PRODUCT INFORMATION

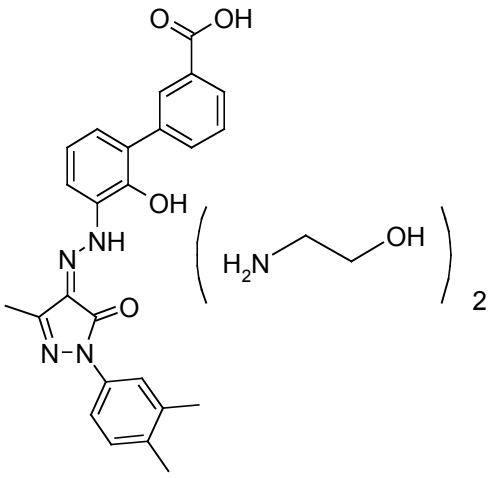
REVOLADE® TABLETS

NAME OF THE MEDICINE

REVOLADE® (Eltrombopag olamine)

REVOLADE film-coated tablets contain eltrombopag olamine. Eltrombopag olamine is an oral small molecule, thrombopoietin receptor (TPO-R) agonist. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethyl-phenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid-2-aminoethanol (1:2).

The structural formula is:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

Molecular formula: C_{25} H_{22} N_4 O_4. 2 (C_2 H_7 N O)
Molecular weight: 564.65.
CAS number: 496775-62-3

DESCRIPTION

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

Each film-coated tablet also contains magnesium stearate, mannitol, cellulose - microcrystalline, 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).

PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

The pharmacokinetic parameters of eltrombopag after administration of eltrombopag to patients with ITP are shown in Table 1.

Table 1 Geometric Mean (95 % CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Adults with Idiopathic Thrombocytopenic Purpura

Regimen of eltrombopag	C_{max} (µg/ml)	$AUC_{(0-t)}$ (µg.hr/ml)
50 mg once daily (n=34)	8.01 (6.73, 9.53)	108 (88, 134)
75 mg once daily (n=26)	12.7 (11.0, 14.5)	168 (143, 198)

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were

combined with data from subjects with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-t)}$ estimates for subjects with HCV enrolled in the Phase III studies are presented for each dose studied in Table 2. A higher eltrombopag exposure was observed in patients with HCV at a given eltrombopag dose.

Table 2 Geometric Mean (95 % CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Subjects with Chronic HCV

Eltrombopag Dose (once daily)	N	Cmax (mg/ml)	AUC(0-t) (mg.h/ml)
25 mg	330	6.40 (5.97, 6.86)	118 (109, 128)
50 mg	119	9.08 (7.96, 10.35)	166 (143, 192)
75 mg	45	16.71 (14.26, 19.58)	301 (250, 363)
100 mg	96	19.19 (16.81, 21.91)	354 (304, 411)

Data presented as geometric mean (95%CI).

AUC (0-t) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

Absorption and Bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see *Dosage and Administration, Interactions).* The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9 %). Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

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 $AUC_{0-¥}$. Minor metabolites, each accounting for < 10 % of the plasma radioactivity, arising from glucuronidation and

oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20 % of a dose is metabolised by oxidation. *In vitro* studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

Excretion

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

Special Patient Populations

Renal Impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-¥}$ 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.

Hepatic Impairment

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

ITP patients with liver cirrhosis (hepatic impairment) should use eltrombopag with caution and close monitoring (see *Precautions*). 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 *Dosage and Administration*).

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 $AUC_{(0-t)}$ values as compared to healthy subjects, and $AUC_{(0-t)}$ increased with increasing Child-Pugh score, HCV patients with mild hepatic impairment had approximately 100-144 % higher plasma eltrombopag $AUC_{(0-t)}$ compared with healthy subjects. For patients with HCV initiate REVOLADE at a dose of 25 mg once daily (see *Dosage and Administration*).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population 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 (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{(0-t)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see *Dosage and Administration*).

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (214 East Asians). On average, East Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-t)}$ values as compared to patients of other races who were predominantly Caucasian (see *Dosage and Administration*).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population 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 $AUC_{(0-t)}$ as compared to male patients, without adjustment for body weight differences.

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

Elderly Population

The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetics 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 $AUC_{(0-t)}$ as compared to younger patients (see *Dosage and Administration*).

CLINICAL TRIALS

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

The safety and efficacy of REVOLADE has 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

TRA102537: In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count ³ 50,000/µl and ≤ 400,000/µl, during the 6 month treatment period, for subjects receiving REVOLADE relative to placebo. One hundred and ninety seven subjects 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. Subjects 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, subjects 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 50,000/µl and 400,000/µl during the 6 month treatment period were 8 times higher for REVOLADE treated subjects than for placebo-treated subjects (Odds Ratio: 8.2 [99 % CI: 3.59, 18.73] p = < 0.001). Median platelet counts were maintained above 50,000/µl at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below 30,000//µl throughout the study.

At baseline, 77 % of subjects in the placebo group and 73 % of subjects 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 subjects in the placebo and REVOLADE groups, respectively. The proportion of subjects 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 subjects. 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 subjects compared to the placebo-treated subjects ($p < 0.001$).

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

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

Four placebo and 14 REVOLADE subjects had at least 1 haemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. Fewer REVOLADE-treated subjects (29 %) required rescue treatment to manage their haemostatic challenge, compared to placebo-treated subjects (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 $\geq$ 50,000/mL at Day 43 from a baseline < 30,000/mL; patients who withdrew prematurely due to a platelet count > 200,000/mL were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 subjects with previously treated chronic ITP were randomised 2:1 into the study, with 76 randomised to REVOLADE and 38 randomized to placebo.

Fifty-nine percent of subjects on REVOLADE responded, compared to 16 % of subjects on placebo. The odds of responding were 9 times higher for REVOLADE treated subjects compared to placebo (Odds Ratio: 9.6 [95 % CI: 3.31, 27.86] $p < 0.001$). At baseline, 61 % of subjects in the REVOLADE group and 66 % of subjects in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39 % of subjects 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 subjects had bleeding (Grade 1-4) at

any point in time over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo group (OR=0.49, 95 % CI=[0.26,0.89], p = 0.021). Two placebo and one REVOLADE subject 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 (≤ 15,000/µl, > 15,000/µl) at randomization.

Open Label Studies

TRA105325: EXTEND is an open label extension study which has evaluated the safety and efficacy of REVOLADE in subjects with chronic ITP who were previously enrolled in a REVOLADE trial. In this study, subjects were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

REVOLADE was administered to 207 patients; 104 completed 3 months of treatment, 74 completed 6 months and 27 patients completed 1 year of therapy. The median baseline platelet count was 18,000/ml prior to REVOLADE administration. REVOLADE increased median platelet counts to ≥ 50,000/µl at the majority of the post-baseline visits on the study. The median count post-baseline increased to ≥50,000/µl beginning at the second week on study and remained elevated until the end of the observation period presented (i.e., 55 weeks), with the exception of weeks 29, 33 and 45 where the median platelet count was 44,000 43,000 and 42,000/µl, respectively. Just over half of the subjects (51%) experienced ≥ 4 weeks of continuous elevation of platelets ≥ 50,000/µl and 2 x baseline while receiving REVOLADE.

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

Seventy percent of subjects 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 subjects maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of subjects completely discontinued at least one baseline ITP medication, and 55 % of subjects permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

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

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of REVOLADE for the treatment of thrombocytopenia in subjects 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, subjects with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label REVOLADE to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl 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 subjects could receive open-label REVOLADE was 9 weeks. If sufficient platelet counts were achieved, subjects 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 subjects with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70 % of subjects were genotype 1/4/6 and 30 % were genotype 2/3. Approximately 30 % of subjects had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately 60,000/µl) were similar among all treatment groups. The median time to achieve the target platelet count ≥ 90,000/µl was 2 weeks. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

In both HCV studies, a significantly greater proportion of subjects treated with REVOLADE achieved SVR compared to those treated with placebo (see Table 3). Significantly fewer subjects treated with REVOLADE had any antiviral dose reductions compared to placebo. The proportion of subjects with no antiviral dose reductions was 45 % for REVOLADE compared to 27 % for placebo. Significantly fewer subjects treated with REVOLADE prematurely discontinued antiviral therapy compared to

placebo (45 % vs. 60 %, p < 0.0001). The majority of subjects treated with REVOLADE (76 %) had minimum platelet counts that were ≥ 50,000/µl compared to 19 % for placebo. A greater proportion of subjects in the placebo group (20 %) had minimum platelet counts fall below 25,000/µl during antiviral treatment compared to the REVOLADE group (3 %). In the REVOLADE group, SVR rates in subjects with high viral loads (> 800,000) were 18 % as compared to 8 % in the placebo group. Significantly more subjects reached the 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 3 ENABLE 1 and ENABLE 2 Virological Response

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

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

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

c Target platelet count was ³ 90,000/µl for HCV Study 1 and ³ 100,000/µl for HCV Study 2.

d *P* value < 0.05 for REVOLADE versus placebo

INDICATIONS

REVOLADE is indicated for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

REVOLADE is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

CONTRAINDICATIONS

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

PRECAUTIONS

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.

Hepatic monitoring: REVOLADE administration can cause hepatobiliary laboratory abnormalities. In clinical studies in chronic ITP trials with REVOLADE, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed (*see Adverse Events)*.

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 chronic ITP, adverse events of ALT increase were reported in 5.7 % and 4.0 % of eltrombopag and placebo treated patients respectively.

In 2 controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST ^{3} 3 x ULN were reported in 34 % and 38 % of the REVOLADE and placebo groups, respectively. REVOLADE administration in combination with peginterferon/ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76 % and 50 % of the REVOLADE and placebo groups, respectively.

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 3X the upper limit of normal [ULN] in patients with normal liver function or ³ 3X baseline in patients with elevations in transaminases before treatment and are:

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

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 impartment (see *Dosage and Administration*).

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 (Use with interferons): 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 where REVOLADE was used as necessary to achieve the target platelet count required to enable antiviral therapy, safety findings suggestive of hepatic decompensation were reported more frequently in the REVOLADE arm (13 %) than in the placebo arm (7 %). Patients with low albumin levels (≤ 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score ³ 10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. Refer to the respective interferon prescribing information for discontinuation criteria. REVOLADE should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Renal Impairment: The efficacy and safety of REVOLADE has not been established in patients with moderate to severe renal impairment (see *Dosage and Administration*).

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 *Pharmacology, Special Patient Populations*).

Thrombotic/Thromboembolic Complications: Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In REVOLADE clinical trials 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 *Dosage and Administration*).

In ITP studies, 21 thromboembolic/thrombotic events were observed in 17 out of 446 subjects (3.8%). The TEE events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke, and suspected PRIND (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.

REVOLADE should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering REVOLADE to patients with hepatic impairment (see *Dosage and Administration and Adverse Effects*).

In 2 controlled studies in thrombocytopenic patients with HCV (n = 1439, safety population), 31 out of 955 subjects (3 %) treated with REVOLADE experienced a TEE (3 %) and 5 out of 484 subjects (1 %) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1 % in patients treated with REVOLADE versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were 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 thrombotic complications were reported within the group that received REVOLADE and one within the placebo group.

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 return to baseline levels within 2 weeks in the majority of patients (see *Clinical Trials*), which increases the bleeding risk and in some cases may lead to bleeding. Platelet counts must be monitored weekly for 4 weeks following discontinuation of REVOLADE.

Bone Marrow Reticulin Formation and Risk of Bone Marrow Fibrosis: Thrombopoietin (TPO) receptor agonists, including REVOLADE, may increase the risk for development or progression of reticulin fibers within the bone marrow. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

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

Malignancies and progression of malignancies: There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS (see *Carcinogenicity*). Across the clinical trials in ITP (n = 493) and HCV (n = 1439) no difference in the incidence of malignancies or haematological malignancies was demonstrated between placebo- and REVOLADE treated patients.

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

Cataracts: Treatment related cataracts were detected in rodents; an effect that was both dose- and time-dependent. Cataract formation was observed after 6 weeks of treatment at systemic exposure [3] 6 times and 3 times that anticipated in humans in ITP at 75

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

In the 3 controlled ITP clinical studies, cataracts developed or worsened in 15 (7%) of patients who received 50 mg REVOLADE daily and 8 (7%) placebo-group patients. Perform a baseline ocular examination prior to administration of REVOLADE and, during therapy with REVOLADE, regularly monitor patients for signs and symptoms of cataracts.

In 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*. *In vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic (³ 15 µg/ml) in the presence of high ultraviolet (UV) light exposures (700 mJ/cm2). There was no evidence of *in vivo* cutaneous phototoxicity in mice (10 times the human clinical exposure in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day based on AUC) or photo-ocular toxicity in mice or rats (up to 10 and 6 times the human clinical exposure in ITP patients at 75 mg/day and 5 and 3 times the human clinical exposure in HCV patients at 100 mg/day based on AUC). Furthermore, a clinical pharmacology study in 36 subjects 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.

Effects on Fertility

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

Use in Pregnancy (Category B3)

Eltrombopag was not teratogenic in rats or rabbits at doses up to 20 mg/kg/day and 150 mg/kg/day respectively. The doses resulted in exposures 2 and 0.5 fold the expected clinical AUC in ITP patients at 75 mg/day and subclinical exposures in HCV patients at 100 mg/day. At the maternally toxic dose of 60 mg/kg/day in rats, 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.

Use in Lactation

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

Ability to perform tasks that require judgement, motor or cognitive skills

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.

Carcinogenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures greater than 3 times the anticipated clinical exposure based on plasma AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV at 100 mg/day). Eltrombopag activates TPO receptors on the surface of haematopoietic cells and has been shown to stimulate the proliferation of megakaryocytic leukaemia cells *in vitro.* There is therefore a theoretical possibility that eltrombopag may increase the risk for haematologic malignancies.

Genotoxicity

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

INTERACTIONS WITH OTHER MEDICINES

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

Based on a human study with radiolabelled eltrombopag, approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. *In vitro* eltrombopag was an inhibitor of CYP2C8 and CYP2C9 (IC_{50} 20-25 mM; 8.9-11 mg/mL) , but eltrombopag did not inhibit or induce the metabolism of the CYP2C9 probe substrate flurbiprofen in a clinical drug interaction study when eltrombopag was administered as 75 mg once daily for 7 days to 24 healthy adult subjects. 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.

<u>*Rosuvastatin*</u>*: In vitro* studies demonstrated that REVOLADE is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter with an IC50 value of 2.7 mM (1.2 mg/mL). *In vitro* studies also demonstrated that REVOLADE is a breast cancer resistance protein (BCRP) substrate and inhibitor with an IC50 value of 2.7 mM (1.2 mg/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 subjects increased plasma rosuvastatin C_{max} 103 % (90 % CI: 82 %, 126 %) and $AUC_{0-¥}$ 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 trials 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 REVOLADE. A study in 40 healthy volunteers showed that the co-administration of single dose REVOLADE 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in REVOLADE plasma $AUC_{(0-¥)}$ 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 in order to ensure appropriate medical management of the dose of REVOLADE when lopinavir/ritonavir therapy is initiated or discontinued.

Polyvalent Cations (Chelation): REVOLADE chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-¥}$ by 70 % (90 % CI: 64 %, 76 %)and C_{max} by 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations such as mineral supplements should be administered at least four hours apart from REVOLADE dosing to avoid significant reduction in REVOLADE absorption (see *Dosage and Administration)*.

Food Interaction: Administration of a single 50 mg-dose of REVOLADE 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_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [<50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see *Dosage and Administration).*

ADVERSE EFFECTS

Clinical Trial Data

In the ITP studies, the safety and efficacy of REVOLADE has been demonstrated in two randomised, double-blind, placebo controlled studies (TRA102537 RAISE and TRA100773B) in adults with previously treated chronic ITP. In the RAISE study 197 subjects were randomised 2:1, REVOLADE (n=135) to placebo (n=62). Subjects received study medication for up to 6 months.

Table 4 On-therapy Adverse Events reported by 5% or More of Subjects in Either Treatment Group in RAISE

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

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 subjects with HCV infection who were otherwise eligible to initiate antiviral therapy.

In the HCV studies the safety population consisted of all randomized subjects who received double-blind study drug during Part 2 of ENABLE 1 (REVOLADE treatment N=449, placebo N=232) and ENABLE 2 (REVOLADE treatment N=506, placebo N=252). Subjects are analysed according to the treatment received (total safety double blind population, REVOLADE N=955 and placebo N=484).

Adverse reactions considered as possibly related to REVOLADE are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

Very common ³ 1 in 10
Common ³ 1 in 100 and < 1 in 10
Uncommon ³ 1 in 1,000 and < 1 in 100
Rare ³ 1 in 10,000 and < 1 in 1,000

The adverse reactions identified in subjects treated with REVOLADE are presented below.

ITP study population

Infections and infestations

Common	Pharyngitis
	Urinary tract infection

Gastrointestinal disorders

Very Common	Nausea
	Diarrhoea
Common	Dry mouth
	Vomiting

Hepatobiliary disorders

Common	Increased aspartate aminotransferase
	Increased alanine aminotransferase

Skin and subcutaneous tissue disorders

Common	Alopecia
	Rash

Musculoskeletal and connective tissue disorders

Common	Back pain
	Musculoskeletal chest pain
	Musculoskeletal pain
	Myalgia

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

HCV study population (REVOLADE in combination with interferon based therapies)

Blood and lymphatic system disorders

Very Common	Anaemia

Metabolism and nutrition disorders

Very Common	Decreased appetite

Psychiatric disorders

Very Common	Insomnia

Nervous systems disorders

Very Common	Headache

Respiratory, thoracic and mediastinal disorders

Very Common	Cough

Gastrointestinal disorders

Very Common	Nausea
	Diarrhoea

Hepatobiliary disorders

Common	Hyperbilirubinaemia

Skin and subcutaneous tissue disorders

Very Common	Pruritus
	Alopecia

Musculosketal and connective tissue disorders

Very Common	Myalgia

General disorders and administrative conditions

Very Common	Fatigue
	Pyrexia
	Chills
	Asthenia
	Oedema peripheral

Influenza like illness

Post marketing data

No post-marketing data are currently available.

DOSAGE AND ADMINISTRATION

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 *Clinical Trials*).

REVOLADE should be taken at least four hours before or 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 *Interactions, Pharmacokinetics – Absorption).*

REVOLADE may be taken with food containing little (< 50 mg) or preferably no calcium *(*see *Interactions, Pharmacokinetics).*

Adults

Chronic immune (idiopathic) thrombocytopenia

Use the lowest dose of REVOLADE to achieve and maintain a platelet count ³ 50,000/µl 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 is 50 mg once daily. For patients of East Asian ancestry (e.g. Chinese Japanese, Taiwanese, Korean or Thai), REVOLADE should be initiated at a reduced dose of 25 mg once daily (see *Pharmacology, Special Patient Populations*).

Monitoring and dose adjustment

After initiating REVOLADE, adjust the dose to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding (see Table 3). Do not exceed a dose of 75 mg daily.

Clinical haematology and liver function tests should be monitored regularly throughout therapy with REVOLADE and the dose of REVOLADE modified based on platelet counts as outlined in Table 3. 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/µl 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.

Table 5 Dose adjustments for REVOLADE in ITP patients

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

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 *Precautions)*.

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 associated thrombocytopenia

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

Use the lowest dose of 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.

Initial Dose Regimen

Initiate REVOLADE at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry (e.g. Chinese Japanese, Taiwanese, Korean or Thai), or with hepatic impairment.

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 6). Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy adjust the dose of REVOLADE as necessary to avoid dose reduction of peginterferon. Monitor platelet counts weekly during antiviral therapy until a stable platelet count is achieved. CBC'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 peginterferon alfa or ribavirin, refer to their respective prescribing information.

Table 6 Dose adjustments of REVOLADE in HCV patients during antiviral therapy

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

* - For patients taking 25 mg REVOLADE once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

Discontinuation

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

REVOLADE treatment should be terminated when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 6 or important liver test abnormalities may also necessitate discontinuation of REVOLADE (see *Precautions*).

Populations

Children

The safety and efficacy of REVOLADE in children 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 subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see *Pharmacology, Special Patient Populations*).

Hepatic Impairment

Exercise caution when administering REVOLADE to ITP patients with hepatic impairment (Child-Pugh score ≥ 5) (see *Precautions*).

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 should initiate REVOLADE at a dose of 25 mg once daily (see *Pharmacology, Special Patient Populations*).

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

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg REVOLADE once daily for two weeks in preparation for invasive procedures (see *Precautions*).

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 Pharmacology, Special Patient Populations)*.

East Asian Patients

For ITP or HCV patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai), REVOLADE should be initiated at a dose of 25 mg once daily (see *Pharmacology, Special Patient Populations*).

Initiate REVOLADE at a dose of 25 mg once daily in thrombocytopenic patients of East Asian ancestry with chronic HCV (see *Pharmacology, Special Patient Populations*).

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

For ITP or HCV patients of East Asian ancestry with hepatic impairment initiate REVOLADE at a dose of 25 mg once daily (see *Pharmacology, Special Patient Populations*).

OVERDOSAGE

Symptoms and Signs

In the clinical trials there was one report of overdose where the subject ingested 5000 mg of REVOLADE. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Liver enzymes measured between Days 2 and 18 after ingestion peaked at 1.6-fold ULN in AST, 3.9-fold ULN in ALT, and 2.4-fold ULN in total bilirubin. The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. 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.

PRESENTATION AND STORAGE CONDITIONS

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

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

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

Shelf-Life

48 months.

Storage

Store below 30°C.

Nature and Contents of Container

REVOLADE film-coated tablets are supplied in aluminium-aluminium foil blisters in packs of 14, 28 or 84 tablets*.

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

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4
436 Johnston St,
Abbotsford Victoria 3067

POISON SCHEDULE OF THE MEDICINE - S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 16 July 2010

DATE OF MOST RECENT AMENDMENT: 27 August 2013

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