Revolade™

Eltrombopag olamine

QUALITATIVE AND QUANTITATIVE COMPOSITION

25 mg Tablet

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

Round, biconvex, white film-coated tablet debossed with 'GS NX3' and '25' on one side.

50 mg Tablet

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

Round, biconvex, brown film-coated tablet debossed with 'GS UFU' and '50' on one side.

PHARMACEUTICAL FORM

Film-coated tablets

CLINICAL PARTICULARS

Indications

Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

Dosage and Administration

Eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk (> 50,000/µl).

In most patients, measurable elevations in platelet count take 1-2 weeks (See Clinical studies)

Adults

The recommended starting dose of REVOLADE is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily.

Monitoring and dose adjustment

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

Clinical haematology and liver tests should be monitored regularly throughout therapy with REVOLADE and the dose regimen of REVOLADE modified based on platelet counts as outlined in Table 1. During therapy with REVOLADE complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. CBCs including platelet counts 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 1 Dose adjustments of REVOLADE

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

Eltrombopag 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 eltrombopag.

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.

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

Discontinuation

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

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment.

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.

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 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

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis.

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

The risk of thromboembolic events (TEEs) has been found to be increased in thrombocytopenic patients (platelet count < 50,000/µl) with chronic liver disease (CLD), without concomitant ITP, treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures.

Paediatric population

Revolade is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

East Asian Patients

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

Method of administration

The tablets should be administered orally. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc).

Contraindications

Hypersensitivity to eltrombopag or to any of the excipients.

Warnings and Precautions

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

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. In two placebo controlled studies, adverse events of ALT increase were reported in 5.7 % and 4.0 % of REVOLADE 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 (≥ 3X the upper limit of normal [ULN]) and are:

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

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

Thrombotic/Thromboembolic Complications: Thromboembolic (TEE) events may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In REVOLADE clinical trials 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).

Use caution when administering REVOLADE to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing REVOLADE treatment if the platelets 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 vein thrombosis was increased in patients treated with 75 mg REVOLADE once daily for 14 days. Six of 143 (4 %) adult patients with chronic liver disease receiving 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 µl.

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 Studies),* which increases the bleeding risk and in some cases may lead to bleeding. Platelet counts must be monitored weekly for 4 weeks following discontinuation of REVOLADE.

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, 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.

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. 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. This is consistent with information derived from non-clinical research, where no malignant cell proliferation has been demonstrated upon co-incubation of REVOLADE with MDS cell lines, multiple leukemic cell lines and solid tumour cell lines (colon, prostate, ovary and lung).

Cataracts: Cataracts were observed in toxicology studies of REVOLADE in rodents *(see Non-clinical Information).* The clinical relevance of this finding is unknown. Routine monitoring of patients for cataracts is recommended.

Interactions

Rosuvastatin: 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 Pharmacokinetics)* there was increased plasma rosuvastatin exposure. 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): Eltrombopag chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc *(see Pharmacokinetics).* 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 eltrombopag absorption *(see Dosage and Administration).*

Food Interaction: Administration of a single 50 mg-dose of REVOLADE with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ 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).*

Pregnancy and Lactation

Fertility

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 Non-Clinical Information).*

Pregnancy

Eltrombopag was not teratogenic when studied in pregnant rats and rabbits but caused a low incidence of cervical ribs (a foetal variation) and reduced foetal body weight at doses that were maternally toxic *(see Non-Clinical Information).*

There are no adequate and well-controlled studies of REVOLADE in pregnant women. The effect of REVOLADE on human pregnancy is unknown. REVOLADE should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lactation

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.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of REVOLADE on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of eltrombopag. 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.

Adverse Reactions

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. In TRA100773B, 114 patients were randomised and treated for up to 42 days with either placebo (n=38) or REVOLADE (n=76).

Most undesirable reactions associated with REVOLADE were mild to moderate in severity, early in onset and rarely treatment limiting.

Adverse reactions 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

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 disorder

Common	Back pain
	Musculoskeletal chest pain
	Musculoskeletal pain
	Myalgia

Postmarketing Data

No post marketing data are currently available.

Overdose

Symptoms and Signs

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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

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

Pharmacokinetics

The pharmacokinetic parameters of eltrombopag after administration of REVOLADE 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 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)

Absorption and Bioavailability

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

Distribution

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

Metabolism

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon $AUC_{0-\infty}$. 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.

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 (11µg/ml) and 20.2 µM (8.9 µg/ml), respectively.
Administration of REVOLADE 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 REVOLADE 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 REVOLADE 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 Interactions).*
Administration of a single dose of REVOLADE 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %) and C_{max} by 70 % (90 % CI: 62 %, 76 %) *(see Dosage and Administration, 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 AUC(0-∞) by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Whereas, low-calcium food [<50mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content *(see Dosage and Administration, Interactions).*

Special Patient Populations

Renal Impairment

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

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 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 REVOLADE with caution and close monitoring (see Warnings and Precautions). For patients with mild, moderate and severe hepatic impairment, initiate REVOLADE at a reduced dose of 25 mg once daily *(see Dosage and Administration).*

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{0-\tau}$ 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 Studies

The safety and efficacy of REVOLADE has been demonstrated in two, randomised, double-blind, placebo-controlled studies **(TRA102537 RAISE and TRA100773B)** and two open label studies **(REPEAT TRA108057 and 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 ≥ 50,000/µl and ≤ 400,000/µl, during the 6 month treatment period, for subjects receiving REVOLADE relative to placebo. One hundred and ninety seven subjects were randomized 2:1, REVOLADE (n=135) to placebo (n=62), and were stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. Subjects received study medication for up to 6 months, during which time the dose of REVOLADE could be adjusted based on individual platelet counts. In addition, subjects could have tapered off concomitant ITP medications and received rescue treatments as dictated by local standard of care.
The odds of achieving a platelet count between 50,000/µl and 400,000/µl during the 6 month treatment period were 8 times higher for REVOLADE treated subjects than for placebo-treated subjects (Odds Ratio: 8.2 [99 % CI: 3.59, 18.73] p = < 0.001).
Median platelet counts were maintained above 50,000/µl at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below 30,000/µl throughout the study.
At baseline, 77 % of subjects in the placebo group and 73 % of subjects in the REVOLADE group reported any bleeding (WHO Grades 1-4); clinically significant bleeding (WHO Grades 2-4) at baseline was reported in 28 % and 22 % of subjects in the placebo and REVOLADE groups, respectively. The proportion of subjects with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% throughout the 6 month treatment period in REVOLADE -treated subjects. When compared to the placebo group, the odds of any bleeding (Grades 1-4) and the odds of clinically significant bleeding (Grades 2-4) were 76 % and 65 % lower in the REVOLADE-treated subjects compared to the placebo-treated subjects (p < 0.001).
REVOLADE therapy allowed significantly more subjects to reduce or discontinue baseline ITP therapies compared to placebo (59 % vs. 32 %; p < 0.016).
Significantly fewer REVOLADE-treated subjects required rescue treatment compared to placebo-treated subjects [19 % 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 ≥ 50,000/µl at Day 43 from a baseline < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 subjects with previously treated chronic ITP were randomised 2: 1 into the study, with 76 randomised to REVOLADE and 38 randomized to placebo.
Fifty-nine percent of subjects on REVOLADE responded, compared to 16 % of subjects on placebo. The odds of responding were 9 times higher for REVOLADE treated subjects compared to placebo (Odds Ratio: 9.6 [95 % CI: 3.31, 27.86] p < 0.001). At baseline, 61 % of subjects in the REVOLADE group and 66 % of subjects in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39 % of subjects in the REVOLADE treatment group had bleeding compared with 60 % in the placebo group. Analysis over the treatment period using a repeated measures model for binary data confirmed that a lower proportion of REVOLADE subjects had bleeding (Grade 1-4) at any point in time over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo group (OR=0.49, 95 % CI=[0.26,0.89], p = 0.021). Two placebo and one REVOLADE subject had at least one haemostatic challenge during the study.
In both RAISE and TRA100773B the response to REVOLADE relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomization.
Open Label Studies
TRA108057: REPEAT was an open-label, repeat-dose, study which evaluated the efficacy, safety and consistency of response following repeated, intermittent, short-term dosing of REVOLADE over 3 cycles of therapy in adults with previously treated 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 ≥ 50,000/µl and at least 2x baseline in Cycle 2 or 3, given this response in Cycle 1.

10000000103430

SIDE 3

GlaxoSmithKline Artwork Information Panel | **RSC A/W Version: 2**

Item Number: 10000000103430

Manufacturing Site: GSK-ESP-Aranda-ESARA

Market or Pack Owner: Gulf and Near East-GNE

Market Trade Name: Revolade

No. of Colours: 1
(does NOT include Varnish, if applicable)

List Colours:
(include sample in fields provided below; e.g. spot / spot-CMYK equivalent)

K			

Technical Reference No(s).: 02-01-XX-273-17
(do NOT include the technical reference doc[s] version no[s].)

ATTENTION • ATTENTION

To Ensure Accurate PDF Viewing and Printing:
FOR SCREEN VIEWING: Use Adobe Acrobat 5 Professional or Adobe Acrobat Reader, Standard or Professional (higher than 5). **Overprint Preview** must be activated for accurate on screen viewing.
FOR PRINTING: Use only Acrobat Professional version 5 or higher. **"Apply Overprint Preview"** or **"Simulate Overprinting"** must be activated in the print settings for printing accurate hard copies.

AIP_VERT_NAD_INDD - APR_2010 Version 2

180 mm Measuring Bar

If a status identification banner DOES NOT appear on this document, THEN this document has NOT been printed from the Global Pack Management system.

TYPE SIZE: 8/9
HORIZONTAL SCALE: 85%

IMPORTANT

GSK Market is responsible for this product, its design and content.
Ensure the artwork is thoroughly checked, all the text proof-read and approved.
RSC GSK is responsible for site technical requirements and pre-press suitability.
GSK Market is responsible to advise RSC in case changes required impact the followings:
Formulation, Tablet embossing, Storage conditions, Shelf Life

PHARMA CODE N° 4174

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

Of the 52 subjects who responded in Cycle 1, 33 (63 %) achieved a platelet count of ≥ 50,000 µl 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.
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.
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 an 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/µl prior to REVOLADE administration. Median platelet counts at 3, 6, and 9 months on study were 86,000/µl, 67,000/µl, and 92,500/µl, respectively. The median daily dose of REVOLADE following 6 months of therapy was 50 mg (n = 74).
At baseline, 59 % of subjects had any bleeding (WHO Bleeding Grades 1–4) and 18 % 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.
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.

Pre-clinical Safety Data

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 and 5 times the human clinical exposure based on AUC, respectively). 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 C_{max}). 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 REVOLADE does not pose a genotoxic risk to humans.
Eltrombopag was not teratogenic in rats or rabbits. Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.5 times the human clinical exposure based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss) in the female fertility study, a low incidence of cervical ribs (a non-teratogenic foetal variation) in the embryofoetal development study and reduced foetal body weight in both studies. Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC).
Eltrombopag is phototoxic and photoclastogenic *in vitro.* However, *in vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic (≥ 15 µg/ml) in the presence of high UV light exposure intensity (30 MED, minimal erythematous dose). 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 mice or rats at exposures up to 11 and 6.0 times the human clinical exposure based on AUC, respectively. Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of REVOLADE 75 mg once daily for six days. This was measured by delayed phototoxic index.
Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure based on AUC, 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, 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 2 times the human clinical exposure based on AUC. The clinical relevance of these findings is unknown *(see Warnings and Precautions).*
Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC. 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 based on AUC. The clinical relevance of these findings is unknown.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet Core 25 mg and 50 mg:
Magnesium stearate
Mannitol
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet Coating - 25mg
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

Tablet Coating - 50 mg
Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 400
Titanium dioxide (E171)

Incompatibilities
No known incompatibilities

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Do not store above 30°C

Nature and Contents of Container
Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.
Not all pack sizes may be marketed.

Instructions for Use/Handling
No special requirements

Manufactured by:
Glaxo Operations UK Limited*,
Ware,UK

Packed by :
Glaxo Wellcome S.A.*, Aranda de Duero, Spain.
*Member of the GlaxoSmithKline group of companies.

Version number: GDS05/IPI03
Date of issue: 30 January 2011
Revolade™ is a trademark of the GlaxoSmithKline group of companies

GlaxoSmithKline

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

ان هذا الدواء
- الدواء مستحضر يؤثر على صحتك و استهلاكه خلافا للتعليمات يعرضك للخطر.
- اتبع بدقة وصفة الطبيب و طريقة الاستعمال المنصوص عليها و تعليمات الصيدلانى الذى صرفها لك.
- فالطبيب و الصيدلانى هما الخبيران بالدواء و بنفعه و ضرره.
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
- لا تكرر صرف الدواء بدون وصفة طبية.

لا تترك الأدوية فى متناول أيدى الأطفال

مجلس وزراء الصحة العرب
و اتحاد الصيادلة العرب

10000000103430

SIDE 4

GlaxoSmithKline Artwork Information Panel — RSC A/W Version: 2

Item Number: 10000000103430

Manufacturing Site: GSK-ESP-Aranda-ESARA

Market or Pack Owner: Gulf and Near East-GNE

Market Trade Name: Revolade

No. of Colours: 1
(does NOT include Varnish, if applicable)

List Colours:
(include sample in fields provided below; e.g. spot / spot-CMYK equivalent)

K			

Technical Reference No(s).: 02-01-XX-273-17
(do NOT include the technical reference doc[s] version no[s].)

ATTENTION • ATTENTION

To Ensure Accurate PDF Viewing and Printing:
FOR SCREEN VIEWING: Use Adobe Acrobat 5 Professional or Adobe Acrobat Reader, Standard or Professional (higher than 5). **Overprint Preview** must be activated for accurate on screen viewing.
FOR PRINTING: Use only Acrobat Professional version 5 or higher. **"Apply Overprint Preview"** or **"Simulate Overprinting"** must be activated in the print settings for printing accurate hard copies.

180 mm Measuring Bar

If a status identification banner DOES NOT appear on this document, THEN this document has NOT been printed from the Global Pack Management system.

AIP_VERT_NAD_INDD - APR_2010 Version 2

TYPE SIZE: 8/9
HORIZONTAL SCALE: 85%

Page 4 of 4

IMPORTANT

GSK Market is responsible for this product, its design and content.
Ensure the artwork is thoroughly checked, all the text proof-read and approved.
RSC GSK is responsible for site technical requirements and pre-press suitability.
GSK Market is responsible to advise RSC in case changes required impact the followings:
Formulation, Tablet embossing, Storage conditions, Shelf Life