ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of 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 counts take 1-2 weeks (see section 5.1).

Adults

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating eltrombopag, 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 eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag 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 eltrombopag

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 eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag 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 (see section 4.4).

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 (see section 5.2).

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 (see section 4.4).

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 (see sections 4.4 and 4.8).

Paediatric population

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

Elderly

There are limited data on the use of eltrombopag in patients aged 65 years and older. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag 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.

East Asian patients

Initiation of eltrombopag 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 section 5.2). 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) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In clinical studies with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies,

1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued 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 eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment (see section 4.2).

Thrombotic/Thromboembolic complications

Thrombotic/Thromboembolic complications may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk of thrombotic/thromboembolic complications. In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag 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), 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 eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag.

Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate exercise caution when administering eltrombopag to ITP patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag 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 eltrombopag.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, complete blood count (CBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined 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), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing Myelodysplastic Syndromes (MDS)

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-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia in particular the diagnosis of MDS must be excluded. 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 such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.

Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). The clinical relevance of this finding is unknown. Routine monitoring of patients for cataracts is recommended.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

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. 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 %). 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 eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken.

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

Cytochrome P450 substrates

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. 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 are co-administered.

Effects of other medicinal products on eltrombopag

Polyvalent cations (Chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ 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, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation (see section 4.2).

Food interaction

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 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see section 4.2).

Lopinavir/ritonavir

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 %). 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.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag / metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue / abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Based on an analysis of all chronic ITP patients receiving eltrombopag in 3 controlled and 2 uncontrolled clinical studies, the overall incidence of adverse events in subjects treated with eltrombopag was 82 % (367/446). The median duration of exposure to eltrombopag was 304 days and patient year's exposure was 377 in this study population.

The adverse events listed below by MedDRA system organ class and by frequency are those that the investigator considered treatment related (N = 446). The frequency categories are defined as:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

Infections and infestations

Uncommon Pharyngitis, Urinary tract infection, Influenza, Nasopharyngitis, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Upper respiratory tract infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Increased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Common Insomnia

Uncommon Sleep disorder, Anxiety, Depression, Apathy, Mood altered, Tearfulness

Nervous systems disorders

Very Common Headache

Common Paraesthesia

Uncommon Dizziness, Dysgeusia, Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Cataract, Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Conjunctival haemorrhage, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Palpitations, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Hypertension, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Uncommon Epistaxis, Pulmonary embolism, Pulmonary infarction, Cough, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea, Constipation, Abdominal pain upper

Uncommon Abdominal discomfort, Abdominal distension, Dry mouth, Dyspepsia, Vomiting, Abdominal pain, Gingival bleeding, Glossodynia, Haemorrhoids, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Blood bilirubin increased, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Pruritus, Alopecia

Uncommon Ecchymosis, Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Night sweats, Pigmentation disorder, Skin discolouration, Skin exfoliation, Swelling face

Musculoskeletal and connective tissue disorder

Common Arthralgia, Myalgia, Muscle spasm, Bone pain

Uncommon Muscular weakness, Pain in extremity, Sensation of heaviness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

General disorders and administrative site conditions

Common Fatigue, Oedema peripheral

Uncommon Chest pain, Feeling hot, Pain, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Ill-defined disorder, Inflammation of wound, Influenza like illness, Malaise, Mucosal inflammation, Non-cardiac chest pain, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Weight increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Contusion, Sunburn

Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (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 section 4.4).

In a placebo-controlled study (n = 288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1 %) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl.

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section 4.4).

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 section 4.4).

4.9 Overdose

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 eltrombopag in accordance with dosing and administration recommendations (see section 4.2).

In the ITP clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse events included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the 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.

Clinical studies

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 eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All subjects initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28 % of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53 % received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36 % had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue medication was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period,

p < 0.001. Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period.

Table 2: Secondary efficacy results from RAISE

	Eltrombopag N = 135	Placebo N = 62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
P value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medication at baseline permanently discontinued all baseline ITP medications.

At baseline, more than 70 % of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n = 76) to placebo (n = 38).

Table 3: Efficacy results from TRA100773B

	Eltrombopag N = 74	Placebo N = 38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
P value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
P value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42 % of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60 % of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 ITP patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/µl prior to eltrombopag administration. Median platelet counts at 12, 18 and 24 months on study were 68,000/µl, 75,000/µl and 119,000/µl, respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revolade in one or more subsets of the paediatric population in chronic idiopathic thrombocytopenic purpura (ITP) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP subjects are presented (Table 4).

Table 4: Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

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 section 4.2). 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 %), predominantly to albumin. 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 due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

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.

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. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50 % was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max}. Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag 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. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2).

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with 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 79 patients with chronic liver disease (37 mild hepatic impairment, 40 with moderate hepatic impairment, and 2 with severe hepatic impairment). Based on estimates from the population pharmacokinetic analysis, patients with 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. Therefore, 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 (see sections 4.2 and 4.4).

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 section 4.2).

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.

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

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 section 4.4).

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.

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.

At poorly tolerated doses in rats and dogs (> 10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times maximum human clinical exposure based on AUC.

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). 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 eltrombopag does not pose a genotoxic risk to humans.

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), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC). In 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). Eltrombopag 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 eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure based on AUC) or ocular phototoxicity (≥ 5 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. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate Type A

Tablet coating
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 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.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
6900 Cork Airport Business Park
Kinsale Road
Cork
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001
EU/1/10/612/002
EU/1/10/612/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of 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 counts take 1-2 weeks (see section 5.1).

Adults

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating eltrombopag, 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 eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag 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 eltrombopag

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 eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag 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 (see section 4.4).

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 (see section 5.2).

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 (see section 4.4).

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 (see sections 4.4 and 4.8).

Paediatric population

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

Elderly

There are limited data on the use of eltrombopag in patients aged 65 years and older. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag 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.

East Asian patients

Initiation of eltrombopag 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 section 5.2). 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) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In clinical studies with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies,

1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued 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 eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment (see section 4.2).

Thrombotic/Thromboembolic complications

Thrombotic/Thromboembolic complications may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk of thrombotic/thromboembolic complications. In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag 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), 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 eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4 %) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag.

Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate exercise caution when administering eltrombopag to ITP patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag 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 eltrombopag.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, complete blood count (CBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined 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), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing Myelodysplastic Syndromes (MDS)

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-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. 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 such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.

Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). The clinical relevance of this finding is unknown. Routine monitoring of patients for cataracts is recommended.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

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. 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 %). 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 eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken.

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

Cytochrome P450 substrates

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. 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 are co-administered.

Effects of other medicinal products on eltrombopag

Polyvalent cations (Chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ 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, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation (see section 4.2).

Food interaction

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 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see section 4.2).

Lopinavir/ritonavir

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 %). 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.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag / metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue / abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Based on an analysis of all chronic ITP patients receiving eltrombopag in 3 controlled and 2 uncontrolled clinical studies, the overall incidence of adverse events in subjects treated with eltrombopag was 82 % (367/446). The median duration of exposure to eltrombopag was 304 days and patient year’s exposure was 377 in this study population.

The adverse events listed below by MedDRA system organ class and by frequency are those that the investigator considered treatment related (N = 446). The frequency categories are defined as:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

Infections and infestations

Uncommon Pharyngitis, Urinary tract infection, Influenza, Nasopharyngitis, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Upper respiratory tract infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Increased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Common Insomnia

Uncommon Sleep disorder, Anxiety, Depression, Apathy, Mood altered, Tearfulness

Nervous systems disorders

Very Common Headache

Common Paraesthesia

Uncommon Dizziness, Dysgeusia, Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Cataract, Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Conjunctival haemorrhage, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Palpitations, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Hypertension, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Uncommon Epistaxis, Pulmonary embolism, Pulmonary infarction, Cough, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea, Constipation, Abdominal pain upper

Uncommon Abdominal discomfort, Abdominal distension, Dry mouth, Dyspepsia, Vomiting, Abdominal pain, Gingival bleeding, Glossodynia, Haemorrhoids, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Blood bilirubin increased, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Pruritus, Alopecia

Uncommon Ecchymosis, Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Night sweats, Pigmentation disorder, Skin discolouration, Skin exfoliation, Swelling face

Musculoskeletal and connective tissue disorder

Common Arthralgia, Myalgia, Muscle spasm, Bone pain

Uncommon Muscular weakness, Pain in extremity, Sensation of heaviness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

General disorders and administrative site conditions

Common Fatigue, Oedema peripheral

Uncommon Chest pain, Feeling hot, Pain, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Ill-defined disorder, Inflammation of wound, Influenza like illness, Malaise, Mucosal inflammation, Non-cardiac chest pain, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Weight increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Contusion, Sunburn

Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (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 section 4.4).

In a placebo-controlled study (n = 288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1 %) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl.

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section 4.4).

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 section 4.4).

4.9 Overdose

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 eltrombopag in accordance with dosing and administration recommendations (see section 4.2).

In the ITP clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse events included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, ATC code: B02BX 05

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the 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.

Clinical studies

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 eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All subjects initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment 15 to 28 % of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53 % received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36 % had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue medication was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period,

p < 0.001. Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period.

Table 2: Secondary efficacy results from RAISE

	Eltrombopag N = 135	Placebo N = 62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
P value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medication at baseline permanently discontinued all baseline ITP medications.

At baseline, more than 70 % of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n = 76) to placebo (n = 38).

Table 3: Efficacy results from TRA100773B

	Eltrombopag N = 74	Placebo N = 38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/μl after up to 42 days of dosing (compared to a baseline count of < 30,000/μl), n (%)	43 (59)	6 (16)
P value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
P value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count (≤ 15,000/μl, > 15,000/μl) at randomisation.

In RAISE and TRA100773B studies in the subgroup of ITP patients with baseline platelet count ≤ 15,000/μl the median platelet counts did not reach the target level (> 50,000/μl) although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42 % of patients with baseline platelet count ≤ 15,000/μl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60 % of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 ITP patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/μl prior to eltrombopag administration. Median platelet counts at 12, 18 and 24 months on study were 68,000/μl, 75,000/μl and 119,000/μl, respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revolade in one or more subsets of the paediatric population in chronic idiopathic thrombocytopenic purpura (ITP) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP subjects are presented (Table 4).

Table 4: Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

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 section 4.2). 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 %), predominantly to albumin. 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 due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

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.

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. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50 % was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max}. Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag 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 Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2).

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with 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 79 patients with chronic liver disease (37 mild hepatic impairment, 40 with moderate hepatic impairment, and 2 with severe hepatic impairment). Based on estimates from the population pharmacokinetic analysis, patients with 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. Therefore, 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 (see sections 4.2 and 4.4).

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 section 4.2).

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.

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

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 section 4.4).

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.

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.

At poorly tolerated doses in rats and dogs (> 10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times maximum human clinical exposure based on AUC.

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). 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 eltrombopag does not pose a genotoxic risk to humans.

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), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC). In 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). Eltrombopag 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 eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure based on AUC) or ocular phototoxicity (≥ 5 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. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate Type A

Tablet coating
Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 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.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
6900 Cork Airport Business Park
Kinsale Road
Cork
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/004
EU/1/10/612/005
EU/1/10/612/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Herts SG12 0DJ
United Kingdom

Or

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing

all physicians are provided with a healthcare professional information pack containing the following:

- Educational material
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

Key elements to be included in the educational material

Hepatotoxicity

• Educate patients about the potential for hepatic enzyme elevations, importance of monthly laboratory monitoring of ALT and AST, as well as the signs and symptoms associated with liver injury (e.g. jaundice).
• 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.
• 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 eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment.

Thromboembolic events

• Eltrombopag should not be used in patients with hepatic impairment (Child Pugh score≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of eltrombopag is deemed necessary, the starting dose must be 25mg once daily.
• Educate patients about the potential for thromboembolic events (TEE) in patients with chronic ITP and those known risk factors for thromboembolic events (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
• Educate patients about chronic liver disease and the risk of thromboembolic events.
• In patients with chronic liver disease treated with eltrombopag there was an association between TEE and platelet counts ≥ 200,000µl.
• A dose reduction is recommended for ITP patients with platelet counts between 150,000-250,000/µl.• Revolade should be interrupted if platelet counts increase to > 250,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

Posology

• Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-drug interaction, dose recommendations for special populations [e.g. east Asians]).
• Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or lactating females, other off label uses).

Food Interactions

• Educate patients about the potential food-drug interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
• Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

• Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).
• Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
• Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

• Educate patients about the potential for bone marrow reticulin fibre formation.
• Background information on reticulin in the bone marrow (i.e. background rates of reticulin in bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to Revolade).
• 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.

Haematological malignancies

• The diagnosis of ITP in adults and elderly patients should have been confirmed by excluding other clinical entities 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.
• Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.
• Importance of not using Revolade outside the context of its license unless in a clinical trial setting.

Potential for Off-label Use

• The risk-benefit for the treatment of thrombocytopenia in non ITP patient populations has not been established.
• The risk-benefit of Revolade in paediatric ITP has not been established.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 25 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
6900 Cork Airport Business Park

Kinsale Road
Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001 (14 film-coated tablets)
EU/1/10/612/002 (28 film-coated tablets)
EU/1/10/612/003 Multipack containing 84 (3 packs of 28) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 50 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets
eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited

6900 Cork Airport Business Park
Kinsale Road
Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/004 (14 film-coated tablets)
EU/1/10/612/005 (28 film-coated tablets)
EU/1/10/612/006 Multipack containing 84 (3 packs of 28) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 mg

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Component of a multipack comprising 3 packs, each containing 28 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Kinsale Road
Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets
eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Component of a multipack comprising 3 packs, each containing 28 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
6900 Cork Airport Business Park
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Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets
eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets

eltrombopag

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects,talk to your doctor or pharmacist. This includes any possible side effect not listed in this leaflet.

What is in this leaflet:

1. What Revolade is and what it is used for

Revolade belongs to a group of medicines called *thrombopoietin receptor agonists.* It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

Revolade is used to treat a bleeding disorder called *immune* (*idiopathic) thrombocytopenic purpura* (ITP) in adult patients (aged 18 years and over) who have had their spleen removed and have received prior treatment with corticosteroids or immunoglobulins, and these medicines did not work. ITP is caused by a low blood platelet count (*thrombocytopenia*). People with ITP have an increased risk of bleeding, and may notice symptoms such as *petechiae* (pinpoint sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

Revolade may also be used in previously treated adult patients (aged 18 years and over) with chronic ITP where surgery to remove the spleen is not an option.

2. What you need to know before you take Revolade

Don’t take Revolade
- **if you are allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under ‘What Revolade contains’).

➔ **Check with your doctor** if you think this applies to you.

Take special care with Revolade

Your doctor needs to know before you take Revolade:
- if you have **liver problems.** You should not be given Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots

- if you are **at risk of blood clots in your veins or arteries**, or you know that blood clots are common 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 (*malignancy*), if you are taking the contraceptive birth control pill or hormone replacement therapy, if you have undergone recent surgery or received a physical injury (*trauma*), if you are overweight (*obese*), if you are a smoker.
    - If any of these circumstances apply to you please tell your doctor before starting treatment.
- if you have **cataracts** (the lens of the eye getting cloudy)

➔ **Tell your doctor** if any of these apply to you.

Checking for cataracts
Your doctor may recommend that you are checked for cataracts as part of routine eye tests.

You will need regular blood tests
Before you start taking Revolade your doctor will carry out blood tests to check your blood cells including platelets. These tests will be repeated at intervals while you are taking it.

Revolade can increase some blood markers indicating liver damage. You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get physical signs of liver damage.

➔ **Tell your doctor** i**mmediately** if you have any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes *(jaundice)*
- unusually dark-coloured urine.

If you stop taking Revolade a low blood platelet count (*thrombocytopenia*) is likely to reoccur within several days. If you stop taking Revolade your platelet count will have to be monitored, and your doctor will discuss appropriate precautions with you.

If you have very high blood platelet counts, this may increase the risk of blood clotting, however blood clots can occur with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

➔ **Tell your doctor** i**mmediately** if you have any of these signs and symptoms of a blood clot:

swelling, pain or tenderness in one leg (*Deep vein thrombosis*)

sudden shortness of breath especially when accompanied with sharp pain in the chest and/or rapid breathing (*Pulmonary embolism*)

abdominal pain, enlargered abdomen, blood in stool (*Portal vein thrombosis*)

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you can obtain without a prescription.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:

- antacid medicines to treat **indigestion**, **heartburn** or **stomach ulcers**
- medicines called statins, used to **lower cholesterol**
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements**

- medicines such as methotrexate and topotecan, used to treat **cancer**

See Section 3, 'How to take Revolade', for more information about taking antacids, vitamins and mineral supplements

➔ **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade,, or your dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements 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. Your doctor will discuss this with you.
If you are taking corticosteroids, danazol, and/or azathioprine these may be reduced or stopped when given together with Revolade.

Revolade with food and drink

Revolade is not to be taken with dairy foods or drinks as the absorption of the medicine is affected by the calcium in dairy products. For details, see Section 3, *How to take Revolade*.

Pregnancy and breast-feeding

Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.
- **Tell your doctor if you are pregnant** or planning to become pregnant.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.
- **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines

No studies on the effects of Revolade on the ability to drive or use machines have been performed.

3. How to take Revolade

Always take Revolade exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

The usual starting dose is one 50 mg tablet of Revolade a day. People of East Asian origin (Chinese, Japanese, Taiwanese or Korean) may need to start at a **lower dose of 25 mg.**

Swallow the tablet whole, with some water.

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

Revolade is not recommended for people aged under 18, as the safety and effectiveness have not yet been shown.

When to take it

Don’t take Revolade in the **4 hours** before or after:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks made with milk, yoghurt or cream
- **antacids,** which are medicines for indigestion
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.

For more advice about suitable foods, talk to your doctor.

If you take more Revolade than you should

Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet.
It is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

If you forget to take Revolade

Take the next dose at the usual time. Don’t take a double dose to make up for a forgotten dose.

If you stop taking Revolade

Don’t stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Bleeding after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before you started taking Revolade. The lower platelet count 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** if you have any bruising or bleeding after you stop taking Revolade.

Problems with your bone marrow
People with ITP may have problems with their bone marrow. Medicines like Revolade could make this problem worse. 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
Your doctor will check your blood platelet count during treatment. If your platelet count gets too high, your dose of Revolade may need to be changed, or you may need to stop taking it.

Worsening of blood cancers
Before you started Revolade your doctor will have carried out tests to ensure that you have ITP and not another condition such as Myelodysplastic Syndrome (MDS). If you have MDS and receive Revolade your MDS condition may worsen. For more advice talk to your doctor.

Higher risk of blood clots
People with ITP may have a higher risk of blood clots, and medicines like Revolade could make this problem worse.

If you develop signs and symptoms of a blood clot, such as:

swelling, pain or tenderness in one leg (*Deep vein thrombosis*)

sudden shortness of breath, especially when accompanied with sharp pain in the chest and/or rapid breathing (*Pulmonary embolism*)

abdominal pain, enlargered abdomen, blood in stool (*Portal vein thrombosis*)

➔ **Contact a doctor immediately**.

Very common side effects
These may affect **more than 1 in 10** people
- headache

Common side effects
These may affect **up to 1 in 10** people
- difficulty in sleeping (*insomnia)*
- constipation, pain in stomach
- feeling sick (*nausea)*
- diarrhoea
- cloudy lens in the eye (*cataract*)
- dry eye
- increase in bilirubin (a substance produced by the liver) (*hyperbilirubinaemia*)
- liver not working well (*hepatic function abnormal)*
- unusual hair loss or thinning (*alopecia*)
- skin rash
- itching (*pruritus*)
- joint pain (*arthralgia*)
- muscle pain (*myalgia*), muscle spasm
- bone pain
- lack of energy (fatigue)
- tingling or numbness of the hands or feet (*paraesthesia)*
- swelling of the hands, ankles or feet (*oedema peripheral*)

Common side effects that may show up in blood tests:

- increase of liver enzymes (*aspartate* and *alanine transaminases*)
- increase in *bilirubin* (a substance produced by the liver)
- increase in the amounts of proteins

Uncommon side effects
These may affect **up to 1 in 100** people
- interruption of blood supply to part of the heart (*acute myocardial infarction*)
- sudden blocking of a blood vessel by blood clot (*embolism*)
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing (*pulmonary embolism*)
- the loss of function of part of the lung caused by a blockage in the lung artery (*pulmonary infarction*)
- heart beating faster (*tachycardia*), palpitations, fast or irregular heart beat, bluish discolouration of the skin (*cyanosis*) high blood pressure (*hypertension*)
- inflammation of a vein (*thrombophlebitis superficial*)
- localised swelling filled with blood from a break in a blood vessel (*haematoma*)

- sore throat and discomfort when swallowing, inflammation of the lungs, sinuses, tonsils, nose and throat
- loss of appetite (*anorexia*)
- painful swollen joints caused by uric acid (food break down product) (*Gout*)
- problems sleeping, anxiety, depression, lack of interest, mood changes
- dizziness, feeling drowsy, problems with balance, taste, speech and nerve function, migraine, shaking (*tremor*)
- problems with the liver including: level of substances (enzymes) produced by the liver increased, bile produced by liver to aid digestion of food cannot flow properly (*cholestasis*)
- problems with the eyes, including blurred and less clear vision
- ear pain, spinning sensation (*vertigo*)
- cough, problems with nose, throat and sinuses, breathing problems when sleeping
- problems with digestive system including: being sick (*vomiting*), painful swollen stomach, wind, bowel movements frequent and discoloured, haemorrhoids, dry or sore mouth, indigestion, sensitive tongue, bleeding gums, nose bleed
- changes to skin including, excessive sweating, itching bumpy rash, red spots, changes in appearance
- muscular weakness, pain in arms and legs, sensation of heaviness
- kidney problems including: inflammation of the kidney, excessive urination at night
- generally feeling unwell, high temperature, feeling hot, chest pain, bruising

Uncommon side effects that may show up in blood tests:

- decrease in number of red blood cells (*anaemia*), white blood cells and platelets
- changes in the make-up of the blood
- changes in levels of uric acid, calcium and potassium

If you get side effects

➔ **Tell your doctor or pharmacist** if any of the side effects becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.

5. How to store Revolade

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away, dispose of medicines you no longer require. These measures will help to protect the environment.

6. Contents of the pack and other information

What Revolade contains

25 mg film-coated tablets

The active substance in Revolade is eltrombopag olamine. Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

The other ingredients are: hypromellose, macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, polysorbate 80, povidone (K30), sodium starch glycolate Type A titanium dioxide (E171).

50 mg film-coated tablets

The active substance in Revolade is eltrombopag olamine. Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

The other ingredients are: hypromellose, iron oxide red (E172), iron oxide yellow (E172), macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K30), sodium starch glycolate Type A, titanium dioxide (E171).

What Revolade looks like and contents of the pack

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

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

They are supplied in aluminum blisters in a carton containing 14 or 28 film-coated tablets and multipacks containg 84 (3 packs of 28) film-coated tablets).

Not all pack sizes may be available in your country.

Marketing authorisation holder
GlaxoSmithKline Trading Services Ltd
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Manufacturer
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Or

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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