Revolade and placebo groups, respectively.

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

Dosage adjustment

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

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

Caution should be exercised when administering Revolade to patients with hepatic disease. In ITP and refractory SAA patients, a lower starting dose of Revolade should be used when administering to patients with hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION, HEPATIC IMPAIRMENT).

Severe liver injury:

Isolated cases of severe liver injury were identified in clinical studies. The elevation of liver laboratory values improved or resolved following Revolade interruption or discontinuation. No cases of severe liver injury related to Revolade were identified in a clinical study in patients with refractory SAA, however, the number of exposed patients in this indication was limited. As the highest authorized dose is administered to patients in the SAA indications (150 mg/day) and due to the nature of the reaction, drug-induced liver injury might be expected in this patient population.

Hepatic decompensation (use with interferon):

Chronic HCV patients with cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving alpha-interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation occurred more frequently in the Revolade arm (13%) than in the placebo arm (7%). Patients with low albumin levels (<3.5 g/dL) or with a Model for End-Stage Liver Disease (MELD) score ≥10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon prescribing information for discontinuation criteria should be referred to. Revolade should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/thromboembolic complications:

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

Caution should be used when administering Revolade to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, 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 DOSAGE REGIMEN AND ADMINISTRATION).

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

No cases of TEEs were identified in a clinical study in refractory SAA patients, however the number of exposed patients in this indication was limited. As the highest authorized 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 population.

Revolade should not be used in patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution should be exercised when administering Revolade to patients with hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION AND ADVERSE DRUG REACTIONS, HEPATIC IMPAIRMENT).

In 2 controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy, 31 out of 955 patients (3%) treated with Revolade experienced a TEE and 5 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1% in patients treated with Revolade versus <1% for placebo). No specific temporal relationship between start of treatment and occurrence of TEE was observed. The majority of TEEs resolved and did not lead to the discontinuation of antiviral therapy.

In a controlled study in thrombocytopenic patients with chronic liver disease (n=288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg Revolade once daily for 14 days. Six of 143 (4%) adult patients with chronic liver disease receiving Revolade experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five Revolade-treated patients with a TEE experienced the event within 14 days of completing Revolade dosing and at a platelet count above 200,000/ microL.

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

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 CLINICAL STUDIES), 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 TPO-R agonists may stimulate the progression of existing hematological malignancies such as 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 randomized, double-blind, placebo-controlled, multicenter 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 favored the placebo arm: a total of 57 (32%) patients died on the Revolade arm versus 51 (29%) patients in the placebo arm.

Cataracts:

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section NON-CLINICAL SAFETY DATA).

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

Routine monitoring of patients for cataracts is recommended.

Interference with serological testing:

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

Immune thrombocytopenia in adult and pediatric patients

The safety of Revolade (N=763) was assessed in adult patients with previously treated ITP using data from pooled double-blind, placebo controlled studies TRA100773A and B, TRA102537 (RAISE), and TRA113765 in which patients were exposed to Revolade (N=403) and to placebo (N=179), in addition to data from completed open label studies (N=360) TRA108057, TRA105325 (EXTEND), and TRA112940. Patients received study medication for up to 8 years (in EXTEND). Adverse drug reactions for the adult ITP study population (N=360) are shown in Table 4.

The safety of Revolade was assessed in pediatric patients (aged 1 to 17 years) with previously treated ITP using the all-treated population from two studies (N=171). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomized, placebo-controlled study. Patients were randomized 2:1 and received Revolade (n=63) or placebo (n=29) for up to 13 weeks in the randomized period of the study. PETIT (TRA108062) was a three-part, staggered cohort, open-label and double-blind, randomized, placebo controlled study. Patients were randomized 2:1 and received Revolade (n=44) or placebo (n=21), for up to 7 weeks. Additional adverse drug reactions occurring in the pediatric ITP study population are shown in Table 5.

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, multicenter 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 treatment n=232) and ENABLE 2 (Revolade treatment n=506, placebo treatment n=253). Patients were analyzed according to the treatment received (total safety double-blind population, Revolade n=955 and placebo n=484). Adverse drug reactions for the HCV study population (N=1520) are shown in Table 6.

Refractory severe aplastic anemia in adult patients

The safety of Revolade in refractory severe aplastic anemia was assessed in a single-arm, open-label study (n = 43) in which 11 patients (26%) were treated for >6 months and 7 patients (16%) were treated for >1 year. Adverse drug reactions for the refractory SAA study population (N=43) are shown in Table 7.

Most adverse drug reactions associated with Revolade were mild to moderate in severity, early in onset and rarely treatment limiting.

Tabulated summary of reactions from clinical studies

Adverse drug reactions from clinical studies are listed below by MedDRA body system organ class and by frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

Adverse drug reaction	Revolade %	Frequency category
Infections and infestations		
Pharyngitis	4.2	common
Eye disorders		
Cataract	5.0	common
Vascular disorders		
Thromboembolic events	5.5	common
Thrombotic microangiopathy with acute renal failure	1.2	common
Gastrointestinal disorders		
Diarrhoea	12.6	very common
Nausea	11.1	very common
Vomiting	7.3	common
Dry mouth	0.9	uncommon
Hepatobiliary disorders		
Increased alanine aminotransferase	10.5	very common
Increased aspartate aminotransferase	9.7	common
Hyperbilirubinaemia	1.8	common
Drug-induced liver injury	0.1	uncommon
Skin and subcutaneous tissue disorders		
Rash	7.5	common
Alopecia	3.0	common
Musculoskeletal and connective tissue disorders		
Back pain	10.5	very common
Myalgia	4.2	common
Musculoskeletal pain (incl. musculoskeletal chest pain)	3.7	common

These additional adverse drug reactions were observed in the pediatric studies.

Table 5 Additional adverse drug reactions in the pediatric ITP study population aged 1 to 17 years (N=171).

Adverse drug reactions	Revolade %	Frequency category
Infections and infestations		
Upper respiratory tract infection	25.7	very common
Nasopharyngitis	15.8	very common
Respiratory, thoracic and mediastinal disorders		
Cough	13.5	very common
Oropharyngeal pain	9.4	common
Rhinorrhoea	4.1	common
Gastrointestinal disorders		
Abdominal pain	17.5	very common
Toothache	5.8	common
General disorders and administration site conditions		
Pyrexia	18.1	very common

Table 6 Adverse drug reactions in the HCV study population (N=1520)

Revolade in combination with interferon anti-viral therapy.

Adverse drug reactions	Revolade %	Frequency category
Blood and lymphatic system disorders		
Anaemia	30.6	very common
Metabolism and nutrition disorders		
Decreased appetite	14.4	very common
Nervous system disorders		
Headache	22.2	very common
Eye disorders		
Cataract	2.4	common
Vascular disorders		
Thromboembolic events (incl. portal vein thrombosis)	2.1	common
Respiratory, thoracic and mediastinal disorders		
Cough	11.8	very common
Gastrointestinal disorders		
Nausea	17.7	very common
Diarrhoea	15.5	very common
Hepatobiliary disorders		
Hyperbilirubinaemia	6.4	very common
Drug-induced liver injury	2.1	common

Adverse drug reactions	Revolade %	Frequency category
Hepatic failure	0.7	common
Skin and subcutaneous tissue disorders		
Pruritus	12.2	very common
Rash	7.3	common
Alopecia	7.0	common
Musculoskeletal and connective tissue disorders		
Myalgia	11.2	very common
General disorders and administration site conditions		
Pyrexia	26.1	very common
Fatigue	25.0	very common
Influenza like illness	16.4	very common
Asthenia	13.2	very common
Chills	11.8	very common
Oedema	1.3	common

Table 7 Adverse drug reactions in the refractory SAA study population (N=43)

Adverse drug reactions	Revolade %	Frequency category
Nervous system disorders		
Headache	20.9	very common
Dizziness	14.0	very common
Eye disorders		
Cataract	2.3	common
Respiratory, thoracic and mediastinal disorders		
Cough	23.3	very common
Oropharyngeal pain	14.0	very common
Rhinorrhoea	11.6	very common
Gastrointestinal disorders		
Nausea	32.6	very common
Diarrhoea	20.9	very common
Abdominal pain	11.6	very common
Hepatobiliary disorders		
Transaminases increased	11.6	very common
Hyperbilirubinaemia	4.7	common
Skin and subcutaneous tissue disorders		
Rash	7.0	common
Musculoskeletal and connective tissue disorders		
Pain in extremity	18.6	very common
Arthralgia	11.6	very common
Muscle spasms	11.6	very common

Adverse drug reactions	Revolade %	Frequency category
General disorders and administration site conditions		
Fatigue	30.2	very common
Pyrexia	14.0	very common

In the single-arm, open-label study in refractory 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.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been reported during post-approval use of Revolade. These include spontaneous case reports as well as serious adverse events from registries, investigator sponsored studies, clinical pharmacology studies and exploratory studies in unapproved indications. Because they are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 8 Adverse drug reactions identified during post-approval use

Skin and subcutaneous tissue disorders
Skin discoloration*

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

INTERACTIONS

Effects of other drugs on Revolade

Cyclosporine: A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg cyclosporine (a BCRP inhibitor). Administration of a single dose of Revolade 50 mg with 200 mg cyclosporine) decreased the Cmax and the AUCinf of eltrombopag by 25% (90% CI: 15%, 35%) and 18% (90% CI: 8%, 28%), respectively. The co-administration of 600 mg cyclosporine decreased the Cmax and the AUCinf of eltrombopag by 39% (90% CI: 30%, 47%) and 24% (90% CI: 14%, 32%), respectively. This decrease in exposure is not considered clinically meaningful. Revolade dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section DOSAGE REGIMEN AND ADMINISTRATION). Platelet count should be monitored at least weekly for 2 to 3 weeks when Revolade is co-administered with cyclosporine. Revolade dose may need to be increased based on these platelet counts.

Polyvalent Cations (Chelation): Eltrombopag chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium, and zinc (see section CLINICAL PHARMACOLOGY). Administration of a single dose of Revolade 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag AUCinf by 70% (90% CI: 64%, 76%) and Cmax by 70% (90% CI: 62%, 76%) (see section DOSAGE REGIMEN AND ADMINISTRATION).). 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 to avoid significant reduction in eltrombopag absorption (see section DOSAGE REGIMEN AND ADMINISTRATION, METHOD OF ADMINISTRATION).

Lopinavir/ritonavir: Co-administration of Revolade with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of Revolade with repeat dose lopinavir/ritonavir 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma AUCinf by 17% (90% CI: 6.6%, 26.6%).

Therefore, caution should be used when co-administration of Revolade with lopinavir/ritonavir takes place. Platelet count should be monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of Revolade when lopinavir/ritonavir therapy is initiated or discontinued.

HCV protease inhibitors: Co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of Revolade 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Effects of Revolade on other drugs

Rosuvastatin: Administration of Revolade 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adults increased plasma rosuvastatin Cmax 103% (90% CI: 82%, 126%) and AUCinf 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.

Cytochrome P450 substrates: Administration of Revolade 75 mg once daily for 7 days to 24 healthy males did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates, inducers or inhibitors are co-administered.

HCV Protease inhibitors: Co-administration of a single dose of Revolade 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure. Co-administration of a single dose of Revolade 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir AUCtau, increased Cmax by 19%, and decreased Cmin by 32 %. Dose adjustment is not required when Revolade is co-administered with either telaprevir or boceprevir.

Drug-food/drink interactions

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 AUCinf by 59% (90% CI: 54%, 64%) and Cmax by 65% (90% CI: 59%, 70%). Administration of a single 25-mg dose of Revolade powder for oral suspension with a high-calcium, moderate fat and calorie meal reduced plasma eltrombopag AUCinf by 75% (90% CI: 71%, 88%) and Cmax by 79% (90% CI: 76%, 82%). Administration of a single 25 mg-dose of Revolade powder for oral suspension 2 hours before a high-calcium meal attenuated the effect, where plasma eltrombopag AUCinf was decreased by 20% (90% CI: 9%, 29%) and Cmax by 14% (90% CI: 2%, 25%). Administration of a single 25 mg dose of Revolade powder for oral suspension 2 hours after the high-calcium meal reduced plasma eltrombopag AUCinf by 47% (90% CI: 40%, 53%) and Cmax by 48% (90% CI: 40%, 54%). Food low in calcium (<50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see section DOSAGE REGIMEN AND ADMINISTRATION, METHOD OF ADMINISTRATION).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies of Revolade in pregnant women to inform a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of eltrombopag to pregnant rats and rabbits throughout organogenesis resulted in developmental toxicity in rats (see Animal data). The effect of eltrombopag on human pregnancy is unknown. Pregnant women or women of childbearing potential should be advised of the potential risk of Revolade to a fetus. Revolade should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Animal data

In embryo-fetal developmental toxicity studies in rats and rabbits, oral eltrombopag was administered to pregnant animals during organogenesis. In rats, a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day) resulted in decreased fetal weights and a slight increase in the incidence of the fetal variation, cervical rib. No evidence of major structural malformations was observed. In rabbits, there was no evidence of embryo-fetal toxicity or teratogenicity up to 150 mg/kg/day (0.5 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

In a pre-and postnatal developmental toxicity study in pregnant rats, oral eltrombopag was administered from gestation day 6 through lactation Day 20. No adverse effects on maternal reproductive function or on the development of the offspring were observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was detected in the plasma of offspring. The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

Lactation

Risk summary

There is no information regarding the presence of eltrombopag or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. However, eltrombopag was detected in the pups of lactating rats 10 days postpartum suggesting the potential for transfer during lactation. A decision must be made whether to discontinue breastfeeding or to continue/abstain from Revolade therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Females and males of reproductive potential

Contraception

Based on animal reproduction studies, Revolade can cause fetal harm when administered to a pregnant woman (see section PREGNANCY). Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Revolade during treatment and for at least 7 days after stopping treatment with Revolade.

Infertility

There is no effect of Revolade on fertility based on animal studies (see section NON-CLINICAL SAFETY DATA). Eltrombopag did not affect female or male fertility in rats at doses 2 and 3 times respectively the human clinical exposure based on AUC in patients with ITP at 75 mg/day and in patients with chronic Hepatitis C at 100 mg/day (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

In the clinical studies, there was one report of overdose where the patient ingested 5,000 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 672,000/microL on day 18 after ingestion and the maximum platelet count was 929,000/microL. All events resolved without sequelae following treatment.

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption should be considered. Platelet counts should be closely monitored. Treatment with Revolade should be reinitiated in accordance with dosing and administration recommendations (see section DOSAGE REGIMEN AND ADMINISTRATION).

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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

Pharmacodynamics (PD)

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 antagonize platelet aggregation induced by ADP or collagen.

Pharmacokinetics (PK)

The pharmacokinetic parameters of eltrombopag after administration of Revolade to adult patients with ITP are shown in Table 9.

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

Revolade dose (once daily)	N	Cmax (microg/mL)	AUCtau (microg.h/mL)
50 mg	34	8.01 (6.73, 9.53)	108 (88, 134)
75 mg	26	12.7 (11.0, 14.5)	168 (143, 198)

Data presented as geometric mean (95 % CI). AUCtau and Cmax based on population PK post-hoc estimates.

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 adults in a population pharmacokinetic analysis. Plasma eltrombopag Cmax and AUCtau 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 Revolade dose.

Table 10 Steady-state plasma eltrombopag pharmacokinetic parameters in adults with chronic HCV

Revolade dose (once daily)	N	Cmax (microg/mL)	AUCtau (microg.h/mL)
25 mg	330	6.40 (5.97, 6.86)	118 (109, 128)
50 mg	119	9.08 (7.96, 10.35)	166 (143, 192)
75 mg	45	16.71 (14.26, 19.58)	301 (250, 363)
100 mg	96	19.19 (16.81, 21.91)	354 (304, 411)

Data presented as geometric mean (95%CI). AUCtau and Cmax based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of Revolade concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section INTERACTIONS). In a relative bioavailability study in adults, Revolade powder for oral suspension delivered a 22% higher plasma AUCinf than the film-coated tablet formulation. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg Revolade solution dose was estimated to be at least 52%.

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/metabolism

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 AUCinf. 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 metabolized by oxidation.

Elimination

Absorbed eltrombopag is extensively metabolized. The predominant route of eltrombopag excretion is via feces (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

feces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

In vitro evaluation of drug interaction potential

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag 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 studies utilizing human liver microsomes, eltrombopag (up to 100 microM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates, with IC50 values of 24.8 microM (11 microgram/mL) and 20.2 microM (8.9 microgram/mL), respectively.

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter, with an IC_{50} value of 2.7 microM (1.2 microg/mL) and an inhibitor of the BCRP transporter, with an IC_{50} value of 2.7 microM (1.2 microg/mL).

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.

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

Special populations

Pediatric population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Approximately 30% lower plasma eltrombopag CL/F was observed in patients of Asian race and 20% lower CL/F was observed in female patients. The bioavailability of the powder for oral suspension in pediatric patients was estimated as 29% lower than the film-coated tablet.

The pharmacokinetic parameters of eltrombopag in pediatric patients with ITP are shown in Table 11.

Table 11 Steady-state plasma eltrombopag pharmacokinetic parameters in pediatric patients with ITP

Age	Cmax (microgram/mL)	AUCtau (microgram.hr/mL)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n =68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). AUCtau and Cmax based on population PK post-hoc estimates for a 50 mg once daily dose.

Geriatric patients (60 years of age or above)

The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetic analysis in 28 healthy subjects 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 AUCtau as compared to younger patients.

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50% higher plasma eltrombopag AUCtau as compared to male ITP patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using a population pharmacokinetic analysis in 663 patients with HCV (260 females). Based on model estimates, female HCV patients had approximately 41% higher plasma eltrombopag AUCtau as compared to male patients.

Race/Ethnicity

ITP: The influence of Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (31 Asians) and 88 patients with ITP (18 Asians). Based on estimates from the population pharmacokinetic analysis, Asian (i.e., Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87% higher plasma eltrombopag AUCtau values as compared to non- Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see section DOSAGE REGIMEN AND ADMINISTRATION).

HCV: The influence of Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 663 patients with HCV (214 East/Southeast). Based on estimates from the population pharmacokinetic analysis, East Asian and Southeast Asian patients had similar pharmacokinetics of eltrombopag. On average, Asian patients had approximately 55% higher plasma eltrombopag AUCtau values as compared to patients of other

races who were predominantly Caucasian (see section DOSAGE REGIMEN AND ADMINISTRATION).

Renal impairment

The pharmacokinetics of eltrombopag have been studied after administration of Revolade to adult patients with renal impairment. Following administration of a single 50 mg-dose, the AUCinf 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.

Hepatic impairment

The pharmacokinetics of eltrombopag have been studied after administration of Revolade to adult patients with liver cirrhosis (hepatic impairment). Following the administration of a single 50-mg dose, the AUCinf 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.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 79 patients with chronic liver disease. Based on estimates from the population pharmacokinetic analysis, patients with liver cirrhosis (hepatic impairment) had higher plasma eltrombopag AUCtau values as compared to healthy volunteers, and AUCtau increased with increasing Child-Pugh score. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 87% to 110% higher plasma eltrombopag AUCtau values and patients with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag AUCtau 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 AUCtau values as compared to healthy subjects, and AUCtau increased with increasing Child-Pugh score, HCV patients with mild hepatic impairment had approximately 100% to 144% higher plasma eltrombopag AUCtau compared with healthy subjects. For patients with HCV, Revolade should be initiated at a dose of 25 mg once daily (see section DOSAGE REGIMEN AND ADMINISTRATION, HEPATIC IMPAIRMENT).

CLINICAL STUDIES

Immune thrombocytopenia (ITP) studies

Adults

The safety and efficacy of Revolade in adult patients with previously treated ITP have been demonstrated in two, randomized, double-blind, placebo-controlled studies (TRA102537 [RAISE] and TRA100773B) and two open label studies (TRA108057 [REPEAT] and TRA105325 [EXTEND]).

Double-blind placebo-controlled studies

TRA102537 (RAISE):

In TRA102537, the primary efficacy endpoint was the odds of achieving a platelet count ≥50,000/microL and ≤400,000/microL, during the 6 month treatment period, for patients receiving Revolade relative to placebo. One hundred and ninety-seven patients were randomized 2:1 to Revolade (n = 135) and to placebo (n = 62). Stratification was 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 according to local standard of care.

The odds of achieving a platelet count between 50,000/microL and 400,000/microL during the 6-month treatment period were 8 times higher for Revolade treated patients than for placebo-treated patients (Odds Ratio (OR): 8.2 (99% CI: 3.59, 18.73) p = <0.001). Median platelet counts were maintained above 50,000/microL at all on-therapy visits starting at Day 15 in the Revolade group; in contrast, median platelet counts in the placebo group remained below 30,000/microL 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 hemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. Fewer Revolade treated patients (29%) required rescue treatment to manage their hemostatic 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 ≥50,000/microL at Day 43 from a baseline platelet count <30,000/microL; patients who withdrew prematurely due to a platelet count >200,000/microL 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 ITP were randomized 2:1 study, with 76 randomized to Revolade and 38 randomized 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 (OR: 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 hemostatic 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 (≤15,000/microL, >15,000/microL) at randomization.

Open label studies

TRA108057 (REPEAT):

TRA108057 was an open-label, repeat-dose study which evaluated the efficacy, safety and consistency of response following repeated, intermittent, short-term dosing of Revolade over 3 cycles of therapy in adults with previously treated ITP. A cycle was defined as an up to 6-week on-therapy period followed by an up to 4-week off-therapy period. The duration of both the on-

therapy and the off-therapy periods was defined by the patient's platelet count. Patients were to interrupt treatment for the cycle if they achieved a platelet count >200,000/microL, or when they reached Week 6. Patients were to begin the next cycle when their platelet counts fell below 20,000/microL, or when they reached Week 4 of the off-therapy period. The primary endpoint was the proportion of patients who achieved a platelet count ≥ 50,000/microL and at least 2 x baseline in Cycle 2 or 3, given this response in Cycle 1.

Table 12 Evaluable and responding patients in TRA108057

	Revolade 50 mg (N=66)
Evaluable in Cycle 1, n	65
Responders in Cycle 1, n (%)	52 (80)
Evaluable in Cycle 2 or 3, n	52
Responders in Cycle 1 and in Cycle 2 or 3, n (%)	45 (87)
Proportion	0.87
95% CI for Proportion (Exact Methods)	(0.74, 0.94)

Of the 52 patients who responded in Cycle 1, 33 (63%) achieved a platelet count of ≥50,000 microL and at least 2 x baseline on Day 8 in Cycle 1; on Day 15, 37 (79%) of 47 evaluable patients achieved this level of response.

A reduction in any bleeding (WHO Grade 1-4) and clinically significant bleeding (WHO Grade 2-4) during the treatment phases was demonstrated in each cycle. At the baseline visit of Cycle 1, 50% and 19% of patients reported any bleeding and clinically significant bleeding, respectively. At the Day 43 Visit of Cycle 1, the proportion of patients bleeding was reduced; 12% and 0% of patients reported any bleeding and clinically significant bleeding. Similar results were found during the subsequent treatment cycles.

Eight patients successfully managed 10 hemostatic challenges without need for additional therapy to elevate platelet counts and without unexpected bleeding.

TRA105325 (EXTEND)**:**

TRA105325 was an open label extension study which has evaluated the safety and efficacy of Revolade in patients with ITP at least 6 months from diagnosis 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 19,000/microL prior to Revolade administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/microL, 85,000/microL, 105,000/microL, 64,000/microL, 75,000/microL, 119,000/microL and 76,000/microL respectively. The median daily dose of Revolade following 6 months of therapy was 50 mg (n = 74).

At baseline, 59% of patients had any bleeding (WHO Bleeding Grades 1-4) and 18% had clinically significant bleeding. The proportion of patients with any bleeding and clinically

significant bleeding decreased from baseline by approximately 50% for the majority of assessments up to 1 year.

One-hundred and one patients were taking ITP medications at baseline upon entry into EXTEND study, and 39 patients were able to permanently discontinue or achieve a sustained reduction of at least one baseline ITP medication without needing rescue medication. 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 hemostatic challenge during the study. No patient experienced unexpected bleeding complications related to the procedure while on study.

Pediatric patients (aged 1 to 17 years)

The safety and efficacy of Revolade in pediatric patients with previously treated ITP have been demonstrated in two studies.

Double-blind placebo-controlled studies

TRA115450 (PETIT2):

The primary endpoint was a sustained response, defined as the proportion of patients receiving Revolade, compared to placebo, achieving platelet counts ≥50,000/microL for at least 6 out of 8 weeks (in the absence of rescue therapy), between Weeks 5 to 12 during the double-blind randomized period. Patients were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count <30,000/microL. Ninety-two patients were randomized by three age cohort strata (2:1) to Revolade (n = 63) or placebo (n = 29). The dose of Revolade could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Revolade patients (40%) compared with placebo patients (3%) achieved the primary endpoint (OR: 18.0 (95% CI: 2.3, 140.9) p< 0.001) which was similar across the three age cohorts (Table 13).

Table 13 Sustained platelet response rates by age cohort in pediatric patients with ITP at least 12 months from diagnosis

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

A significantly greater proportion of patients treated with Revolade (75%) compared with placebo (21%) had a platelet response (at least one platelet count >50,000/microL during the first 12 weeks of randomized treatment in absence of rescue therapy) (OR: 11.7, (95% CI: 4.0,

34.5), p <0.001). The proportion of patients who responded to Revolade in the open-label 24-week period (80%) was similar to that observed during the randomized portion of the study.

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

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

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

TRA108062 (PETIT):

The primary endpoint was the proportion of patients achieving platelet counts ≥50,000/ microL at least once between Weeks 1 and 6 of the randomized period. Patients were refractory or relapsed to at least one prior ITP therapy with a platelet count <30,000/ (n = 67). During the randomized period of the study, patients were randomized by 3 age cohort strata (2:1) to Revolade (n = 45) or placebo (n = 22). The dose of Revolade could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Revolade patients (62%) compared with placebo patients (32%) met the primary endpoint (OR: 4.3 (95% CI: 1.4, 13.3) p = 0.011). Table 14 shows platelet response across the three age cohorts.

Table 14 Platelet response rates in pediatric patients with ITP at least 6 months from diagnosis

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

A significantly greater proportion of patients treated with Revolade (36%) compared with placebo (0%) had a platelet response (platelet counts >50,000/microL for at least 60% of assessments between Weeks 2 and 6) (OR: 5.8, (95% CI: 1.2, 28.9), p = 0.002).

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

At baseline, 77.7% of patients in the Revolade group and 81.8% in the placebo group reported any bleeding (WHO Grades 1-4). The proportion of Revolade patients reporting any bleeding decreased to 22.2% at Week 6. In comparison, 72.7% of placebo patients reported any bleeding at Week 6.

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

Chronic hepatitis C associated thrombocytopenia 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. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. In both studies, patients with a platelet count of <75,000/microL were enrolled and stratified by platelet count (<50,000/microL and ≥50,000/microL to <75,000/microL), screening HCV RNA (<800,000 IU/mL and ≥800,000 IU/mL), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The studies consisted of two phases-a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label Revolade to increase the platelet count to ≥90,000/microL for ENABLE 1 and ≥100,000/microL 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 prescribing information for up to 48 weeks.

The primary efficacy endpoint for both studies was sustained virological response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70% of patients were genotype 1/4/6 and 30% were genotype 2/3. Approximately 31% of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately 60,000/microL) were similar among all treatment groups. The median time to achieve the target platelet count ≥ 90,000/microL (ENABLE 1) or ≥100,000/microL (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 ≥50,000/microL compared to 19% for placebo. A greater proportion of patients in the placebo group (20%) had minimum platelet counts fall below 25,000/microL during treatment compared to the Revolade group (3%). In the Revolade group, SVR rates in patients with high viral loads (>800,000) were 18% as compared to 8% in the placebo group. Significantly more patients reached the later antiviral milestones of early virologic response (EVR), complete early virologic response (cEVR), end

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

Table 15 ENABLE 1 and ENABLE 2 virologic response

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

a Revolade given in combination with peginterferon alfa-2a (180 microg once weekly for 48 weeks for genotypes 1 or 4; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

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

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

d *P* value <0.05 for Revolade versus placebo

Refractory severe aplastic anemia study

Revolade was studied in a single-arm, single-center open-label study in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count ≤30,000/microL.

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. The primary endpoint was hematological response assessed after 12 weeks of Revolade treatment.

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

Hematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/microL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by >1.5 g/dL (for patients with pre-treatment hemoglobin <9 g/dL), or a reduction in the volume of RBC transfusions of at least 4 units for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% (for patients with pre-treatment ANC <500/microL) or an ANC increase 500/microL.

The treated population had median age of 45 years (range 17 to 77 years) and 56% of patients were male. At baseline the median platelet count was 20,000/microL hemoglobin was 8.4 g/dL, and ANC was 580/microL. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

A total of 17 patients (40%) met the hematologic response criteria in at least 1 lineage at the Primary Response Assessment (95% CI: 25, 56).

Multi-lineage responses were observed in 4/17 responders (24%) at the initial response assessment and in 9/17 responders (53%) at last assessment. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off Revolade, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

The majority of responders met platelet response criteria (65%), followed by neutrophil and hemoglobin response criteria (47% and 18% respectively). The 15 responders who had at least 2 response assessments were evaluable for assessment of response duration and had a median duration of response of 12.0 months.

Nine of the 17 responders had a multi-lineage best response. Of the 14 patients who entered the extension, seven had improvement in more than one lineage following continuation of treatment: five patients with uni-lineage response improved to multi-lineage response (bi- or tri-lineage) and two patients with bi-lineage response improved to tri-lineage response. Three of the four bi-lineage responders also had meaningful improvements in hemoglobin (>1.5 g/dL); however, as their baseline hemoglobin was above 9 g/dL they are not counted as having an erythroid response.

The longest platelet transfusion free period in responders ranged from 8 to 1,190 days with a median of approximately 287 days. The longest RBC transfusion free period in responders ranged from 15 to 1,190 days with a median of approximately 266 days. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off Revolade, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥6 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 3 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥4 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from Days 4-32 (approximately equating to a 2-year old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human

clinical exposure in pediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in pediatric ITP patients, based on AUC. Cataracts have not been observed in dogs after 52 weeks of dosing at 2 times the human 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 AUC (see section WARNINGS AND PRECAUTIONS).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on AUC in HCV patients at 100 mg/day. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Carcinogenicity and mutagenicity

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 and 5 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure, based on 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). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity

Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day) (see also section FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Juvenile animal studies

At non-tolerated doses in pre-weaning rats, ocular opacities were observed. However, at tolerated doses, no ocular opacities were observed (see section 13 Non-clinical safety data, Safety pharmacology and repeat dose toxicity). There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in pediatric vs. adult patients.

INCOMPATIBILITIES

No known incompatibilities

STORAGE

See folding box.

Revolade should not be used after the date marked "EXP" on the pack.

Revolade must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Film-coated tablets

No special requirements.

Powder for oral suspension

Follow the handling procedures carefully. Avoid direct contact with the medicine. Wash any exposed area immediately with soap and water. Revolade powder for oral suspension produces a reddish-brown suspension when reconstituted with water.

The oral suspension is intended for immediate use once reconstituted with water, but may be stored for a maximum period of 30 minutes.

The contents of the prescribed number of sachets (depending on the recommended dose) should be added to the provided mixing bottle containing 20 mL of water. The bottle should be capped with threaded closure with syringe-port capability and gently shaken for 20 seconds. To prevent foaming, the bottle should not be shaken vigorously. The entire contents of the bottle should be given to the patient using the accompanying oral syringe. Some medication will remain in the mixing bottle so the bottle should be rinsed as follows to ensure the patient receives their full prescribed dose. An additional 10 mL of water should be added to the mixing bottle. After gently mixing, the entire contents of the bottle should be given to the patient using the accompanying oral syringe.

Do not re-use the oral dosing syringe. A new single-use oral dosing syringe should be used to prepare each dose of Revolade for oral suspension.

Special precautions for disposal

No special precautions for disposal.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: Jun 2019

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