PRODUCT MONOGRAPH

PrREVOLADE®

Eltrombopag Tablets

25 mg, 50 mg and 75 mg Eltrombopag (as Eltrombopag Olamine)

Thrombopoietin Receptor Agonist

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PrREVOLADE®

Eltrombopag Tablets
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets/25 mg, 50 mg and 75 mg eltrombopag (as eltrombopag olamine)	Magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, hypromellose, macrogol, titanium dioxide. REVOLADE® 25 mg tablets also contain polysorbate. REVOLADE® 50 mg tablets also contain iron oxide yellow and iron oxide red. REVOLADE® 75 mg tablets also contain iron oxide red and iron oxide black.

INDICATIONS AND CLINICAL USE

Immune Thrombocytopenia Purpura

REVOLADE® (eltrombopag) tablets are indicated for adult chronic immune thrombocytopenia purpura (ITP) to increase platelet counts in splenectomized patients who are refractory to first-line treatments (e.g. corticosteroids, immunoglobulins). REVOLADE® may be considered as second line treatment for adult non-splenectomized patients where surgery is contraindicated.

REVOLADE® therapy should not exceed 1 year of continuous treatment. After 1 year of continuous treatment, therapeutic options should be reassessed.

Hepatitis C Virus (HCV) related Thrombocytopenia

REVOLADE® is indicated to increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy.

Pediatrics (< 18 years of age):

The safety and effectiveness of REVOLADE® has not been established in patients < 18 years of age.

Geriatrics (≥ 65 years of age):

Clinical studies of REVOLADE® did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of REVOLADE® in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

CONTRAINDICATIONS

REVOLADE® (eltrombopag) is contraindicated in patients

- with severe hepatic impairment (Child-Pugh Class C) (see **WARNINGS AND PRECAUTIONS**, **Hepatic**, **Hepatic Impairment**, and **Hepatotoxicity**)
- who are hypersensitive to REVOLADE® or to any of its excipients. For a complete listing of excipients (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**)

In patients with chronic hepatitis C virus (HCV) infection, the Product Monographs for both pegylated interferon and ribavirin should be consulted for relevant contraindications associated with the use of these products.

WARNINGS AND PRECAUTIONS

Chronic hepatitis C patients with cirrhosis may be at risk of hepatic decompensation and death when receiving therapy with pegylated interferon and ribavirin. Patients with low albumin levels (<35 g/L) or 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 (see **WARNINGS AND PRECAUTIONS, Hepatic, Hepatic Decompensation - Use with Interferon**).

The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the

disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.

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

In patients with chronic hepatitis C virus (HCV) infection, the Product Monographs for both pegylated interferon and ribavirin should be consulted for relevant warnings and precautions associated with the use of these products.

The safety and efficacy of REVOLADE® has not been established in combination with direct acting antiviral agents used in the treatment of chronic hepatitis C virus (see **DRUG INTERACTIONS, Drug-Drug Interactions, HCV Protease Inhibitors**).

Hematologic

Thrombotic or thromboembolic complications: Platelet counts above the normal range may present an increased risk of thrombotic complications. The risk of thromboembolic events (TEE), such as portal vein thrombosis, 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. Therefore, REVOLADE® should not be used in ITP patients with hepatic impairment (Child-Pugh Class A and B) unless the expected benefit outweighs the identified risk of portal venous thrombosis, an adverse event which may lead to death (see **DOSAGE AND ADMINISTRATION**, and **ADVERSE REACTIONS, Thromboembolic Events**).

Due to limited data in patients with severe hepatic impairment (Child-Pugh Class C) a risk-benefit profile could not be established in this patient population. REVOLADE® is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

In clinical trials with REVOLADE® 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 including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome and systemic lupus erythematosus), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing REVOLADE® if the platelet count exceeds the target levels (see DOSAGE and ADMINISTRATION). The risk-benefit balance should be considered in patients at risk of thromboembolic events of any aetiology.

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n = 1439), 38 out of 955 subjects (4 %) treated with REVOLADE® and 6 out of 484 subjects (1%) in the placebo group experienced TEEs. Patients with low albumin

levels (≤ 35 g/L), MELD score ≥ 10, or age greater than 60 years demonstrated an increased risk of TEE (see **ADVERSE REACTIONS, Chronic Hepatitis C Virus Infection**). REVOLADE® should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with REVOLADE® versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were observed (see **DOSAGE AND ADMINISTRATION, Chronic Hepatits C-related Thrombocytopenia**).

During post-market experience, cases of thrombotic microangiopathy with acute renal failure have been reported in association with REVOLADE® administration in ITP patients. Renal function recovered partially with discontinuation of REVOLADE® and in one case renal function worsened on treatment. In some of these reported cases of thrombotic microangiopathy with acute renal failure the patients had concurrent risk factors for thromboembolism (e.g. antiphospholipid syndrome and systemic lupus erythematosus).

Re-occurrence of thrombocytopenia following discontinuation of REVOLADE®: Thrombocytopenia is likely to reoccur upon discontinuation of treatment with 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. This risk is increased if REVOLADE® is discontinued in the presence of anticoagulants or antiplatelet agents. It is recommended that, if treatment with REVOLADE® is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. 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.

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®, examine peripheral blood smears and complete blood counts (CBC) monthly 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.

Hematologic malignancies: Thrombopoietin receptor (TPO-R) agonists are growth

factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO receptor agonists there is a theoretical concern that they may stimulate the progression of existing haematopoietic malignancies such as myelodysplasia (MDS).

Hepatic

Hepatotoxicity

REVOLADE® administration can cause abnormal liver function. In the controlled clinical studies in chronic ITP with REVOLADE® (see CLINICAL TRIALS), increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed.

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. One patient in the placebo group and one patient in the REVOLADE® group experienced a Grade 4 liver test abnormality.

In 2 controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST ≥ 3 x the upper limit of normal (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 abnormalities resolve, stabilize, or return to baseline levels. Discontinue REVOLADE® if ALT levels increase ≥3X ULN in patients with normal liver function or ≥ 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.

Hepatic Impairment

Exercise caution when administering REVOLADE® to patients with any degree of hepatic disease, since exposure to eltrombopag increases with increasing degrees of

hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**). In ITP patients, use a lower starting dose of REVOLADE® when administering REVOLADE® to patients with hepatic impairment (Child-Pugh Class A and B). No dosage adjustment is necessary for HCV patients (see **DOSAGE AND ADMINISTRATION, Hepatic Impairment**).

REVOLADE® should not be used in ITP patients with hepatic impairment (Child-Pugh Class A and B) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see **DOSAGE AND ADMINISTRATION, Hepatic Impairment**, and **ADVERSE REACTIONS, Thromboembolic Events)**.

REVOLADE® is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**). Due to limited data in patients with severe hepatic impairment (Child-Pugh Class C), a risk-benefit profile could not be established in this patient population.

Hepatic Decompensation – Use with Interferon
Chronic hepatitis C virus infected patients with cirrhosis may be at risk of hepatic decompensation and death when receiving therapy with pegylated interferon and ribavirin. REVOLADE® should only be administered to such patients after careful consideration of the expected benefits compared to the associated risks. In patients with low albumin levels (<35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline, there was a 3-fold greater risk of hepatic decompensation, and an increase in the risk of a fatal adverse event compared to those without advanced liver disease. REVOLADE® should only be administered to such patients after careful consideration of the expected benefits compared to the associated risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation.

In 2 controlled clinical trials in patients with chronic hepatitis C virus infection and thrombocytopenia, adverse events related to hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, and spontaneous bacterial peritonitis) were reported more frequently in the REVOLADE® arm (11%) than in the placebo arm (6%).

Ophthalmologic

Cataracts:

In 2 controlled clinical studies in thrombocytopenic patients with HCV (n=1439), receiving interferon therapy, progression of pre-existing baseline cataract(s) or incident cataract was reported in 8 % of patients treated with REVOLADE® and 5 % of patients treated with placebo. Perform a baseline ocular examination prior to administration of REVOLADE®, and during therapy with REVOLADE®, regularly monitor patients for signs and symptoms of cataracts.

Cataracts were observed in toxicology studies of eltrombopag in rodents (see **TOXICOLOGY, Repeat Dose Toxicity**).

Renal

Renal Impairment

Patients with renal impairment may have decreased exposure to eltrombopag (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment**).

REVOLADE® should be used with caution in patients with impaired renal function, and close monitoring performed, for example, by testing serum creatinine and/or urine analysis (see **DOSAGE AND ADMINISTRATION, Renal Impairment**).

There are limited data with the use of REVOLADE® in patients with severe renal impairment (creatinine clearance < 30ml/min), therefore it is generally not recommended for use in these patients.

Reproduction

Eltrombopag did not affect female or male fertility in rats at doses 2 and 3 times respectively, the human clinical exposure based on AUC (see **TOXICOLOGY, Reproductive and Developmental Toxicity**).

Special Populations

Pregnant Women: REVOLADE® has not been studied in pregnant women. REVOLADE® should only be used during pregnancy if the expected benefit justifies the potential risk to the fetus.

Eltrombopag was studied in pregnant rats and rabbits, and caused a low incidence of cervical ribs (a fetal variation) along with reduced fetal body weight at doses that were maternally toxic (see **TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

In patients with chronic hepatitis C virus infection, REVOLADE® must be used in combination with pegylated interferon and ribavirin. Teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin, while interferons have been shown to have abortifacient effects in animals. Refer to the prescribing information for pegylated interferon and ribavirin for full details.

Nursing Women: It is not known whether eltrombopag is excreted in human milk. REVOLADE® is not recommended for nursing mothers unless the expected benefit justifies the potential risk to the infant.

Pediatrics (<18 years of age): The safety and efficacy of REVOLADE® in pediatric patients have not been established.

Geriatrics (>65 years of age): Clinical studies of REVOLADE® did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the

administration and monitoring of REVOLADE® in elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

East Asian Patients: A reduced dose of REVOLADE® may be required in East Asian patients (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

Complete Blood Counts (CBC): Monitor CBC, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of therapy with REVOLADE®. Prior to the initiation of REVOLADE®, examine the peripheral blood differential to establish the extent of red and white blood cell abnormalities. Obtain CBC, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with REVOLADE® and then monthly following establishment of a stable dose of REVOLADE®. Obtain CBC, including platelet counts, weekly for 4 weeks following discontinuation of REVOLADE® (see **DOSAGE AND ADMINISTRATION**, and **WARNINGS AND PRECAUTIONS**).

Liver Tests: Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of REVOLADE®, then every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormalities resolve, stabilize, or return to baseline levels. Discontinue REVOLADE® if important liver test abnormalities occur (see **DOSAGE AND ADMINISTRATION**, and **WARNINGS AND PRECAUTIONS**, and **CONTRAINDICATIONS**).

Refer to the pegylated interferon and ribavirin Product Monographs for directions regarding dose reduction or discontinuation, as well as pregnancy testing requirements.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the ITP clinical studies, hemorrhage was the most common serious adverse reaction and most hemorrhage reactions followed discontinuation of REVOLADE® (eltrombopag). Other serious adverse reactions included liver test abnormalities and thromboembolic complications.

Based on an analysis of all chronic ITP patients receiving REVOLADE® in 3 controlled and 2 uncontrolled clinical studies, the median duration of exposure to REVOLADE® was 379 days and patient year's exposure was 584 in this study population.

In the HCV clinical studies, the safety of REVOLADE® in combination with interferon and ribivarin is supported by a clinical database of 1576 eltrombopag-treated adult subjects enrolled in two pivotal, placebo-controlled, phase III studies and one supportive

phase II study. The total patient years of exposure to eltrombopag in this study population was 674.06.

The most commonly reported adverse events were fatigue, headache, myalgia, fever, and rigors.

The Product Monographs for both pegylated interferon and ribavirin should be consulted for relevant safety information.

ADULT CHRONIC IMMUNE THROMBOCYTOPENIA PURPURA (ITP)

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In the ITP studies the safety of REVOLADE® has been demonstrated in two randomised, double-blind, placebo controlled studies in 211 adults with previously treated chronic ITP. Most adverse reactions associated with REVOLADE® were mild to moderate in severity, early in onset and rarely treatment limiting. The most common adverse events were nausea, vomiting, diarrhea and headache.

The drug-related adverse events occurring in ≥1% of patients, and which were more common in the treatment group as compared to placebo in the Phase III, double-blind, placebo-controlled 6 week study, TRA100773B, and 6 month study, RAISE (TRA102537), are presented in Table 1 and Table 2, respectively.

Table 1 Drug-Related Adverse Events ≥ 1% in ITP Patients over 6 weeks (Study TRA100773B)

Body System/Adverse Event	Treatment Group, n (%)	
	REVOLADE® N=76	Placebo N=38
Cardiac disorders		
Sinus tachycardia	1(1)	0
Gastrointestinal		
Nausea	4(5)	0
Vomiting	2(3)	0
Abdominal distension	1(1)	0
Constipation	1(1)	0
Diarrhea	1(1)	0
Hemorrhoids	1(1)	0
Hepatobiliary disorders		
Hepatic function abnormal	1(1)	0
General disorders and administration site conditions		
Fatigue	2(3)	0
Malaise	1(1)	0
Investigations		
Protein total increased	3(4)	1(3)
ALT increased	2(3)	0
AST increased	2(3)	0
Metabolism and nutrition disorders		
Hypokalemia	1(1)	0
Muscoskeletal and connective tissue disorder		
Myalgia	3(4)	0
Arthralgia	1(1)	0
Bone pain	1(1)	0
Nervous system disorders		
Headache	4(5)	1(3)
Psychiatric disorders		
Sleep disorder	1(1)	0
Skin and subcutaneous tissue disorders		
Alopecia	1(1)	0
Night sweats	1(1)	0

Table 2 Drug-Related Adverse Events ≥ 1% in ITP Patients over 6 months (RAISE)

Body System/Adverse Event	Treatment Group, n (%)	
	REVOLADE® N=135	Placebo N=61
Eye disorders		
Dry eye	2(1)	0
Gastrointestinal		
Nausea	6(4)	0
Constipation	3(2)	1(2)
Diarrhea	4(3)	0
Dry mouth	3(2)	0
Vomiting	2(1)	0
General Disorders and Administration Site Conditions		
Feeling hot	2(1)	0
Hepatobiliary disorders		
Hepatic function abnormal	2(1)	0
Investigations		
ALT increased	6(4)	2(3)
Hemoglobin increased	2(1)	0
Transaminases increased	2(1)	0
Muscoskeletal and connective tissue disorder		
Arthralgia	2(1)	0
Nervous system disorder		
Headache	15(11)	5(8)
Paraesthesia	3(2)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	3(2)	0
Rash	2(1)	0

Clinical Trial Adverse Drug Reactions occurring in <1% of Patients

The drug-related adverse events occurring in <1% of REVOLADE® treated patients (with a higher incidence compared to placebo) in the Phase III, double-blind, placebo-controlled studies are presented below. The events are categorized by body system.

Cardiac Disorders: tachycardia

Ear and labyrinth disorders: vertigo

Eye Disorders: eye pain, lacrimation increased, lenticular opacities, retinal depigmentation hemorrhage, visual acuity reduced

Gastrointestinal: abdominal pain, abdominal pain upper, dyspepsia, feces discoloured, glossodynia, oral discomfort

General disorders and administration site conditions: asthenia, inflammation of wound, sensation of foreign body

Hepatobiliary disorders: hepatic lesions, hyperbilirubinemia

Infections and infestations: oral herpes, pharyngitis, sinusitis

Investigations: blood albumin increased, blood alkaline phosphatase increased, blood creatinine increased, hepatic enzyme increased

Metabolism and nutrition disorder: decreased appetite,

Neoplasms, benign, malignant and unspecified (incl. cysts and polyps): Rectogsigmoid cancer

Nervous system disorder: dysaesthesia, dysgeusia, hypoasthesia, somnolence

Skin and subcutaneous tissue disorders: cold sweat, pruritus, pruritus generalized, skin exfoliation, swelling face, urticaria

Respiratory, thoracic and mediastinal disorder: oropharyngeal blistering, pulmonary embolism, pulmonary infarction, sinus disorder

Vascular disorders: deep vein thrombosis, hot flush, thrombophlebitis superficial

Thromboembolic events (TEE)

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 **WARNINGS AND PRECAUTIONS**).

In a placebo-controlled study known as the ELEVATE trial, conducted in thrombocytopenic patients with chronic liver disease (n=288) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg eltrombopag once daily for 14 days. Six of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced thromboembolic events (all of them portal venous thrombosis), while one of 145 (1%) in the placebo group experienced portal vein thrombosis. Five of the eltrombopag-treated patients who experienced portal vein thrombosis did so within 14 days of completing eltrombopag dosing, and having a platelet count above 200,000/mL.

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

Increased Bone Marrow Reticulin

Across the programme, no subjects had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see **WARNINGS AND PRECAUTIONS, Hematologic**).

CHRONIC HEPATITIS C VIRUS INFECTION

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

ENABLE 1 (N=716) and ENABLE 2 (N=805) were randomized, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of REVOLADE® in thrombocytopenic subjects with HCV infection who were otherwise eligible to initiate antiviral therapy (see CLINICAL TRIALS).

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® N=449, placebo N=232) and ENABLE 2 (REVOLADE® N=506, placebo N=252).

Table 3 presents the most common adverse reactions, as determined by higher incidence in the eltrombopag arm and reported during the double-blind phase of ENABLE 1 and ENABLE 2 (experienced by ≥ 3 % of patients receiving REVOLADE®, compared to placebo).

Table 3 Adverse Drug Reactions (Grades 2-4) ≥ 3% in Two Placebo-Controlled Studies in Adults With Chronic Hepatitis C Virus (ENABLE 1 and ENABLE 2)

Body System/Adverse Event	Eltrombopag (N=955)	Placebo (N=484)
ANY EVENT	769 (81%)	392 (81%)
Blood and lymphatic system disorders		
Anaemia	236 (25%)	112 (23%)
Lymphopenia	26 (3%)	10 (2%)
General disorders and administration site conditions		
Fatigue	104 (11%)	45 (9%)
Pyrexia	71 (7%)	33 (7%)
Asthenia	54 (6%)	16 (3%)
Influenza like illness	52 (5%)	23 (5%)
Oedema peripheral	38 (4%)	5 (1%)
Irritability	25 (3%)	6 (1%)
Chills	24 (3%)	10 (2%)
Gastrointestinal disorders		
Diarrhea	60 (6%)	15 (3%)
Ascites	51 (5%)	14 (3%)
Abdominal pain	30 (3%)	11 (2%)
Vomiting	22 (2%)	8 (2%)
Abdominal pain upper	18 (2%)	6 (1%)
Investigations		
Blood bilirubin increased	58 (6%)	11 (2%)
White blood cell count decreased	44 (5%)	21 (4%)
Weight decreased	43 (5%)	14 (3%)
Haemoglobin decreased	41 (4%)	16 (3%)
Infections and infestations		
Urinary tract infection	34 (4%)	12 (2%)
Bronchitis	19 (2%)	6 (1%)
Pneumonia	15 (2%)	8 (2%)
Psychiatric disorders		
Insomnia	51 (5%)	22 (5%)
Depression	38 (4%)	18 (4%)

Nervous system disorders		
Headache	54 (6%)	24 (5%)
Hepatic encephalopathy	21 (2%0	1 (<1%)
Skin and subcutaneous tissues disorders		
Pruritus	26 (3%)	7 (1%)
Rash	26 (3%)	9 (2%)
Hepatobiliary disorders		
Hyperbilirubinaemia	68 (7%)	14 (3%)
Musculoskeletal and connective tissue disorders		
Arthralgia	27 (3%)	14 (3%)
Myalgia	26 (3%)	5 (1%)
Back pain	21 (2%)	4 (<1%)
Respiratory, thoracic and mediastinal disorders		
Cough	30 (3%)	7 (1%)
Dyspnea	21 (2%)	7 (1%)
Metabolism and nutrition disorders		
Decreased appetite	30 (3%)	15 (3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Hepatic neoplasm, malignant	34 (4%)	13 (3%)

The most common adverse events occurring during open-label treatment with REVOLADE® in Part 1 of ENABLE 1 and 2 (see CLINICAL TRIALS) were headache, fatigue, nausea, diarrhea, and insomnia.

Thromboembolic events (TEE)

In controlled studies in thrombocytopenic patients with HCV where REVOLADE® was used as necessary to achieve the target platelet count required to initiate and maintain antiviral therapy (n = 1439), 38 out of 955 subjects (4 %) treated with REVOLADE® experienced a TEE (3 %) and 6 out of 484 subjects (1 %) in the placebo group experienced a TEE. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with REVOLADE®, versus < 1 % for placebo). Patients with low albumin levels (≤ 35 g/L), MELD score ≥ 10, or age greater than 60 years demonstrated an increased risk of TEE. 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. A higher incidence of TEEs was

seen in patients being treated with pegylated interferon alfa-2b (26 patients)(5%) compared to pegylated interferon-2a (12 patients) (2.7%).

Post-Market Adverse Drug Reactions

The following adverse 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.

Vascular disorders: There have been reports of thrombotic microangiopathy with acute renal failure. In some of these cases, the patients had concurrent risk factors for thromboembolism (e.g. antiphospholipid syndrome and systemic lupus erythematosus).

DRUG INTERACTIONS

Overview

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 . No clinically significant interactions are expected when REVOLADE® (eltrombopag) and CYP450 substrates, inducers or inhibitors are co-administered (see **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**).

Drug-Drug Interactions

HMG CoA reductase inhibitors/OATP1B1 and BCRP substrates: *In vitro* studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. When REVOLADE® and rosuvastatin were co-administered in a clinical drug interaction study (see **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**) there was increased plasma rosuvastatin exposure. Interactions are also expected with other HMG CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin, however, clinically significant interactions are not expected between eltrombopag and atorvastatin or fluvastatin. When co-administered with REVOLADE®, a reduced dose of statins should be considered and careful monitoring should be undertaken. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for co-administration of rosuvastatin and eltrombopag. Concomitant administration of REVOLADE® and other OATP1B1 and BCRP substrates should be undertaken with caution.

Lopinavir/ritonavir: Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag (see DETAILED PHARMACOLOGY, Pharmacokinetic Interactions). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the

dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

Polyvalent cations (chelation): Eltrombopag chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc (see **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**). 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**, and **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**).

Peginterferon alfa-2a/b and ribavirin therapy: Co-administration of peginterferon alfa 2a (PEGASYS®) or 2b (PEGETRON®) and ribavirin did not affect eltrombopag exposure in 2 randomized, double-blind, placebo-controlled trials with adult patients with chronic hepatitis C.

HCV protease inhibitors: A study in 56 healthy volunteers was conducted with eltrombopag and the HCV protease inhibitors boceprevir and telaprevir. Co-administration of eltrombopag with either telaprevir or boceprevir did not alter plasma concentrations of eltrombopag. Eltrombopag did not affect plasma concentrations of telaprevir. Elrombopag did not affect the AUC or Cmax of boceprevir, but reduced the Cτ by 32% (see **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**).

Drug-Food Interactions

Administration of a single 50 mg-dose of REVOLADE® with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag concentrations. Food low in calcium (<50 mg calcium) did not significantly impact plasma eltrombopag exposure, regardless of calorie or fat content (see **DOSAGE AND ADMINISTRATION**, **and DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**).

DOSAGE AND ADMINISTRATION

Chronic Immune Thrombocytopenia Purpura (ITP)

Dosing Considerations

REVOLADE® (eltrombopag) treatment should be initiated and maintained by a physician who is experienced in the treatment of haematological diseases, who understands the benefits and risks associated with the treatment of ITP, and who is experienced in counselling patients for whom REVOLADE® is indicated.

Prior to prescribing REVOLADE®, physicians should:

- Ensure the eligibility of patients to meet the above criteria, and
- Counsel each patient on the risks and benefits of REVOLADE®.

REVOLADE® dosing regimens must be individualised based on the patient's platelet counts. The objective of treatment with REVOLADE® should not be to normalise platelet counts but to maintain platelet counts above the level for hemorrhagic risk (>50 x 10^9/L), and generally below 150 – 200 x 10^9/L. Use the lowest effective dosing regimen to maintain platelet counts, as clinically indicated.

In most patients, measurable elevations in platelet counts take 1-2 weeks to occur (see **CLINICAL TRIALS**).

Recommended Dose and Dosage Adjustment

Adults (≥18 years of age):

The recommended starting dose of REVOLADE® is 50 mg once daily. If after 2 to 3 weeks of initial therapy, the platelet counts are below the clinically indicated levels (e.g. 50 x 10^9/L), the dose may be increased to a maximum of 75 mg once daily (see Table 4).

A dose reduction should be considered with platelet counts increasing to over 150 x 10^9/L. At platelet counts at or over 200 x 10^9/L dose reduction is recommended (see Table 4).

REVOLADE® should be interrupted if platelet counts increase to >300 x 10^9/L. Once the platelet count is <150 x 10^9/L; reinitiate therapy at a reduced dose. If platelet counts remain at >300 x 10^9/L after 2 weeks of therapy of the lowest dose of REVOLADE®, discontinue treatment (see Table 4).

Table 4 Dose Adjustments of REVOLADE® in ITP patients

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of REVOLADE®	Increase daily dose by 25 mg to a maximum of 75 mg/day
≥50 x 10^9/L to ≤200 x 10^9/L	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
≥200 x 10^9/L to ≤300 x 10^9/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments
>300 x 10^9/L	Stop REVOLADE®. Increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg.
>300 x 10^9/L after 2 weeks of therapy at lowest dose of REVOLADE®	Discontinue REVOLADE®

The standard dose adjustment, whether decreased or increased, would be 25 mg once daily. However, in a few patients an alternate dosing of different tablet strengths on different days may be required.

After any REVOLADE® dose adjustment, platelet counts should be monitored at least once weekly for 2 to 3 weeks. Wait for at least two (2) weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment. In patients with liver disease, wait at least three (3) weeks before considering dose adjustment, see *Hepatic Impairment*, below.

Monitor clinical hematology and liver tests regularly throughout therapy with REVOLADE® and modify the dose of REVOLADE® based on platelet counts as outlined in Table 4. During therapy with REVOLADE®, assess complete blood counts (CBC), including platelet count and peripheral blood smears, weekly until a stable platelet count (≥50 x 10^9/L for at least 4 weeks) has been achieved. Obtain CBC including platelet count and peripheral blood smears, monthly thereafter.

REVOLADE® can be administered in addition to other ITP medicinal products. Modify the dose regimen of concomitant ITP medicinal products, as medically appropriate, to avoid excessive increases in platelet counts during therapy with REVOLADE®.

Discontinuation

Discontinue REVOLADE® if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with REVOLADE® at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 4, or important liver test abnormalities also necessitate discontinuation of REVOLADE® (see **WARNINGS AND PRECAUTIONS**).

The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment.

Chronic Hepatitis C-related Thrombocytopenia

Dosing Considerations

REVOLADE® is given in combination with pegylated interferon and ribavirin. Reference should be made to the full Product Monographs for each respective coadministered medicinal product for comprehensive details of administration. The directions regarding the dosage, dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications for pegylated interferon and ribavirin should be followed.

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

Use the lowest dose of REVOLADE® to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy. Dose adjustments are based upon the patient's platelet count response, see Table 5, below. Do not use REVOLADE® to normalize platelet counts. In clinical studies, platelet counts generally increased within 1 week of starting REVOLADE®.

The safety and efficacy of REVOLADE® have not been established in combination with direct acting antiviral agents used in the treatment of chronic hepatitis C virus infection.

Recommended Dose and Dosage Adjustment

Adults (≥18 years of age):

Initiate REVOLADE® at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian / Southeast Asian ancestry or patients with mild hepatic impairment.

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 5). 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 Product Monographs.

Table 5 Dose adjustments of REVOLADE® in HCV patients during antiviral therapy

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9$/L following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 50 \times 10^9$/L to $\leq 150 \times 10^9$/L	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon.
$\geq 150 \times 10^9$/L to $\leq 200 \times 10^9$/L	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$>200 \times 10^9$/L	Stop REVOLADE®; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $< 150 \times 10^9$/L, reinitiate therapy at a lower daily dose*.
$>200 \times 10^9$/L after 2 weeks of therapy at lowest dose of REVOLADE®	Discontinue REVOLADE®

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

Discontinuation

When REVOLADE® is given in combination with antiviral therapies reference should be made to the full Product Monograph of the respective coadministered medicinal products for comprehensive details of administration. The directions regarding the dose, dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications for the respective antiviral medicinal products should be followed.

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 5 or important liver test abnormalities may also necessitate discontinuation of REVOLADE® (see **WARNINGS AND PRECAUTIONS**).

Chronic Immune Thrombocytopenia Purpura (ITP) and Chronic Hepatitis C-related Thrombocytopenia

Food Interactions: REVOLADE® should be taken at least **four hours** before or after antacids, dairy products, or mineral supplements, or any other products containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc).

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

Elderly: There are limited data on the use of REVOLADE® in patients aged 65 years and older and no clinical experience in patients aged over 85 years. In the clinical studies of REVOLADE®, overall no clinically significant differences in the 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 **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

East Asian/Southeast Asian Patients: Initiation of REVOLADE® at a reduced dose of 25 mg once daily may be considered for ITP patients of East Asian / Southeast Asian ancestry (such as Chinese, Japanese, Taiwanese, Thai or Korean) (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Race**).

Initiate REVOLADE® at a dose of 25 mg once daily in thrombocytopenic patients of East Asian / Southeast Asian ancestry with chronic HCV (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

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

No dosage adjustment is necessary for HCV patients of East Asian / Southeast Asian ancestry.

Pediatrics (<18 years of age): The safety and efficacy of eltrombopag in children have not been established.

Renal Impairment: No dose adjustment is generally necessary in patients with renal impairment. REVOLADE® should be used in patients having impaired renal function with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment**).

REVOLADE® is generally not recommended in patients with severe renal impairment (creatinine clearance < 30ml/min) (see **WARNINGS AND PRECAUTIONS, Renal, Renal Impairment,** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment**).

Hepatic Impairment:

Exercise caution when administering REVOLADE® to patients with any degree of hepatic disease, since exposure to eltrombopag increases with increasing degrees of hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

The risk of thromboembolic events of the portal venous system 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 **ADVERSE REACTIONS, Thromboembolic Events**).

REVOLADE® should not be used in ITP patients with hepatic impairment (Child-Pugh Class A and B) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see **WARNINGS AND PRECAUTIONS, Hepatic, Hepatic Impairment**, and **ADVERSE REACTIONS, Thromboembolic Events**).

If the use of REVOLADE® is deemed necessary in ITP patients with liver impairment (Child-Pugh Class A and B), the starting dose must be 25 mg once daily. Attempts to maintain platelet counts below 200 x 10^9/L should be carried out in this patient population.

REVOLADE® is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (See **CONTRAINDICATIONS**).

After initiating REVOLADE® or following any dose increase in patients with liver impairment (Child-Pugh Class A and B) wait a minimum of 3 weeks before increasing the dose.

Thrombocytopenic patients with chronic HCV should initiate REVOLADE® at the usual dose of 25 mg once daily (see **DETAILED PHARMACOLOGY, Pharmacokinetic Interactions**).

Missed Dose

If a dose of REVOLADE® is missed, the patient should be advised to take it as soon as they remember, and then continue with the next dose at the regular interval. Two doses

should not be taken at the same time to make up for a missed dose.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre

Signs and Symptoms

In the clinical trials there was one report of overdose where the subject ingested 5,000 mg of REVOLADE® (eltrombopag). Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Liver enzymes measured between Days 2 and 18 after ingestation peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin. The patient's platelet count increased to a maximum of 929 x 10^9/L at 13 days following the ingestion. After 2 months follow-up, all events resolved without sequelae.

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 preparation at the earliest possible opportunity, 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 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.

ACTION AND CLINICAL 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). REVOLADE® (eltrombopag) interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades similar but not identical to that of endogenous thrombopoietin, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

Pharmacodynamics

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, nor does it antagonise platelet aggregation induced by ADP or collagen.

Pharmacokinetics

The pharmacokinetic parameters of eltrombopag after administration of an oral dose to patients with ITP are shown in Table 6.

Table 6 Geometric Mean (95% CI) Steady–State Plasma Eltrombopag, Pharmacokinetic Parameters in Adults with Idiopathic Thrombocytopenic Purpura

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

Plasma eltrombopag 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 patients in a population PK analysis.

Plasma eltrombopag C_{max} $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase III studies are presented for each dose studied in Table 7.

Table 7 Geometric Mean (95 % CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Patients with Chronic HCV

Eltrombopag Dose (once daily)	N	C_{max} (μg/ml)	$AUC_{(0-\tau)}$ (μg.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-τ) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

Absorption: Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of REVOLADE® concomitantly with antacids, dairy products, mineral supplements or other products containing polyvalent cations significantly reduces eltrombopag exposure (see **DRUG 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%). Eltrombopag 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 $AUC_{0-\infty}$. Minor metabolites, each accounting for <10% of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabeled 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 olamine) is not detected in urine. Unchanged eltrombopag olamine excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Special Populations and Conditions

Renal Impairment: The pharmacokinetics of eltrombopag have been studied after administration of REVOLADE® to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and 60% lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

Geriatrics: The geriatric 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 estimate, elderly (> 60 years) patients had approximately 36% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: The pharmacokinetics of eltrombopag has been studied after administration of REVOLADE® to adult subjects with liver cirrhosis (hepatic impairment). Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment, compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

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 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

The population PK/PD analysis of data collected in patients with chronic liver disease determined that the rate of platelet production was linearly related to plasma eltrombopag concentrations. In patients with chronic liver disease, the time to peak platelet count was approximately 3 weeks from the start of dosing.

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 $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see **DOSAGE AND ADMINISTRATON**).

The influence of East Asian and Southeast Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian and Southeast Asian patients had similar pharmacokinetics of eltrombopag. On average, East/Southeast Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian, without adjustment for body weight differences (see **DOSAGE AND ADMINISTRATON**).

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 $AUC_{(0-\tau)}$ 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 estimate, female HCV patients had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

STORAGE AND STABILITY

Store below 30°C, protect from freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REVOLADE® (eltrombopag) is available as round, biconvex, film-coated tablets available in blister packs of 14 or 28 as 25 mg-white, 50 mg-brown and 75mg-pink tablets. The 25 mg tablets are debossed with 'GS NX3' and '25', the 50 mg tablets are debossed with 'GS UFU' and '50' and the 75 mg tablets are debossed with 'GS FFS' and '75'.

Each tablet contains either 25 mg, 50 mg or 75* mg of eltrombopag as eltrombopag olamine. The tablet also contains the following nonmedicinal ingredients: magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, hypromellose, macrogol, titanium dioxide. REVOLADE® 25 mg tablets also contain polysorbate. REVOLADE® 50 mg tablets also contain iron oxide yellow and iron oxide red. REVOLADE® 75 mg tablets also contain iron oxide red and iron oxide black.

* Not available in Canada.

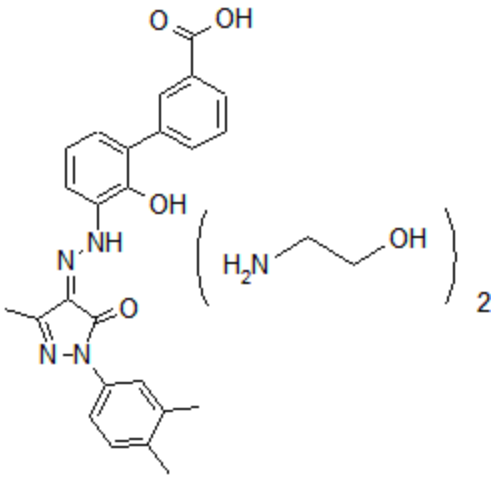
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Eltrombopag olamine
Chemical name:	3'-{(2Z)-2-[1-(3,4-dimethyl-phenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid-2-aminoethanol (1-2)
Molecular formula:	C_{25} H_{22} N_4 O_4. 2 (C_2 H_7 N O),
Molecular mass	564.65 (eltrombopag olamine) 442.48 (eltrombopag)

Structural formula:



Physicochemical properties: Eltrombopag olamine is a red to brown solid, practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

CLINICAL TRIALS

Chronic Immune Thrombocytopenia Purpura (ITP)

Study demographics and trial design

One Phase II, randomised, double blind, placebo-controlled study, TRA100773A, two Phase III, randomised, double blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of REVOLADE® (eltrombopag) in adult patients with previously treated chronic ITP (see Table 8). Overall, eltrombopag was administered to a total of 446 patients, 280 patients for at least 6 months and 228 patients for at least 1 year.

Table 8 Summary of Trial Design and Patient Demographics for Clinical Trials in ITP

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender (%)
RAISE (TRA102537)	Phase III, double-blind, randomized, placebo-controlled.	Eltrombopag 50 mg or matching Placebo; Daily oral dosing for 6 months; Dose modification (to 25 mg or 75 mg) allowed based on individual platelet counts.	N= 197 Placebo: 62 Eltrombopag: 135	Placebo: 52.5 years (18 -77) Eltrombopag: 47 years (18-85)	Female: 69 Male: 31 Female: 69 Male: 31
TRA100773A	Phase II, double-blind, randomized, placebo-controlled.	Eltrombopag 30, 50, or 75 mg or matching Placebo; Daily oral dosing for 6 weeks.	Total N = 118 Placebo: 29 Eltrombopag: 30mg: 30 50mg: 30 75mg: 29	Placebo: 43 years (18-85) Eltrombopag: 30mg: 53 years (23-79) 50mg: 47 years (23-81) 75mg: 54 years (18-85)	Female: 55 Male: 45 Female: 53 Male: 47 Female: 70 Male: 30 Female: 71 Male:29

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender (%)
TRA100773B	Phase III, double-blind, randomized, placebo-controlled.	Eltrombopag 50 mg or matching Placebo; Daily oral dosing for 6 weeks; Dose escalation to 75 mg allowed for non-responders.	N = 114 Placebo: 38 Eltrombopag: 76	Placebo: 51 years (21-79) Eltrombopag: 47 years (19-84)	Female: 71 Male: 29 Female: 57 Male: 43
REPEAT (TRA108057)	Single arm, open-label, intermittent dose.	Eltrombopag 50 mg; Daily oral dosing for up to 6 weeks, off-therapy for up to 4 weeks for 3 cycles; Dose escalation to 75 mg after Day 21 allowed.	N = 66 (Completed = 48)	Eltrombopag: 50 years (20-79)	Female: 68 Male: 32
EXTEND (TRA105325)	Single arm, open-label, extension study, previously enrolled in an eltrombopag study.	Eltrombopag 50 mg Daily oral dosing Dose modification (to 25 mg or 75 mg once daily) allowed based on individual platelet counts.	N = 299 (Received treatment = 298 Ongoing = 154 Withdrawn = 122)	Eltrombopag: 50 years (18-86)	Female: 198 Male: 101

Study Results

RAISE *(TRA102537)*: In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count ≥50 x 10^9/L and ≤400 x 10^9/L, during the 6 month treatment period, for subjects receiving eltrombopag relative to placebo. One hundred and ninety seven subjects were randomized 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 eltrombopag 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.

A summary of baseline disease characteristics and key efficacy results is provided in Table 9. One week after treatment with study medication, platelet counts rose to between 50-400 x 10^9/L in 37% of eltrombopag-treated subjects compared to 7% of placebo-treated subjects. The proportion of responders in the eltrombopag group was between 37% and 56% for all nominal on-therapy visits, with a minimum of 37% at Day 8 and a maximum of 56% at Day 36. In comparison, the proportion of responders in the placebo group was between 7% and 19% for all nominal on-therapy visits, with a minimum of 7%

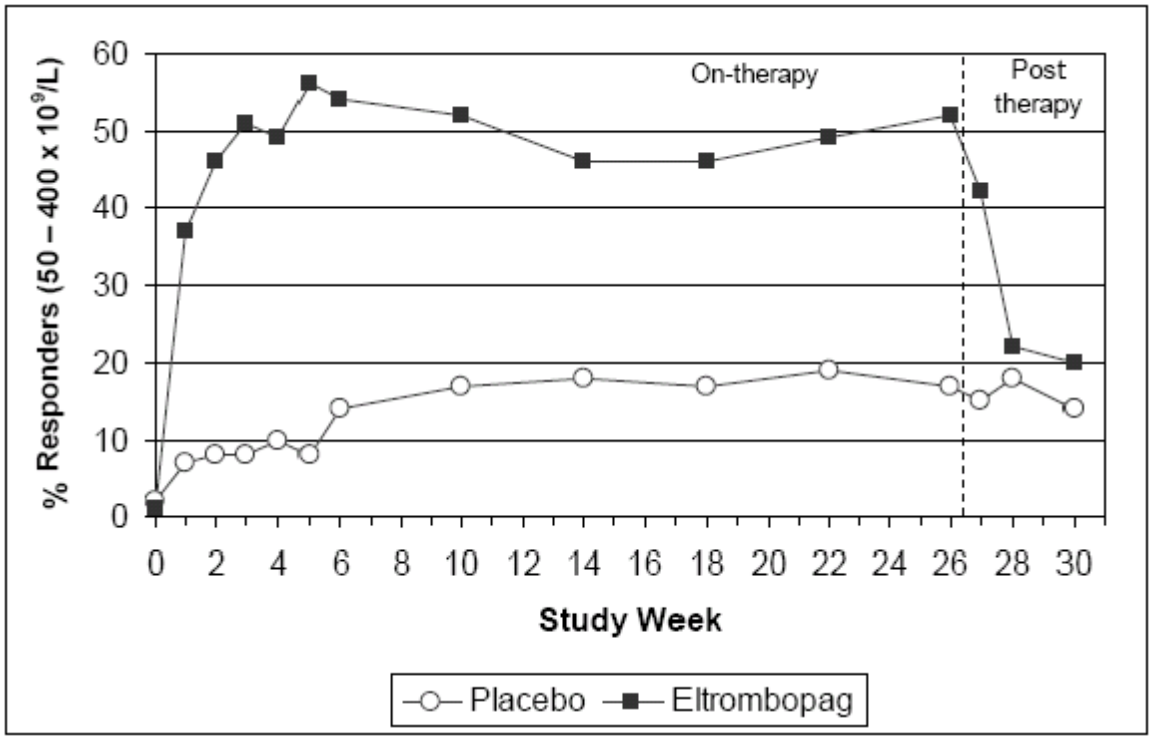
at Day 8 and a maximum of 19% at Week 22 (see Figure 1). One week after discontinuation of treatment, more than 40% of subjects treated with eltrombopag maintained platelet counts between 50-400 x 10^9/L, compared to placebo (15%). Two weeks after the end of treatment, the proportion of responders in the eltrombopag was similar to the placebo group.

The odds of achieving a platelet count between 50 x 10^9/L and 400 x 10^9/L during the 6 month treatment period were 8 times higher for eltrombopag treated subjects than for placebo-treated subjects.

Median platelet counts were maintained above 50 x 10^9/L at all on-therapy visits starting at Day 15 in the eltrombopag group; in contrast, median platelet counts in the placebo group remained below 30 x 10^9/L throughout the study.

At baseline, 77% of subjects in the placebo group and 73% of subjects in the elbrombopag 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 eltrombopag 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 eltrombopag-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 eltrombopag-treated subjects compared to the placebo-treated subjects. Significantly fewer eltrombopag-treated subjects required rescue treatment compared to placebo-treated subjects.

Figure 1 **Summary of Responders (Platelet Counts ≥50 x 10^9/L and ≤400 x 10^9/L). Day 8 to 4-weeks post treatment discontinuation, Primary Dataset (ITT Population)**



Eltrombopag therapy allowed significantly more subjects to reduce or discontinue baseline ITP therapies compared to placebo.

Four placebo and 14 eltrombopag subjects had at least 1 haemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. However, fewer eltrombopag-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 eltrombopag group with 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 eltrombopag 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 eltrombopag than placebo.

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

Table 9 Summary of Efficacy Results for the RAISE Study

	Eltrombopag N=135	Placebo (PBO) N=62
Baseline Disease Characteristics		
Subjects with baseline platelet count ≤15 x 10^9/L[a], n (%)	67 (50)	30 (48)
Subjects with baseline platelet count >15 x 10^9/L, n (%)	68 (50)	31 (50)
Proportion of subjects that used ITP medication at randomization, n (%)	63 (47)	31 (50)
Splenectomised subjects, n (%)	50 (37)	21 (34)
Non-Splenectomised subjects, n (%)	85 (63)	41 (66)
Primary Endpoint		
Odds ratio (OR) for responding to treatment, Eltrombopag/Placebo[b, c]	8.2	
99% CI	3.59, 18.73	
p-value (two-sided vs. PBO)	<0.001	
Key Secondary Endpoints		
Analysis of Any Bleeding (WHO Grades 1-4)		
OR bleeding throughout 6 months, Eltrombopag/Placebo[c]	0.24	
95% CI	0.16, 0.38	
p-value (two-sided vs. PBO)	<0.001	
Subjects with bleeding at any time during 6 months, n (%)	106 (79)	56 (93)
OR bleeding at any time in 6 months, Eltrombopag/Placebo[d]	0.21	
95% CI	0.06, 0.71	
p-value (two-sided vs. PBO)	0.012	
Analysis of Clinically Significant Bleeding (WHO Grades 2-4)		
OR bleeding throughout 6 months, Eltrombopag/Placebo[c]	0.35	
95% CI	0.19, 0.64	
p-value (two-sided, vs. PBO)	<0.001	
Subjects with bleeding at any time during 6 months, n (%)	44 (33)	32 (53)
OR bleeding at any time in 6 months, Eltrombopag/Placebo[d]	0.30	
95% CI	0.14, 0.66	
p-value (two-sided vs. PBO)	0.002	
Concomitant Medication Reduction/Use of Rescue Medications		
Proportion of subjects receiving rescue treatment, n (%)[d]	25 (19)	25 (40)
OR Eltrombopag/Placebo[d]	0.33	
95% CI	0.16, 0.64	
p-value (two-sided vs. PBO)	0.001	
Subjects who reduced/discontinued ≥1 baseline ITP Medication, n (%)[e]	37 (59)	10 (32)
OR Eltrombopag/Placebo[d]	3.10	
95% CI	1.24, 7.75	
p-value (two-sided vs. PBO)	0.016	

a. One subject in the placebo group has a missing baseline platelet count
b. Responders defined as subjects achieving platelet count between 50 to 400 x 10^9/L,
c. Repeated measures model for binary data adjusted for use of ITP medication at baseline, splenectomy status. baseline platelet count ≤15 x 10^9/L and baseline dichotomized WHO Bleeding Scale for any bleeding and Clinically Significant Bleeding) using GEE methodology.
d. Logistic regression model adjusted for use of ITP medication at baseline, splenectomy status, baseline platelet count ≤15 x 10^9/L (and baseline dichotomized WHO Bleeding Scale for Any bleeding and Clinically Significant Bleeding).
e. Denominator is number of subject taking an ITP medication at baseline.

TRA100773B: In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to ≥50 x 10^9/L at Day 43 from a baseline <30 x 10^9/L; patients who withdrew prematurely due to a platelet count >200 x 10^9/L were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count.

A summary of baseline disease characteristics and key efficacy results is provided in Table 10. Fifty-nine percent of subjects on eltrombopag responded, compared to 16% of subjects on placebo. The odds of responding were 9 times higher for eltrombopag treated subjects compared to placebo. At baseline, 61% of subjects in the eltrombopag group and 66% of subjects in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39% of subjects in the eltrombopag 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 eltrombopag 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 (see Table 10). Two placebo and one eltrombopag subject had at least one haemostatic challenge during the study.

In TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count (≤15 x 10^9/L, >15 x 10^9/L) at randomization.

Table 10 Summary Efficacy Results for Study TRA100773B

	Eltrombopag N=76	Placebo N=38
Baseline Disease Characteristics		
Subjects with baseline platelet count ≤15 x 10^9/L, n (%)	18 (50)	17 (45)
Subjects with baseline platelet count >15 x 10^9/L, n (%)	38 (50)	21 (55)
Proportion of subjects that used ITP medication at randomization, n (%)	32 (42)	17 (45)
Splenectomised subjects, n (%)	31 (41)	14 (37)
Non-Splenectomised subjects, n (%)	45 (59)	24 (63)
Primary Endpoint		
Proportion of subjects who responded to treatment, n (%)	43(59)[a]	6 (16)[a]
Odds ratio (OR) for responding to treatment, Eltrombopag/Placebo[b]	9.61	
99% CI	(3.31, 27.86)	
p-value (two-sided vs. PBO)	<0.001	
Key Secondary Endpoint		
Analysis of Any Bleeding (WHO Grades 1-4)		
OR bleeding at any time during 6 weeks, Eltrombopag/Placebo	0.49	
95% CI	(0.26, 0.89)	
p-value (two-sided, vs. PBO)	< 0.021	

a One subject did not have a platelet count at 6 weeks

b Responder defined as patients who had an increase in platelet counts to ≥ 50 x 10^9/L from baseline < 30 x 10^9/L after up to 6-weeks of dosing

REPEAT *(TRA108057)*: REPEAT evaluated the efficacy, safety and consistency of response following repeated, intermittent, short-term dosing of eltrombopag over 3 cycles of therapy in adults with previously treated chronic 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 primary endpoint in REPEAT was the proportion of subjects who achieved a platelet count ≥50 x 10^9/L and at least 2x baseline in Cycle 2 or 3, given this response in Cycle 1.

Of the 52 subjects who responded in Cycle 1, 33 (63%) achieved a platelet count of ≥50 x 10^9/L and at least 2x baseline on Day 8 in Cycle 1; on Day 15, 37 (79%) of 47 evaluable subjects achieved this level of response (See Table 11).

Table 11 Analysis of Responders in Cycle 1 and Cycle 2 or 3 (ITT Populations)

	Eltrombopag 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)

*1 subject was not evaluable for Cycle 1 due to a missing platelet count assessment at Day 43.

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 subjects reported any bleeding and clinically significant bleeding, respectively. At the Day 43 Visit of Cycle 1, the proportion of subjects bleeding was reduced; 12% and 0% of subjects reported any bleeding and clinically significant bleeding, respectively. Similar results were found during the subsequent treatment cycles.

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

EXTEND *(TRA105325)*: EXTEND evaluated the safety and efficacy of eltrombopag in subjects (n=299) with chronic ITP who were previously enrolled in an eltrombopag trial. In this study, subjects were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

Two hundred and forty-nine patients completed ≥6 months of treatment, 210 completed ≥12 months of treatment, 138 patients completed ≥2 years of treatment, and 24 patients completed ≥3 years of treatment. The median follow up was 100 weeks. The majority of patients had baseline platelet counts of <30 x 10^9/L (70%) The median daily dose of eltrombopag following at least 6 months (Day 182) of therapy was 50 mg (n = 252).

At baseline, 56% of subjects had any bleeding (WHO Bleeding Grades 1–4) and 16% had clinically significant bleeding. The proportion of subjects with any bleeding and clinically significant bleeding decreased from baseline by approximately 50% for the majority of assessments up to 1 year.

Sixty-five 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. Ninety-six percent of these subjects maintained this discontinuation or reduction for at least 24 weeks. Fifty-four percent of subjects completely discontinued at least one baseline ITP medication, and 49% of subjects permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

Fifty-six 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-related Thrombocytopenia

Study demographics and trial design

The efficacy and safety of eltrombopag (REVOLADE®) for the treatment of thrombocytopenia in subjects with HCV infection were evaluated in two randomized, double-blind, placebo-controlled studies. ENABLE 1 utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b (PEGETRON®) plus ribavirin.

Table 12 Summary of Trial Design and Patient Demographics for Clinical Trials in HCV

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender N (%)
ENABLE 1 (TPL103922)	Phase III, double-blind, randomized, placebo-controlled	Pre-antiviral treatment phase: 25 mg once daily, increased in 25 mg increments, up to 100 mg Antiviral treatment phase: Same dose as pre-treatment phase or placebo	Pre-antiviral treatment phase: Eltrombopag N=715 Treatment phase: Placebo N=232 Eltrombopag N=450	Pre-antiviral treatment phase: Eltrombopag 51.8 yrs (19-76 yrs) Treatment phase: Placebo 51.4 yrs (23-72 yrs) Eltrombopag 52.1 yrs (19-76 yrs)	Pre-antiviral treatment phase: F: 269 (38%) M: 446 (62%) Treatment phase: Placebo F: 73 (31%) M: 159 (69%) Eltrombopag F: 186 (41%) M: 264 (59%)
ENABLE 2 (TPL108390)	Phase III, double-blind, randomized, placebo-controlled	Pre-antiviral treatment phase: 25 mg once daily, increased in 25 mg increments, up to 100 mg Antiviral treatment phase: Same dose as pre-treatment phase or placebo	Pre-antiviral treatment phase: Eltrombopag N=805 Treatment phase: Placebo N=253 Eltrombopag N=506	Pre-antiviral treatment phase: Eltrombopag 52.2 yrs (22-83 yrs) Treatment phase: Placebo 52.0 yrs (26-74 yrs) Eltrombopag 52.4 yrs (22-83 yrs)	Pre-antiviral treatment phase: F: 295 (37%) M: 510 (63%) Treatment phase: Placebo F: 93 (37%) M: 160 (63%) Eltrombopag F: 185 (37%) M: 321 (63%)

Study Results

ENABLE 1 and ENABLE 2 were global, multicenter, two-part studies that used a randomized withdrawal design. The studies were identical in design and differed only in the pegylated interferon/ribavirin used (ENABLE 1 utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b (PEGETRON®) plus ribavirin.

They consisted of two phases: an open-label (OL) pre-antiviral treatment phase (Part 1) and randomized, double-blind (DB), placebo-controlled antiviral treatment phase (Part2). In the pre-antiviral treatment phase (Part 1), all subjects received open-label REVOLADE® to increase the platelet count to ≥ 90 x 10^9/L for ENABLE 1 and ≥ 100 x 10^9/L for ENABLE 2. Median baseline platelet counts (approximately 60 x 10^9/L) were similar among all treatment groups.

In both studies, REVOLADE® was administered at an initial dose of 25 mg once daily for 2 weeks. Dose escalations could occur every 2 weeks, in 25 mg increments up to a maximum of 100 mg eltrombopag daily, as needed to reach target platelet counts required to enter Part 2 of the study. The maximal time subjects could receive open-label eltrombopag in Part 1 was 9 weeks.

Once eligible for Part 2, subjects were randomized (2:1) to the same dose of eltrombopag received at the end of the pre-treatment phase (Part 1) or to placebo. REVOLADE® or placebo was administered in combination with pegylated interferon/ribavirin antiviral treatment for up to 48 weeks (actual duration depending on HCV genotype). All subjects in ENABLE 1 and ENABLE 2 were to attend post-treatment follow-up visits up to 24 weeks.

In both ENABLE 1 and ENABLE 2, subjects with a platelet count of < 75 x 10^9/L were enrolled and stratified by platelet count (< 50 x 10^9/L and ≥ 50 x 10^9/L to < 75 x 10^{9I}/L), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The primary efficacy endpoint for both studies was sustained virologic response (SVR) defined as the percentage of patients with non-detectable e HCV-RNA at 24 weeks after completion of the planned treatment period.

Baseline disease characteristics are described in Table 13 below.

Table 13 Baseline Disease Characteristics (Pooled Data, Intent –to-Treat Population)

	Eltrombopag (N=956)	Placebo (N=485)
HCV genotype, n (%)	n=953	n=484
1	612 (64)	309 (64)
2	67 (7)	50 (10)
3	228 (24)	101 (21)
4	41 (4)	22 (5)
6	5 (<1)	2 (<1)
HCV RNA, n (%)	n=954	n=483
<800,000 IU/mL	502 (53)	244 (51)
≥800, 000 IU/ml	452 (47)	239 (49)
Prior Antiviral Medications, n (%)	n=956	n=485
Naive	654 (68)	334 (69)
Experienced	302 (32)	151 (31)
Child-Pugh Classification, n (%)	n=953	n=485
A (score 5-6)	911 (96)	459 (95)
B (score 7-9)	42 (4)	26 (5)
ALT, n(%)	n=956	n=485
Normal	216 (23)	103(21)
Elevated	740(77)	382(79)
Baseline Platelet Count (Gi/L), n(%)	n=956	n=485
< 50	264 (28)	139(29)
≥50	692 (72)	346(71)
MELD Score n(%)	n=941	n=477
< 10	541 (57)	264 (55)
≥10	400 (43)	213 (45)
Baseline Albumin (g/L), n(%)	n=955	n=484
≤35	275 (29)	139(29)
>35	680 (71)	345(71)
FibroSURE Score; n (%)	n=842	n=426
0/1/2	83 (10)	42 (10)
3/4	759 (90)	384 (90)

Note: n represents subjects with evaluable data.

In the pre-antiviral phase (Part 1) of ENABLE 1 and ENABLE 2, platelet counts began to rise within the first week of treatment with eltrombopag, and the median time to achieve the target platelet count ≥90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate antiviral therapy, with over 80% of patients receiving 25 mg or 50 mg eltrombopag at randomization into the antiviral treatment phase (Part 2).

In both studies, a significantly greater proportion of patients treated with eltrombopag achieved SVR (see Table 14). A greater proportion of patients on eltrombopag achieved SVR regardless of baseline platelet count (<50 x 10^9/L versus ≥50 x 10^9/L) compared to placebo. In patients with high viral loads (>800,000), the SVR rate was reported at 18% for eltrombopag versus 8% for placebo. Significantly more patients reached the antiviral

milestones of early virologic response (EVR), complete EVR, end-of-treatment response (ETR), and SVR at 12 weeks when treated with eltrombopag.

Table 14 ENABLE 1 and ENABLE 2 Virologic and Platelet Response in Adults With Chronic Hepatitis C Virus

	ENABLE 1[a]		ENABLE 2[b]		Pooled Data	
Pre-antiviral Treatment Phase	N = 715		N = 805		N =1520	
% Patients who achieved target platelet counts and initiated antiviral therapy[c]	95%		94%		95%	
Antiviral Treatment Phase	**Eltrombopag N = 450 %**	**Placebo N = 232 %**	**Eltrombopag N = 506 %**	**Placebo N = 253 %**	**Eltrombopag N=956 %**	**Placebo N = 485 %**
Overall SVR24[d]	23	14	19	13	21	13
HCV Genotype 2,3	35	24	34	25	35	25
HCV Genotype 1,4,6	18	10	13	7	15	8
Platelet count <50 Gi/L	23	16	18	6	20	11
Platelet count ≥50 Gi/L	23	14	20	15	21	14
HCV RNA <800,000 IU/mL	28	20	20	17	24	18
HCV RNA ≥800,000 IU/mL	18	9	18	8	18	8

[a] Eltrombopag 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 1,200 mg daily in 2 divided doses orally).

[b] Eltrombopag given in 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 1,400 mg orally).

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

[d] SVR: sustained viral response at 24 weeks following commencnemt of anti-viral therapy, p vale < 0.05 for both ENABLE 1 and ENABLE 2

Results of secondary endpoint analyses showed the following: Significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% versus 60%, $P = 0.0001$). A greater proportion of patients on eltrombopag were reported to not require any antiviral dose reduction as compared to placebo (45% versus 27%), while the majority of patients treated with eltrombopag (76%) maintained a platelet count ≥50 x 10^9/L, compared to 19% for placebo. A greater proportion of patients in the placebo group (20%) were seen to have had a platelet count nadir less than 25 x 10^9/L during treatment, compared to patients treated with eltrombopag (3%).

Median platelet counts observed at the start of antiviral therapy were similar in both eltrombopag and placebo groups (134 x 10^9/L versus 135 x 10^9, respectively) for pooled data in the HCV patient population. Four (4) weeks following the initiation of the double-blind treatment phase, platelet counts decreased to approximately 97 x 10^9/L in the eltrombopag group and 48 x 10^9/L in the placebo group. Median platelet counts remained near Week 4 values for the remainder of the double-blind treatment phase (Part 2).

DETAILED PHARMACOLOGY

REVOLADE® (eltrombopag) does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity and therefore data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans.

Pharmacokinetic Interactions

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 μM) 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 IC_{50} values of 24.8 μM (11 μg/mL) and 20.2 μM (8.9 μg/mL), respectively. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects 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.

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter, with an IC_{50} value of 2.7 μM (1.2 μg/mL) and an inhibitor of the BCRP transporter, with an IC_{50} value of 2.7 μM (1.2 μg/mL). Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% CI: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400/100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI:6.6%, 26.6%) (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Co-administration of eltrombopag with the HCV protease inhibitor boceprevir did not have an effect on the concentration of eltrombopag. A study in 28 healthy volunteers showed that the co-administration of single dose eltrombopag 200 mg with repeat dose boceprevir 750 mg three times daily reduced the boceprevir plasma $AUC_{(0-\infty)}$ by 4 % (90 % CI: -14.7 %, 8.5 %). Co-administration of single dose eltrombopag 200 mg with repeat dose boceprevir 800 mg three times daily reduced the boceprevir plasma $AUC_{(0-\infty)}$ by 4 % (90 % CI: 0.8 %, 7.9 %) and the $C\tau$ by 32% (90% CI -41.7%, -21.4%) (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Co-administration of eltrombopag with the HCV protease inhibitor telaprevirdid not have an effect on the concentration of eltrombopag A study in 28 healthy volunteers showed that the co-administration of single dose eltrombopag 200 mg with repeat dose telaprevir 750 mg three times daily reduced the eltrombopag plasma $AUC_{(0-\infty)}$ by 6 % (90 % CI: -14.7 %, 3.5 %). Co-administration of single dose eltrombopag 200 mg with repeat dose telaprevir 750 mg three times daily reduced the telaprevir plasma $AUC_{(0-\infty)}$ by 2 % (90 % CI: -6.1 %, 2.5 %) (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1,524 mg aluminium hydroxide and 1,425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%) (see **DOSAGE AND ADMINISTRATION**, and **DRUG INTERACTIONS, Drug-Drug Interactions**).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ by 59% (90% CI: 54%, 64%) and C_{max} by 65% (90% CI: 59%, 70%). Whereas, low-calcium food (<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**, and **DRUG INTERACTIONS, Drug-Food Interactions**).

TOXICOLOGY

REVOLADE® (eltrombopag) does not stimulate platelet production in mice, rats, or dogs because of unique TPO receptor specificity. These animal species do not therefore model any potential on-target adverse effects related to the pharmacology of eltrombopag in the general toxicology, reproductive toxicology, and carcinogenicity studies. In the absence of nonclinical models to study potential on-target effects, it is acknowledged that the toxicology program lacks the ability to fully evaluate the safety eltrombopag through study of the exaggerated pharmacology. The toxicology evaluation was therefore limited to identify potential off-target effects.

Repeat Dose Toxicity

The toxicity of repeated oral doses of eltrombopag has been assessed in mice, rats, rabbits and dogs in studies of up to 13, 28, 1 and 52 weeks, respectively. Eltrombopag was well tolerated with no adverse treatment-related clinical signs, effects on food consumption or body weight, or mortality for up to 13 weeks in mice at doses ≤100 mg/kg/day (652 μg.h/mL), 28 weeks or 2 years in rats at doses ≤30 or 40 mg/kg/day (661 or 677 μg.h/mL, respectively), 1 week in rabbits at doses ≤150 mg/kg/day (59 μg.h/mL), and 52 weeks in dogs at doses ≤30 mg/kg/day (418 μg.h/mL). Systemic exposures at these dose levels were 4.5-fold the maximum proposed human exposure in mice and rats, 0.4-fold in rabbits and 2.9-fold in dogs.

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. Cataracts have not been observed in dogs after 52 weeks of dosing at 2 times the human clinical exposure in ITP patients and equivalent to the human clinical exposure in HCV patients based on AUC. (see **WARNINGS AND PRECAUTIONS, Ophthalmologic**).

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 respectively, the human clinical exposure in ITP patients and 2 times and equivalent to the human clinical exposure in HCV patients, based on AUC. (see **WARNINGS AND PRECAUTIONS; Renal, Renal Impairment**).

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC.

Carcinogenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in ITP patients and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day).

Genotoxicity

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.

Phototoxicity

In vitro studies with eltrombopag suggest a potential photosafety risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure in ITP patients and 5 times the human clinical exposure in HCV patients, based on AUC) or ocular phototoxicity (≥6 times the human clinical exposure in ITP patients and ≥3 times the human clinical exposure in HCV patients, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. 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.

Reproductive and Developmental Toxicity

REVOLADE® did not affect female fertility, early embryonic development or embryofetal development in rats at doses up to 20 mg/kg/day (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). Also there was no effect on embryofetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP and HCV patients based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients and 3 times the human clinical exposure in HCV patients, based on AUC) in rats, REVOLADE® treatment was associated with embryo lethality (increased pre and post implantation loss), reduced fetal body weight and gravid uterine

weight in the female fertility study and a low incidence of cervical ribs and reduced fetal body weight in the embryofetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Special Populations and Conditions: REVOLADE® 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 in ITP patients and 2 times the human clinical exposure in HCV patients, based on AUC). In the pre and post natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). REVOLADE® was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to REVOLADE® was likely via lactation.

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PART III: CONSUMER INFORMATION

[Pr]REVOLADE®
eltrombopag tablets (as eltrombopag olamine)

This leaflet is part III of a three-part "Product Monograph" published when REVOLADE® eltrombopag tablets (as eltrombopag olamine) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REVOLADE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Chronic immune thrombocytopenia (ITP):
REVOLADE® is used for adults to treat a bleeding disorder known as chronic immune thrombocytopenia (ITP) to increase platelet counts in splenectomized patients when other medications don't work. REVOLADE® may also be used as second line treatment for non-splenectomized adults when surgery is not an option. ITP is a condition where there is a low platelet count (thrombocytopenia). Platelets are blood cells that help the blood clot normally. ITP patients may have an increased risk of bleeding. Symptoms of bleeding are petechiae (pinpoint sized flat round red spots under the skin), purpura (bruising), nosebleeds, bleeding gums, or not being able to control bleeding if cuts or injuries occur.

What it does:

REVOLADE® is a medicine that may help to increase the number of platelets.

When it should not be used:

Do not use REVOLADE® if you:

- are allergic to REVOLADE® or to any of the non-medicinal ingredients (see "What the non-medicinal ingredients are" section)
- have severe liver impairment

What the medicinal ingredient is:

eltrombopag

What the nonmedicinal ingredients are:

Hypromellose, macrogol, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and titanium dioxide.

25 mg tablets also contain polysorbate.

50 mg tablets also contain iron oxide yellow and iron oxide red.

75* mg tablets also contain iron oxide red and iron oxide black

What dosage forms it comes in:

Tablets: 25 mg, 50 mg, and 75* mg.

WARNINGS AND PRECAUTIONS

BEFORE you use REVOLADE®, talk to your doctor or pharmacist if you:

- Have liver problems.
- Have kidney problems.
- Have a history of thrombosis (formation of a clot inside a blood vessel, obstructing the flow of blood), or you know that thrombosis occurs frequently in your family. The risk of blood clots may be increased in the following circumstances: If you are elderly, if you have been bedridden for a long time, if you have cancer, if you are taking the contraceptive birth control pill, or hormone replacement therapy, if you have undergone recent surgery or received a physical injury, if you are overweight, if you are a smoker.
- Have a history of cataracts (problems with sight)
- Are pregnant or plan to become pregnant
- Are breast feeding
- Are over 65 years of age
- Are of East Asian descent

Pregnancy:
You should avoid becoming pregnant while taking REVOLADE® because the effect of REVOLADE® on pregnancy is not known. You should use a reliable method of contraception (a way to prevent you from becoming pregnant). If you become pregnant during treatment, tell your doctor.

* Not available in Canada.

Breast-feeding:
Breast feeding is not recommended while you are taking REVOLADE®. It is not known whether REVOLADE® passes into breast milk.

Cataracts:
In animal studies it was found that REVOLADE® caused the development of cataracts (a clouding of the lens in the eye). Your doctor may recommend that you are checked for cataracts before and during REVOLADE® therapy.

INTERACTIONS WITH THIS MEDICATION

Taking Other Medicines:

There are certain groups of medicines, including prescription and non-prescription medicines and vitamins that interact with REVOLADE® and that you should not take at the same time while receiving a course of REVOLADE®. These medications include some products within the following groups:

- Antacid medicines to treat stomach ulcers, indigestion or heartburn
- Certain drugs used to lower cholesterol (statins)
- Minerals such as aluminum, calcium, iron, magnesium, selenium and zinc which may be found in mineral supplements
- Certain drugs used to treat human immunodeficiency virus (HIV) (lopinavir /ritonavir)

Talk to your doctor if you take any of these medications. In some cases, you may need to adjust the dose or alter the timing of the dose (see Usual dose). Ask your doctor or pharmacist to review the medicines you are currently taking and suggest suitable alternatives if necessary.

If you are also taking medicines which are given to prevent blood clots (anticoagulants or antiplatelet therapy), there is a greater risk of bleeding. You should discuss this with your doctor. If you are taking other medications for the treatment of ITP these may be reduced or stopped when given together with REVOLADE®.

Taking REVOLADE® with Food and Drink:

Do not take REVOLADE® with dairy products (e.g. milk, ice cream, yogurt, etc.).

REVOLADE® may be taken with food low in calcium such as:

- Fruits such as pineapple, raisins and strawberries
- Lean ham, chicken or beef
- Unfortified fruit juice, soy milk and grain. (Unfortified means no added calcium, magnesium or iron).

Please discuss this matter with your doctor or pharmacist; they will be able to give you advice on the most suitable meals to be eaten while you are taking REVOLADE® (eltrombopag).

PROPER USE OF THIS MEDICATION

Usual adult dose:

The usual starting dose for ITP patients is **one 50 mg** REVOLADE® tablet a day. People of East Asian / Southeast Asian origin (Chinese, Japanese, Taiwanese, Thai, or Korean) may need to start at a lower dose of 25 mg**.**

If you have liver disease and your doctor has decided to treat you for ITP, your starting dose should be no more than 25 mg taken once daily.

Based on your response to REVOLADE® your doctor will adapt the dose and may recommend that your daily dose of REVOLADE® be increased or decreased.

Do not stop taking REVOLADE® tablets until your doctor advises you to do so.

After your doctor advises you to stop treatment with REVOLADE®, your platelet count will then be checked each week for 4 weeks.

Don't take REVOLADE® during the 4 hours before or after you take antacid medication (to treat indigestion), mineral supplements (such as aluminium, calcium, iron, magnesium, selenium or zinc), or dairy products. If you do, the medicine will not be properly absorbed into your body. One way to avoid issues with these products would be to take them in the morning and take REVOLADE® in the evening. Ask your doctor or pharmacist for advice if you are unsure.

Do not take REVOLADE® for more than one year at a time. Treatment should be reassessed by your doctor after one year.

Overdose:

The dose of REVOLADE® should not exceed 75 mg/day.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. However, do not take a double dose to make up for a forgotten dose, instead start taking REVOLADE® again at the regular time the next day.

If you have any further questions on the use of REVOLADE®, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REVOLADE® can cause side effects, although not everybody gets them.

Common side effects (These may affect more than 1 in 100 and up to 1 in 10 people)

- Nausea
- Diarrhea
- Dry mouth
- Vomiting
- Rash
- Joint pain
- Dry eye
- Feeling hot
- Headache
- Numbness or tingling of the skin
- increased sweating
- sore throat or discomfort when swallowing

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common (up to 1 in 10 people may be affected)	**Liver problems:** yellow colour to skin, whites of the eyes (jaundice), unusual dark urine, unusual tiredness, right upper stomach area pain		✓	
Uncommon (less than 1 in 100 people may by affected)	**Allergic reactions:** rash, hives, swelling of the face, lips tongue or throat, difficulty swallowing or breathing		✓	
	Bleeding		✓	
	Blood clot in the leg: swelling, pain or tenderness of one leg		✓	
	Unusual hair loss or thinning		✓	
	musculoskeletal chest pain		✓	
	musculoskeletal pain (pain that affects the muscles and tendons along with bones)		✓	
	myalgia (aching muscles)		✓	
	urinary tract infections		✓	

REVOLADE® may cause serious side effects

Liver Problems:
REVOLADE® may damage your liver and cause serious, even life threatening, illness. You must have blood tests to check your liver before you start taking REVOLADE® and during treatment.

Your doctor will order the blood tests and any other tests required. In some cases, REVOLADE® treatment may need to be stopped. Tell your doctor right away if you have any of these signs and symptoms of liver problems:

- Yellowing of the skin or the whites of the eyes (jaundice)
- Unusual darkening of the urine
- Unusual tiredness
- Right upper stomach area pain

Bleeding after you stop treatment:
When you stop taking REVOLADE®, your blood platelet count will drop back down to what it was before you started taking REVOLADE®. These effects are most likely to happen within 4 weeks after you stop taking REVOLADE®. The lower platelet counts may increase your risk of bleeding. Your doctor will check your platelet counts for at least 4 weeks after you stop taking REVOLADE®. Tell your doctor or pharmacist if you have any bruising or bleeding after you stop taking REVOLADE®.

Problems with your bone marrow:
People with the disease for which you are being treated may have problems with their bone marrow. Medicines like REVOLADE® stimulate certain bone marrow cells to make platelets and may increase the risk for progression of underlying MDS or haematological malignancies or for scarring of the bone marrow. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with REVOLADE®.

High platelet counts and higher chance for blood clots:
You have a higher chance of getting a blood clot if your platelet count is too high during treatment with REVOLADE®, but blood clots can occur with normal or even low platelet counts. If you have disease of the liver, you are at risk of a blood clot in a blood vessel that feeds your liver (portal vein thrombosis). You may have severe complications from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. You may have clots in small blood vessels, which may harm organs such as the kidneys. Your doctor will check your blood platelet counts, and change your dose or stop REVOLADE® if your platelet counts get too high. Tell your doctor right away if you have any of these signs and symptoms of a blood clot: swelling or pain/tenderness of one leg, sudden shortness of breath especially when accompanied with sharp pain in the chest and/or rapid breathing; abdominal pain, enlarged abdomen, blood in stool.

This is not a complete list of side effects. For any unexpected effects while taking REVOLADE® contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach of children.

Store below 30°C, protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.gsk.ca or by contacting the sponsor,

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised:

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PART III: CONSUMER INFORMATION

PrREVOLADE®
eltrombopag tablets (as eltrombopag olamine)

This leaflet is part III of a three-part "Product Monograph" published when REVOLADE® eltrombopag tablets (as eltrombopag olamine) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REVOLADE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Chronic hepatitis C (HCV) Associated Thrombocytopenia: Many patients with HCV infections have low platelet counts (thrombocytopenia) not only as a result of the disease but also due to some of the medicines that are used to treat the disease. The use of REVOLADE® to increase and maintain the platelet count prior to and throughout antiviral treatment of HCV infection gives patients a better opportunity to maintain the optimal dose and duration of their antiviral therapy.

What it does:

REVOLADE® is a medicine that may help to increase the number of platelets.

When it should not be used:

Do not use REVOLADE® if you:

- are allergic to REVOLADE® or to any of the non-medicinal ingredients (see "What the non-medicinal ingredients are" section)
- have severe liver impairment

What the medicinal ingredient is:

eltrombopag

What the nonmedicinal ingredients are:

Hypromellose, macrogol, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and titanium dioxide.

25 mg tablets also contain polysorbate.

50 mg tablets also contain iron oxide yellow and iron oxide red.

75* mg tablets also contain iron oxide red and iron oxide black

What dosage forms it comes in:

Tablets: 25 mg, 50 mg and 75* mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Chronic hepatitis patients with liver disease may be at risk of liver failure and death. When also taking pegylated interferon and ribavirin to treat hepatitis C, your doctor may monitor your liver symptoms closely.

Consult the Consumer Information for both pegylated interferon and ribavirin for relevant safety information associated with the use of these products as they are used with REVOLADE® when treating patients with hepatitis C and thrombocytopenia.

BEFORE you use REVOLADE®, talk to your doctor or pharmacist if you:

- Have liver problems.
- Have kidney problems.
- Have a history of thrombosis (formation of a clot inside a blood vessel, obstructing the flow of blood), or you know that thrombosis occurs frequently in your family. The risk of blood clots may be increased in the following circumstances: If you are elderly, if you have been bedridden for a long time, if you have cancer, if you are taking the contraceptive birth control pill, or hormone replacement therapy, if you have undergone recent surgery or received a physical injury, if you are overweight, if you are a smoker.
- Have a history of cataracts (problems with sight).
- Are pregnant or plan to become pregnant.
- Are breast feeding or planning to breast feed.
- Are over 65 years of age.
- Are of East Asian descent.

Pregnancy:
You should avoid becoming pregnant while taking REVOLADE® because the effect of REVOLADE® on

* Not available in Canada.

pregnancy is not known. You should use a reliable method of contraception (a way to prevent you from becoming pregnant). If you become pregnant during treatment, tell your doctor.

Breast-feeding:
Breast feeding is not recommended while you are taking REVOLADE®. It is not known whether REVOLADE® passes into breast milk.

Cataracts:
In animal studies it was found that REVOLADE® caused the development of cataracts (a clouding of the lens in the eye). In HCV trials in patients with thrombocytopenia (low blood platelet count) also receiving interferon, an increased risk in the incidence of cataracts has also been seen. Your doctor may recommend that you are checked for cataracts before and during REVOLADE® therapy.

INTERACTIONS WITH THIS MEDICATION

Taking Other Medicines:

There are certain groups of medicines, including prescription and non-prescription medicines and vitamins that interact with REVOLADE® and that you should not take at the same time while receiving a course of REVOLADE®. These medications include some products within the following groups:

- Antacid medicines to treat stomach ulcers, indigestion or heartburn
- Certain drugs used to lower cholesterol (statins)
- Minerals such as aluminum, calcium, iron, magnesium, selenium and zinc which may be found in mineral supplements
- Certain drugs used to treat human immunodeficiency virus (HIV) (lopinavir /ritonavir)

Talk to your doctor if you take any of these medications. In some cases, you may need to adjust the dose or alter the timing of the dose (see Usual dose). Ask your doctor or pharmacist to review the medicines you are currently taking and suggest suitable alternatives if necessary.

If you are also taking medicines which are given to prevent blood clots (anticoagulants or antiplatelet therapy), there is a greater risk of bleeding. You should discuss this with your doctor. If you are taking other medications for the treatment of ITP these may be reduced or stopped when given together with REVOLADE®.

Taking REVOLADE® with Food and Drink:

Do not take REVOLADE® with dairy products (e.g. milk, ice cream, yogurt, etc.).

REVOLADE® may be taken with food low in calcium such as:

- Fruits such as pineapple, raisins and strawberries
- Lean ham, chicken or beef
- Unfortified fruit juice, soy milk and grain. (Unfortified means no added calcium, magnesium or iron).

Please discuss this matter with your doctor or pharmacist; they will be able to give you advice on the most suitable meals to be eaten while you are taking REVOLADE® (eltrombopag).

PROPER USE OF THIS MEDICATION

Usual adult dose:

The usual starting dose for HCV patients is **one 25 mg** REVOLADE® tablet a day. People of East Asian / Southeast Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) will start on the same 25 mg dose.

Based on your response to REVOLADE® your doctor will adapt the dose and may recommend that your daily dose of REVOLADE® be increased or decreased.

Do not stop taking REVOLADE® tablets until your doctor advises you to do so.

After your doctor advises you to stop treatment with REVOLADE®, your platelet count will then be checked each week for 4 weeks.

Don't take REVOLADE® during the 4 hours before or after you take antacid medication (to treat indigestion), mineral supplements (such as aluminium, calcium, iron, magnesium, selenium or zinc), or dairy products. If you do, the medicine will not be properly absorbed into your body. One way to avoid issues with these products would be to take them in the morning and take REVOLADE® in the evening. Ask your doctor or pharmacist for advice if you are unsure.

Do not take REVOLADE® for more than one year at a time. Once your anti-viral therapy has been discontinued treatment with REVOLADE® will be stopped.

Overdose:

For HCV patients, the dose of REVOLADE® should not exceed 100 mg/day.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. However, do not take a double dose to make up for a forgotten dose, instead start taking REVOLADE® again at the regular time the next day.

If you have any further questions on the use of REVOLADE®, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REVOLADE® can cause side effects, although not everybody gets them.

Common side effects (These may affect more than 1 in 100 and up to 1 in 10 people treated with REVOLADE® and antiviral agents)

- Fever
- Fatigue
- Chills
- Headache
- Cough
- Nausea
- Diarrhea
- Unusual hair loss or thinning
- Muscle pain
- Itching
- Feeling weak
- Difficulty sleeping
- Loss of appetite
- Flu-like symptoms
- Swelling of the hands, ankles or feet

Very common side effects that may show up in the blood tests (These may affect more than 1 in 10 people)

- Reduced number of red blood cells (*anemia)*

Common side effects that may show up in the blood tests (These may affect more than 1 in 100 and up to 1 in 10 people treated with REVOLADE® and antiviral agents)

- Increase in bilirubin (a substance produced by the liver)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common (up to 1 in 10 people may be affected)	**Liver problems:** yellow colour to skin, whites of the eyes (jaundice), unusual dark urine, unusual tiredness, right upper stomach area pain		✓	
Uncommon (less than 1 in 100 people may by affected)	**Allergic reactions:** rash, hives, swelling of the face, lips tongue or throat, difficulty swallowing or breathing		✓	
	Bleeding		✓	
	Blood clot in the leg: swelling, pain or tenderness of one leg		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Unusual hair loss or thinning		✓	
	musculoskeletal chest pain		✓	
	musculoskeletal pain (pain that affects the muscles and tendons along with bones)		✓	
	myalgia (aching muscles)		✓	
	urinary tract infections		✓	

REVOLADE® may cause serious side effects

Liver Problems:
REVOLADE® may damage your liver and cause serious, even life threatening, illness. You must have blood tests to check your liver before you start taking REVOLADE® and during treatment. When you are given antiviral treatments together with REVOLADE®, some liver problems can get worse.

Your doctor will order the blood tests and any other tests required. In some cases, REVOLADE® treatment may need to be stopped. Tell your doctor right away if you have any of these signs and symptoms of liver problems:

- Yellowing of the skin or the whites of the eyes (jaundice)
- Unusual darkening of the urine
- Unusual tiredness
- Right upper stomach area pain

Bleeding after you stop treatment:
When you stop taking REVOLADE®, your blood platelet count will drop back down to what it was before you started taking REVOLADE®. These effects are most likely to happen within 4 weeks after you stop taking REVOLADE®. The lower platelet counts may increase your risk of bleeding. Your doctor will check your platelet counts for at least 4 weeks after you stop taking REVOLADE®. Tell your doctor or pharmacist if you have any bruising or bleeding after you stop taking REVOLADE®.

Problems with your bone marrow:
People with the disease for which you are being treated may have problems with their bone marrow. Medicines like REVOLADE® stimulate certain bone marrow cells to make platelets and may increase the risk for progression of underlying MDS or haematological malignancies or for scarring of the bone marrow. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with REVOLADE®.

High platelet counts and higher chance for blood clots:
You have a higher chance of getting a blood clot if your platelet count is too high during treatment with REVOLADE®, but blood clots can occur with normal or even low platelet counts. If you have disease of the liver, you are at risk of a blood clot in a blood vessel that feeds your liver (portal vein thrombosis). You may have severe complications from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. You may have clots in small blood vessels, which may harm organs such as the kidneys. Your doctor will check your blood platelet counts, and change your dose or stop REVOLADE® if your platelet counts get too high. Tell your doctor right away if you have any of these signs and symptoms of a blood clot: swelling or pain/tenderness of one leg, sudden shortness of breath especially when accompanied with sharp pain in the chest and/or rapid breathing; abdominal pain, enlarged abdomen, blood in stool.

This is not a complete list of side effects. For any unexpected effects while taking REVOLADE® contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach of children.

Store below 30°C, protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.gsk.ca or by contacting the sponsor,

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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