

# DATA SHEET

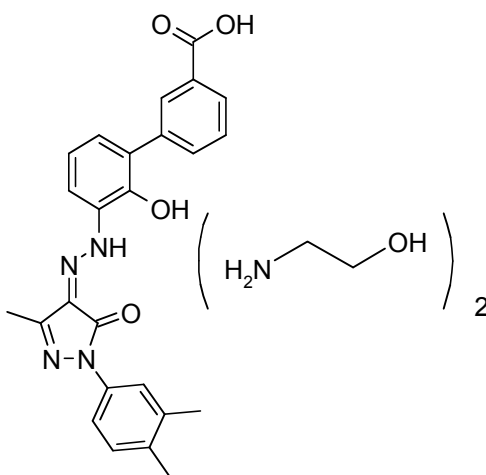
## REVOLADE® TABLETS

### NAME OF THE MEDICINE

REVOLADE® (Eltrombopag olamine)

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

The structural formula is:



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

Molecular formula: C<sub>25</sub> H<sub>22</sub> N<sub>4</sub> O<sub>4</sub> · 2 (C<sub>2</sub> H<sub>7</sub> N O)

Molecular weight: 564.65.

CAS number: 496775-62-3

### DESCRIPTION

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

Each film-coated tablet also contains magnesium stearate, mannitol, cellulose - microcrystalline, povidone, sodium starch glycolate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80 (25mg tablet only), iron oxide red CI77491 (50mg tablet only) and iron oxide yellow CI77492 (50mg tablet only).

## PHARMACOLOGY

### Mechanism of Action

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

### Pharmacodynamic Effects

Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, eltrombopag treatment of normal human platelets does not enhance adenosine diphosphate (ADP)-induced aggregation or induce P-selectin expression. Eltrombopag does not antagonise platelet aggregation induced by ADP or collagen.

### Pharmacokinetics

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

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

Regimen of eltrombopag	C <sub>max</sub> (µg/ml)	AUC <sub>(0-τ)</sub> (µg.hr/ml)
50mg once daily (n=34)	8.01 (6.73, 9.53)	108 (88, 134)
75mg once daily (n=26)	12.7 (11.0, 14.5)	168 (143, 198)

### Absorption and Bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see *Dosage and Administration, Interactions*). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites

eliminated in faeces, the oral absorption of drug-related material following administration of a single 75mg eltrombopag solution dose was estimated to be at least 52%.

### ***Distribution***

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

### ***Metabolism***

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon  $AUC_{0-\infty}$ . Minor metabolites, each accounting for <10% of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20% of a dose is metabolised by oxidation. *In vitro* studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

### ***Elimination***

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

### ***Special Patient Populations***

#### **Renal Impairment**

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50mg-dose, the  $AUC_{0-\infty}$  of eltrombopag was decreased by 32% (90% CI: 63% decrease, 26% increase) in patients with mild renal impairment, 36% (90% CI: 66% decrease, 19% increase) in patients with moderate renal impairment, and 60% (90% CI: 18% decrease, 80% decrease) in patients with severe renal impairment compared with healthy volunteers. There was a trend for reduced plasma eltrombopag exposure in patients with renal impairment, but there was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Patients with impaired renal function should use eltrombopag with caution and close monitoring.

### Hepatic Impairment

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

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 79 patients with chronic liver disease. Based on estimates from the population pharmacokinetic analysis, patients with liver cirrhosis (hepatic impairment) had higher plasma eltrombopag  $AUC_{(0-\tau)}$  values as compared to healthy volunteers, and  $AUC_{(0-\tau)}$  increased with increasing Child-Pugh score. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 87% to 110% higher plasma eltrombopag  $AUC_{(0-\tau)}$  values and patients with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag  $AUC_{(0-\tau)}$  values.

Patients with liver cirrhosis (hepatic impairment) should use eltrombopag with caution and close monitoring (see *Precautions*). For patients with mild, moderate and severe hepatic impairment, initiate eltrombopag at a reduced dose of 25mg once daily (see *Dosage and Administration*).

### Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87% higher plasma eltrombopag  $AUC_{(0-\tau)}$  values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see *Dosage and Administration*).

### Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50% higher plasma eltrombopag  $AUC_{(0-\tau)}$  as compared to male patients, without adjustment for body weight differences.

## **CLINICAL TRIALS**

The safety and efficacy of REVOLADE has been demonstrated in two, randomised, double-blind, placebo-controlled studies (**TRA102537 RAISE** and **TRA100773B**) and one open label study (**EXTEND TRA105325**) in adult patients with previously treated chronic ITP.

#### *Double-Blind Placebo-Controlled Studies*

*TRA102537:* In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count  $\geq 50,000/\mu\text{L}$  and  $\leq 400,000/\mu\text{L}$ , during the 6 month treatment period, for subjects receiving REVOLADE relative to placebo. One hundred and ninety seven subjects were randomized 2:1, REVOLADE (n=135) to placebo (n=62), and were stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. Subjects received study medication for up to 6 months, during which time the dose of REVOLADE could be adjusted based on individual platelet counts. In addition, subjects could have tapered off concomitant ITP medications and received rescue treatments as dictated by local standard of care.

The odds of achieving a platelet count between  $50,000/\mu\text{L}$  and  $400,000/\mu\text{L}$  during the 6 month treatment period were 8 times higher for REVOLADE treated subjects than for placebo-treated subjects (Odds Ratio: 8.2 [99% CI: 3.59, 18.73]  $p < 0.001$ ). Median platelet counts were maintained above  $50,000/\mu\text{L}$  at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below  $30,000/\mu\text{L}$  throughout the study.

At baseline, 77% of subjects in the placebo group and 73% of subjects in the REVOLADE group reported any bleeding (WHO Grades 1-4); clinically significant bleeding (WHO Grades 2-4) at baseline was reported in 28% and 22% of subjects in the placebo and REVOLADE groups, respectively. The proportion of subjects with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% throughout the 6 month treatment period in REVOLADE-treated subjects. When compared to the placebo group, the odds of any bleeding (Grades 1-4) and the odds of clinically significant bleeding (Grades 2-4) were 76% and 65% lower in the REVOLADE-treated subjects compared to the placebo-treated subjects ( $p < 0.001$ ).

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

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

Four placebo and 14 REVOLADE subjects had at least 1 haemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. Fewer REVOLADE-treated subjects (29%) required rescue treatment to manage their haemostatic challenge, compared to placebo-treated subjects (50%).

In terms of improvements in health related quality of life, statistically significant improvements from baseline were observed in the REVOLADE group in fatigue, including severity and impact on thrombocytopenia-impacted daily activities and concerns [as measured by the vitality subscale of the SF36, the motivation and energy inventory, and the 6-item extract from the thrombocytopenia subscale of the FACIT-Th]. Comparing the REVOLADE group to the placebo group, statistically significant improvements were observed with thrombocytopenia impacted activities and concerns specifically regarding motivation, energy and fatigue, as well as physical and emotional role and overall mental health. The odds of meaningful improvement in health related quality of life while on therapy was significantly greater among patients treated with REVOLADE than placebo.

*TRA100773B:* In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to  $\geq 50,000/\mu\text{L}$  at Day 43 from a baseline  $< 30,000/\mu\text{L}$ ; patients who withdrew prematurely due to a platelet count  $> 200,000/\mu\text{L}$  were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 subjects with previously treated chronic ITP were randomised 2:1 into the study, with 76 randomised to REVOLADE and 38 randomized to placebo.

Fifty-nine percent of subjects on REVOLADE responded, compared to 16% of subjects on placebo. The odds of responding were 9 times higher for REVOLADE treated subjects compared to placebo (Odds Ratio: 9.6 [95% CI: 3.31, 27.86]  $p < 0.001$ ). At baseline, 61% of subjects in the REVOLADE group and 66% of subjects in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39% of subjects in the REVOLADE treatment group had bleeding compared with 60% in the placebo group. Analysis over the treatment period using a repeated measures model for binary data confirmed that a lower proportion of REVOLADE subjects had bleeding (Grade 1-4) at any point in time over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo group (OR=0.49, 95% CI=[0.26,0.89],  $p = 0.021$ ). Two placebo and one REVOLADE subject had at least one haemostatic challenge during the study.

In both RAISE and TRA100773B the response to REVOLADE relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count ( $\leq 15,000/\mu\text{L}$ ,  $> 15,000/\mu\text{L}$ ) at randomization.

#### *Open Label Studies*

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

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

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

Seventy percent of subjects who reduced a baseline medication permanently discontinued or had a sustained reduction of their baseline ITP medication and did not require any subsequent rescue treatment. Sixty-five percent of these subjects maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of subjects completely discontinued at least one baseline ITP medication, and 55% of subjects permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

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

## **INDICATIONS**

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

## **CONTRAINDICATIONS**

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

## **PRECAUTIONS**

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

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

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. In two placebo controlled studies, adverse events of ALT increase were reported in 5.7% and 4.0% of eltrombopag and placebo treated patients 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. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue REVOLADE if ALT levels increase  $\geq 5X$  the upper limit of normal [ULN] or to  $\geq 3X$  ULN and are:

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

Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag when administering eltrombopag to patients with liver cirrhosis (hepatic impairment) (see *Dosage and Administration*).

If the potential benefit for reinitiating REVOLADE treatment is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce REVOLADE and measure serum liver tests weekly during the dose adjusted phase. If liver test abnormalities persist, worsen or recur, then permanently discontinue REVOLADE.

*Thrombotic/Thromboembolic Complications:* Thromboembolic events (TEE) may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In clinical trials with REVOLADE thromboembolic events were observed at low and normal platelet counts. In ITP studies, 21 thromboembolic/thrombotic events were observed in 17 out of 446 subjects (3.8%). The TEE events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke, and suspected PRIND (prolonged reversible ischemic neurologic deficiency). Patients who had a prior history of thrombosis AND at least 2 additional proven risk factors for TEE were excluded from the pivotal studies and therefore the safety of the drug in such patients has not been established. Use caution when administering REVOLADE to patients with known risk factors for thromboembolism (e.g., advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity, smoking, Factor V Leiden, ATIII deficiency, and antiphospholipid syndrome). Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing REVOLADE treatment if the platelet count exceeds the target levels (see *Dosage and Administration*).

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

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

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

Prior to initiation of REVOLADE, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of REVOLADE, perform complete blood count (CBC) with white blood cell count (WBC) differential monthly. If immature or dysplastic cells are observed, examine

peripheral blood smears for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with REVOLADE and consider a bone marrow biopsy, including staining for fibrosis. Cytogenetic analysis of the bone marrow sample for clonal abnormality should also be considered.

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

Cataracts:

Treatment related cataracts were detected in rodents; an effect that was both dose- and time-dependent. Cataract formation was observed after 6 weeks of treatment at systemic exposure  $\geq 6$  times that anticipated in humans (based on plasma AUC). This effect was also evident during long-term (2 years) treatment at systemic exposure 4-5 times the anticipated clinical exposure, with the no-effect-dose level being similar to or only slightly higher than the anticipated clinical exposure level. Cataract formation progressed even after the cessation of treatment. Cataracts have not been observed in dogs after 52 weeks of dosing at 3 times the anticipated clinical exposure based on plasma AUC. The clinical relevance of these findings is unknown.

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

Photosensitivity: Eltrombopag is phototoxic and photoclastogenic *in vitro*. *In vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic ( $\geq 15$   $\mu\text{g/ml}$ ) in the presence of high ultraviolet (UV) light exposures ( $700 \text{ mJ/cm}^2$ ). There was no evidence of *in vivo* cutaneous phototoxicity in mice at exposures up to 10 times the human clinical exposure based on AUC or photo-ocular toxicity in rats at exposures up to 10 times the human clinical exposure based on AUC. Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg once daily for six days. This was measured by delayed phototoxic index.

### **Effects on Fertility**

Eltrombopag did not affect female or male fertility in rats at doses 2 to 4 times the human clinical exposure based on AUC. However, due to differences in TPO receptor specificity, data from nonclinical species do not fully model effects in humans.

### **Use in Pregnancy (Category B3)**

Eltrombopag was not teratogenic in rats or rabbits at doses up to 20mg/kg/day and 150mg/kg/day, respectively. The doses resulted in exposures 2 and 0.5-fold the expected clinical AUC. At the maternally toxic dose of 60mg/kg/day in rats, fetal weights were significantly reduced and there was an increase in fetal variation, cervical rib, when administered during the period of organogenesis. Eltrombopag treatment during early embryogenesis was associated with an increase in pre-and post-implantation loss (or embryonic death). Due to the fact that eltrombopag is not pharmacologically active in rats or rabbits, the potential teratogenicity of eltrombopag may not have been fully revealed in the studies with these animal species.

There are no adequate and well-controlled studies of REVOLADE in pregnant woman. The effect of REVOLADE on human pregnancy is unknown. REVOLADE should not be used during pregnancy unless the expected benefit clearly out-weighs the potential risk to the fetus.

### **Use in Lactation**

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

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

There have been no studies to investigate the effect of REVOLADE on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of REVOLADE. The clinical status of the patient and the adverse event profile of REVOLADE should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

### **Carcinogenicity**

Eltrombopag was not carcinogenic in mice at doses up to 75mg/kg/day or in rats at doses up to 40mg/kg/day (exposures greater than 3 times the anticipated clinical

exposure based on plasma AUC). Eltrombopag activates TPO receptors on the surface of haematopoietic cells and has been shown to stimulate the proliferation of megakaryocytic leukaemia cells *in vitro*. There is therefore a theoretical possibility that eltrombopag may increase the risk for haematologic malignancies.

### **Genotoxicity**

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

### **Interactions with other medicines**

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

Based on a human study with radiolabelled eltrombopag, approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. *In vitro* eltrombopag was an inhibitor of CYP2C8 and CYP2C9 ( $IC_{50}$  20-25  $\mu$ M; 8.9-11  $\mu$ g/mL), but eltrombopag did not inhibit or induce the metabolism of the CYP2C9 probe substrate flurbiprofen in a clinical drug interaction study when eltrombopag was administered as 75mg once daily for 7 days to 24 healthy adult subjects. In the same study, eltrombopag also did not inhibit or induce the metabolism of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole) or CYP3A3 (midazolam). No clinically significant interactions are expected when eltrombopag and CYP450 substrates, inducers, or inhibitors are co-administered.

Rosuvastatin: *In vitro* studies demonstrated that REVOLADE is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter with an  $IC_{50}$  value of 2.7 $\mu$ M (1.2 $\mu$ g/mL). *In vitro* studies also demonstrated that REVOLADE is a breast cancer resistance protein (BCRP) substrate and inhibitor with an  $IC_{50}$  value of 2.7 $\mu$ M (1.2 $\mu$ g/mL). Administration of eltrombopag 75mg once daily for 5 days with a single 10mg 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%). When co-administered with REVOLADE, a reduced dose of rosuvastatin should be considered and careful monitoring should be undertaken. In clinical trials with REVOLADE, a dose reduction of rosuvastatin by 50% was recommended for co-administration of rosuvastatin and REVOLADE. Concomitant administration of REVOLADE and other OATP1B1 and BCRP substrates should be undertaken with caution.

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

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

## **ADVERSE EVENTS**

### **Clinical Trial Data**

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

**Table 2 On-therapy Adverse Events reported by 5% or More of Subjects in Either Treatment Group in RAISE**

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

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

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

The adverse reactions identified in subjects treated with REVOLADE are presented below (pooled data from RAISE and TRA100773B).

**Infections and infestations**

*Common*               Pharyngitis  
                              Urinary tract infection

**Gastrointestinal disorders**

*Very Common*        Nausea  
                              Diarrhoea

*Common*                Dry mouth  
                              Vomiting

### **Hepatobiliary disorders**

*Common*                      Increased aspartate aminotransferase  
   Increased alanine aminotransferase

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

*Common*                      Alopecia  
   Rash

### **Musculoskeletal and connective tissue disorders**

*Common*                      Back pain  
   Musculoskeletal chest pain  
   Musculoskeletal pain  
   Myalgia

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

### ***Post marketing data***

No post-marketing data are currently available.

## **DOSAGE AND ADMINISTRATION**

REVOLADE dosing regimens must be individualised based on the patient's platelet counts. 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 (see *Clinical Trials*).

### **Adults**

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

### **Monitoring and dose adjustment**

After initiating REVOLADE, adjust the dose to achieve and maintain a platelet count  $\geq 50,000/\mu\text{L}$  as necessary to reduce the risk for bleeding (see Table 3). Do not exceed a dose of 75mg daily.

Clinical haematology and liver function tests should be monitored regularly throughout therapy with REVOLADE and the dose of REVOLADE modified based on platelet counts as outlined in Table 3. During therapy with REVOLADE complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ( $\geq 50,000/\mu\text{L}$  for at least 4 weeks) has been achieved. CBCs including platelet count and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

**Table 3 Dose adjustments for REVOLADE**

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

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

After any REVOLADE dose adjustment, platelet counts should be monitored at least weekly for 2 to 3 weeks. Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment. In patients with any liver cirrhosis (i.e. hepatic impairment), wait three weeks before increasing the dose (*see Populations; Precautions*).

REVOLADE should be taken at least **four hours** before or after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc) (*see Interactions, Pharmacokinetics – Absorption*).

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

### ***Discontinuation***

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

## **Populations**

### ***Children***

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

### ***Elderly***

There are limited data on the use of REVOLADE in patients aged 65 years and older. In the clinical studies of REVOLADE, overall no clinically significant differences in efficacy and safety of REVOLADE were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### ***Hepatic Impairment***

Administration of REVOLADE to patients with liver cirrhosis (hepatic impairment) should be undertaken with caution and close monitoring (see *Precautions*). If the use of REVOLADE is deemed necessary for ITP patients with liver cirrhosis (Child Pugh score >5), initiate REVOLADE treatment at a dose of 25mg once daily (see *PHARMACOLOGY Special Patient Populations*).

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

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

### ***East Asian Patients***

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean), REVOLADE should be initiated at a reduced dose of 25mg once daily (see *PHARMACOLOGY*). Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

## **OVERDOSAGE**

### **Symptoms and Signs**

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

maximum platelet count was 929,000/ $\mu$ L. All events resolved without sequelae following treatment.

### **Treatment**

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with REVOLADE in accordance with dosing and administration recommendations (*see Dosage and Administration*).

Because 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.

## **PRESENTATION AND STORAGE CONDITIONS**

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

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

### ***Shelf-Life***

36 months.

### ***Storage***

Store below 30°C.

### ***Nature and Contents of Container***

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

\* not all pack sizes may be marketed

## **MEDICINES CLASSIFICATION:**

Prescription Medicine

## **NAME AND ADDRESS:**

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AMP Centre

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Revolade<sup>®</sup> is a registered trade mark of the GlaxoSmithKline group of companies.

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