NOVARTIS

Revolade 25 mg and 50 mg

Eltrombopag

Professional Information

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1 NAME OF THE MEDICINE

REVOLADE® 25 mg Film-coated Tablet

REVOLADE® 50 mg Film-coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3 PHARMACEUTICAL FORM

25 mg: white, round, biconvex film-coated tablet with identity code 'GS NX3' and '25' debossed on one side.

50 mg: brown, round, biconvex film-coated tablet with identity code 'GS UFU' and '50' debossed on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REVOLADE is indicated for the treatment of patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

REVOLADE should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. REVOLADE should not be used in an attempt to normalise platelet count.

REVOLADE is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see Section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

REVOLADE dosing regimens must be individualised based on the patient's platelet counts.

Immune (primary) thrombocytopenia

The lowest dose of REVOLADE to achieve and maintain a platelet count ≥50,000/µl should be used. Dose adjustments are based upon the platelet count response. REVOLADE should not be used in an attempt to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric patients aged 6 to 17 years:

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

For patients of East/Southeast-Asian ancestry, REVOLADE should be initiated at a reduced dose of 25 mg once daily (see Section 5.2).

Paediatric population aged 1 to 5 years

The recommended starting dose of REVOLADE is 25 mg once daily.

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

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

Table 1: Dose adjustments of REVOLADE in ITP patients

Platelet count	Dose adjustment or response
<50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day *
>50,000/µl to ≤150,000/µl	Use lowest dose of REVOLADE 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 REVOLADE; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <100,000/µl, re-initiate therapy at a daily dose of the previously established dose reduced by 25 mg

* For patients taking 25 mg REVOLADE once every other day, increase the dose to 25 mg once daily.

♦ For patients taking 25 mg REVOLADE once daily, consideration should be given to a dose of 25 mg once every other day.

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

After any REVOLADE dose adjustment, platelet counts should be monitored at least weekly for 2 to 3 weeks. Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose increase. In patients with any liver disease (i.e. hepatic impairment), one should wait 3 weeks before increasing the dose] (see "Special populations; Hepatic impairment).

Discontinuation

Treatment with REVOLADE should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of REVOLADE therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see Section 4.4).

Severe aplastic anaemia

Initial dose regimen

REVOLADE should be initiated at a dose of 50 mg once daily. For patients of Asian ancestry, REVOLADE should be initiated at a reduced dose of 25 mg once daily (see Section 5.2). The treatment should not be initiated when the patients has existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting REVOLADE (see Section 5.1). The dose of REVOLADE should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50,000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with REVOLADE and the dosage regimen of REVOLADE modified based on platelet counts as outlined in Table 2.

Table 2 Dose adjustments of REVOLADE in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
<50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily for two weeks before increasing the dose amount by 50 mg.
≥50,000/µl to ≤150,000/µl	Use lowest dose of REVOLADE to maintain platelet counts.
>150,000/µl to ≤250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250,000/µl	Stop REVOLADE for at least one week. Once the platelet count is ≤100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of REVOLADE may be reduced by 50 %.

If counts remain stable after 8 weeks at the reduced dose, then REVOLADE must be discontinued and blood counts monitored. If platelet counts drop to <30,000/µl, haemoglobin drops to < 9 g/dl or absolute neutrophil count (ANC) to <0.5 x 109/l, REVOLADE may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with REVOLADE, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of REVOLADE is appropriate (see Sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 2) or important liver test abnormalities also necessitate discontinuation of REVOLADE (see Sections 4.8).

Special Populations:

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use REVOLADE with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section Section 5.2).

Hepatic impairment

REVOLADE 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 REVOLADE 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 an interval of 3 weeks should be observed before increasing the dose.

Severe aplastic anaemia patients with hepatic impairment should initiate REVOLADE at a dose of 25 mg once daily (see Section 5.2). After initiating the dose of REVOLADE in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with REVOLADE, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections Sections 4.4 and 4.8).

Elderly

There are limited data on the use of REVOLADE in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of REVOLADE, overall no clinically significant differences in safety of eltrombopag were observed between patients aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see Section 5.2).

There are limited data on the use of REVOLADE in SAA patients aged over 75 years. Caution should be exercised in these patients (see Section 4.4).

East-/Southeast-Asian patients

Initiation of REVOLADE at a reduced dose of 25 mg once daily is recommended for patients of East-/Southeast-Asian ancestry.

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

Paediatric population

REVOLADE is not recommended for use in children under the age of one year with ITP due to insufficient data on safety and efficacy. The safety and efficacy of REVOLADE has not been established in children and adolescents (<18 years) with SAA. No data are available.

Method of administration

REVOLADE should be taken at least two hours before or four hours after the ingestion of any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc) (see Section 4.5).

REVOLADE may be taken with 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 to avoid a significant impact on plasma eltrombopag exposure or preferably no calcium (see Section 4.5).

4.3 CONTRA-INDICATIONS:

Hypersensitivity to eltrombopag olamine or any of the excipients of REVOLADE.

Safety in pregnancy and lactation has not been established (see Section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Hepatotoxicity: REVOLADE administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity and potentially fatal liver injury.

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. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated, fractionation should be performed. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests until the abnormality(ies) resolve, stabilise, or return to baseline levels. Discontinue REVOLADE if ALT levels increase (≥ 3 x the upper limit of normal [ULN]) in patients with normal liver function, or ≥ 3 x baseline (or > 5 x ULN, whichever is the lower) in patients with elevations in transaminases before treatment and that are:

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

Exercise caution when administering REVOLADE to patients with hepatic disease. In ITP and SAA patients a lower starting dose of REVOLADE should be used. Close monitoring is required when administering to patients with hepatic impairment (see Section 4.2).

Thrombotic/Thromboembolic Complications: Thromboembolic events may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In clinical studies, thromboembolic events were observed. The thromboembolic events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke and suspected prolonged reversible ischaemic neurological deficiency (PRIND).

Use caution when administering REVOLADE to patients with known risk factors for thromboembolism (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome). Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing 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.

In a controlled clinical study in thrombocytopenic patients with chronic liver disease (n = 288) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg once daily for 14 days.

Six of 143 (4%) adult patients with chronic liver disease receiving REVOLADE/Promacta experienced TEEs (all of the portal venous system) and 2 out of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). REVOLADE is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

No case of TEE was identified from a clinical study in refractory SAA. However the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

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

Bone Marrow Reticulin Formation and Risk of Bone Marrow Fibrosis: Thrombopoietin (TPO) receptor agonists, including REVOLADE, may increase the risk for development or progression of reticulin fibres within the bone marrow.

Prior to the initiation of REVOLADE, examine the peripheral blood smear closely to establish a baseline level of cellular and morphological 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) such as anaemia, discontinue treatment with REVOLADE and a bone marrow biopsy, including staining for fibrosis should be considered.

Malignancies and progression of malignancies: There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. Across the clinical studies in ITP (n = 493) no difference in the incidence of malignancies or haematological malignancy was demonstrated between placebo and REVOLADE treated patients. This is consistent with information derived from non-clinical research, where no malignant cell proliferation has been demonstrated upon co-intubation of eltrombopag with MDS cell lines, multiple leukemic cell lines and solid tumour cell lines (colon, prostate, ovary and lung).

Cataracts: Cataracts were observed in toxicology studies of REVOLADE in rodents. Routine monitoring of patients for cataracts is recommended at intervals not exceeding 6 months.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UDP glucuronosyl transferase 1A1 (UGT1A1) and UDP glucuronosyl transferase 1A3 (UGT1A3) as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes in vitro. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag and potential co-medications.

Based on a human study with radiolabelled eltrombopag, approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. In studies utilising human liver microsomes, eltrombopag (up to 100 µM) showed no in vitro inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates, with IC50 values of 24,8 µM (11 µg/ml) and 20,2 µM (8,9 µg/ml), respectively.

Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates, inducers or inhibitors are co-administered.

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter, with an IC50 value of 2,7 µM (1,2 µg/ml) and an inhibitor of the BCRP transporter, with an IC50 value of 2,7 µM (1,2 µg/ml). Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin Cmax 103 % (90 % CI: 82 %, 126 %) and AUC0-□ 55 % (90 % CI: 42 %, 69 %).

Rosuvastatin: In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. In vitro studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. When REVOLADE and rosuvastatin were co-administered in a clinical drug interaction study (see Section 5.2) there was increased plasma rosuvastatin exposure. When co-administered with REVOLADE, a reduced dose of rosuvastatin should be considered and careful monitoring should be undertaken. In clinical studies with REVOLADE, a dose reduction of rosuvastatin by 50 % was recommended for co-administration of rosuvastatin and REVOLADE. Concomitant administration of REVOLADE and other OATP1B1 and BCRP substrates should be undertaken with caution.

Cyclosporin: A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg cyclosporin (a BCRP inhibitor). This decrease in exposure is not considered clinically meaningful. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see Section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with cyclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent Cations (Chelation): Eltrombopag chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc (see Section 5.2). REVOLADE should be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption (see Section 4.2).

Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1 524 mg aluminium hydroxide and 1 425 mg magnesium carbonate) decreased plasma eltrombopag AUC0-□ by 70 % (90 % CI: 64 %, 76 %) and Cmax by 70 % (90 % CI: 62 %, 76 %) (see section 4.2).

Food Interaction: Administration of a single 50 mg dose of REVOLADE with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag AUC(0 –

inf) by 59 % (90 % CI: 54 %, 64 %) and Cmax 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 – inf) 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 monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of REVOLADE when lopinavir/ritonavir therapy is initiated or discontinued.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy:

Safety in pregnancy has not been established.

Lactation:

REVOLADE is secreted in rat milk. REVOLADE is not recommended for nursing mothers' breastfeeding their babies.

Fertility:

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see Section 5.3).

4.7 Effects on the ability to drive and use machines

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

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

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

The frequency categories used are:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10

Uncommon ≥ 1 in 1 000 and < 1 in 100

Rare ≥ 1 in 10 000 and < 1 in 1 000

Not known (cannot be estimated from the available data).

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

System organ class	Frequency	Adverse reaction
Infections and infestations	*Very common*	Nasopharyngitis♦, upper respiratory tract infection♦
	Common	Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis
	Uncommon	Skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Uncommon*	Rectosigmoid cancer
Blood and lymphatic system disorders	*Common*	Anaemia, eosinophilia, leukocytosis, thrombocytopenia, decreased haemoglobin, decreased white blood cell count
	Uncommon	Anisocytosis, haemolytic anaemia, myelocytosis, increased band neutrophil count, myelocyte present, increased platelet count, increased haemoglobin
Immune system disorders	*Uncommon*	Hypersensitivity
Metabolism and nutrition disorders	*Common*	Hypokalaemia, decreased appetite, increased blood uric acid
	Uncommon	Anorexia, gout, hypocalcaemia
Psychiatric disorders	*Common*	Sleep disorder, depression
	Uncommon	Apathy, mood altered, tearfulness
Nervous system disorders	*Common*	Paraesthesia, hypoaesthesia, somnolence, migraine
	Uncommon	Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, peripheral neuropathy, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache
Eye disorders	*Common*	Dry eye, vision blurred, eye pain, reduced visual acuity
	Uncommon	Lenticular opacities, astigmatism, cataract cortical, increased lacrimation, retinal haemorrhage, retinal pigment epitheliopathy, visual impairment, abnormal visual acuity tests, blepharitis, keratoconjunctivitis sicca
Ear and labyrinth disorders	*Common*	Ear pain, vertigo
Cardiac disorders	*Uncommon*	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged
Vascular disorders	*Common*	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, superficial thrombophlebitis, flushing
Respiratory, thoracic and mediastinal disorders	*Very common*	Cough♦
	Common	Oropharyngeal pain, rhinorrhoea♦

	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	*Very common*	Nausea, diarrhoea♦
	Common	Mouth ulceration, toothache♦, [~~dry mouth~~], vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in paediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	*Very common*	Increased alanine aminotransferase†
	Common	Increased aspartate aminotransferase†, hyperbilirubinaemia, hepatic function abnormalities
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	*Common*	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	*Common*	Myalgia, muscle spasm, musculoskeletal pain, bone pain, back pain
	Uncommon	Muscular weakness
Renal and urinary disorders	*Common*	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡
	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	*Common*	Menorrhagia
General disorders and administration site conditions	*Common*	Pyrexia*, chest pain, asthenia *Very common in paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	*Common*	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	*Uncommon*	Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1 to 17 years).

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

‡ Grouped term with preferred terms acute kidney injury and renal failure

SAA study population

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	*Common*	Neutropenia, splenic infarction
Metabolism and nutrition disorders	*Common*	Iron overload, decreased appetite, hypoglycaemia, increased appetite
Psychiatric disorders	*Common*	Anxiety, depression
Nervous system disorders	*Very common*	Headache, dizziness
	Common	Syncope
Eye disorders	*Common*	Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters
Respiratory, thoracic and mediastinal disorders	*Very common*	Cough, oropharyngeal pain, rhinorrhoea
	Common	Epistaxis
Gastrointestinal disorders	*Very common*	Diarrhoea, nausea, gingival bleeding, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence
Hepatobiliary disorders	*Very common*	Transaminases increased
	Common	Blood bilirubin increased (hyperbilirubinemia), jaundice
	Not known	Drug-induced liver injury* * Cases of drug-induced liver injury have been reported in patients with ITP and HCV when first used
Skin and subcutaneous tissue disorders	*Common*	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not known	Skin discolouration, skin hyperpigmentation
Musculosketal and connective tissue disorders	*Very common*	Arthralgia, pain in extremity, muscle spasms
	Common	Back pain, myalgia, bone pain
Renal and urinary disorders	*Common*	Chromaturia
General disorders and administration site conditions	*Very common*	Fatigue, pyrexia, chills
	Common	Asthenia, peripheral oedema, malaise

Investigations	*Common*	Increased blood creatine phosphokinase

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and Signs:

In the clinical trials there was one report of overdose where the subject ingested 5 000 mg of REVOLADE. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. The platelet counts were 672 000/µl on day 18 after ingestion and the maximum platelet count was 929 000/µl. All events resolved without sequelae following treatment.

Treatment:

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Re-initiate treatment with REVOLADE in accordance with dosing recommendations (see Section 4.2).

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

A 26 Cytostatics

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

inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

Eltrombopag does not antagonise platelet aggregation induced by ADP or collagen.

5.2 Pharmacokinetic Properties:

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 and 4.5).

The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution:

Eltrombopag is highly bound to human plasma proteins (> 99,9 %). Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Metabolism:

Eltrombopag is primarily metabolised 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 – inf). Minor metabolites, each accounting for < 10 % of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20 % of a dose is metabolised by oxidation. In vitro studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

Elimination:

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

In vitro evaluation of drug interaction potential

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes in vitro. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag and potential co-medications.

Based on a human study with radiolabelled eltrombopag, approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. In studies utilizing human liver microsomes, eltrombopag (up to 100 microM) showed no in vitro inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates, with IC50 values of 24.8 microM (11 microgram/mL) and 20.2 microM (8.9 microgram/mL), respectively.

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter, with an IC50 value of 2.7 microM (1.2 microg/mL) and an inhibitor of the BCRP transporter, with an IC50 value of 2.7 microM (1.2 microg/mL).

In vitro studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC50 value of 2.7 microM (1.2 microgram/mL). In vitro studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC50 value of 2.7 microM (1.2 microgram/mL)).

Special Patient Populations:

Paediatric population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Approximately 30% lower plasma eltrombopag CL/F was observed in patients of Asian race and 20% lower CL/F was observed in female patients. The bioavailability of the powder for oral suspension in paediatric patients was estimated as 29% lower than the film-coated tablet.

The pharmacokinetic parameters of eltrombopag in paediatric patients with ITP are shown in the table below.

Steady-state plasma eltrombopag pharmacokinetic parameters in paediatric patients with ITP

Age	**Cmax (microgram/mL)**	**AUCtau (microgram.hr/mL)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). AUCtau and Cmax based on population PK post-hoc estimates for a 50 mg once daily dose

Geriatric patients (60 years of age or above)

The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetic analysis in 28 healthy subjects and 635 patients with HCV ranging from 19 to 74 years old. Based on model estimates, elderly (>60 years) patients had approximately 36% higher plasma eltrombopag AUCtau as compared to younger patients.

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 AUCtau as compared to male ITP patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using a population pharmacokinetic analysis in 663 patients with HCV (260 females). Based on model estimates, female HCV patients had approximately 41% higher plasma eltrombopag AUCtau as compared to male patients.

Race/Ethnicity

ITP: The influence of Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (31 Asians) and 88 patients with ITP (18 Asians). Based on estimates from the population pharmacokinetic analysis, Asian (i.e., Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87% higher plasma

eltrombopag AUCtau values as compared to non-Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see section Section 4.2).

Renal Impairment

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

Hepatic Impairment

The pharmacokinetics of eltrombopag has been studied after administration of REVOLADE to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the AUC(0 – inf) of eltrombopag was increased by 41 % (90 % CI: 13 % decrease, 128 % increase) in patients with mild hepatic impairment, 93 % (90 % CI: 19 %, 213 %) in patients with moderate hepatic impairment, and 80 % (90 % CI: 11 %, 192 %) in patients with severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Patients with hepatic impairment should use REVOLADE with caution and close monitoring (see section 4.4). For patients with moderate and severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily (see section 4.2).

6 LIST OF PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS

Tablet core (25 mg and 50 mg): Magnesium stearate, mannitol, microcrystalline cellulose, povidone (K30), sodium starch glycolate Type A.

Contains sugar (mannitol): 29,7 mg per REVOLADE 25 mg tablet and 59,5 mg per REVOLADE 50 mg tablet.

Excipients of film-coating:

Tablet coating (25 mg): Hypromellose, macrogol 400, polysorbate 80, titanium dioxide (E171).

Tablet coating (50 mg): Hypromellose, iron oxide red (E172), iron oxide yellow (E172), macrogol 400, titanium dioxide (E171).

6.2 SHELF-LIFE

48 months

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C.

Do not remove blisters from the carton until required for use.

Keep out of reach of children.

6.4 NATURE AND CONTENTS OF THE CONTAINER

REVOLADE tablets are packed into silver aluminium-foil blister strips containing 7 tablets each.

The blister strip comprises an orientated polyamide / aluminium foil / polyvinyl chloride (PVC) laminate sealed with an aluminium foil lidding with a vinyl acrylic seal coating.

Two or four blister strips are packed into a carton giving a 14 or 28 tablet pack respectively.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West,

Waterfall City, Jukskei View

Johannesburg, 2090

8 REGISTRATION NUMBER:

REVOLADE 25 mg: 44/26/0548

REVOLADE 50 mg: 44/26/0549

9 DATE OF FIRST AUTHORISATION

9 June 2016

10 DATE OF REVISION OF THE TEXT

03 March 2022