SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medical product is subject to additional monitoring. This triangle will help to identify new safety information more quickly. You can assist by reporting any adverse reactions that occur. To learn how to report adverse reactions, please refer to the section 4.8.

1. NAME OF THE MEDICINAL PRODUCT

REVOPAG 25 mg Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each film-coated tablet contains 30.18 mg of eltrombopag sesqui-ethanolamine, equivalent to 25 mg of eltrombopag.

Excipients:

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex, film-coated tablet, with "25" engraved on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

REVOPAG is indicated for the treatment of patients from 1 year of age with chronic immune thrombocytopenic purpura (ITP) who are resistant to other treatments (e.g., corticosteroids, immunoglobulins, or splenectomy) or in whom splenectomy is contraindicated or not feasible (see Sections 4.2 and 5.1).

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Eltrombopag treatment should be initiated and administered by a physician experienced in the treatment of hematological disorders.

The dose of eltrombopag should be individualized based on the patient's thrombocyte count. The goal of treatment with eltrombopag is not to normalize thrombocyte counts.

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag necessary to achieve and maintain a thrombocyte count ≥50.000/microliter should be used. Dose adjustments should be based on the individual patient's thrombocyte count response. Eltrombopag should not be used to normalize thrombocyte counts. In clinical studies, thrombocyte counts generally increased within 1 to 2 weeks after initiating eltrombopag and decreased within 1 to 2 weeks after discontinuation of the medicinal product.

Paediatric aged 6 to 17 years and adult population
The recommended starting dose of eltrombopag is 50 mg taken once daily. For patients of East/Southeast Asian origin, treatment should be initiated with a reduced dose of eltrombopag, starting with 25 mg once daily (see Section 5.2).

Paediatri aged 1 to 5 years population
The recommended starting dose of eltrombopag is 25 mg once daily.

Monitoring and Dose Adjustment
After initiating eltrombopag therapy, the dose should be adjusted as necessary to achieve and maintain a thrombocyte count ≥50.000/microliter to reduce the risk of bleeding. The daily dose should not exceed 75 mg.

Clinical hematology and liver function tests should be monitored regularly during treatment with eltrombopag and the dose should be adjusted based on thrombocyte counts as outlined in Table 1. During eltrombopag treatment, complete blood count (CBC), including thrombocyte count and peripheral blood smear, should be evaluated weekly until a stable platalet count (≥50.000/microliter for at least 4 weeks) is achieved. Thereafter, CBC including thrombocyte count and peripheral blood smear should be monitored monthly.

Table 1: Dose adjustment of Eltrombopag in patients with ITP

Thrombocyte Count	Dose adjustment or response
Following at least 2 weeks of treatment < 50.000/microliter	The daily dose should be increased in 25 mg increments up to a maximum of 75 mg per day*
≥ 50.000/microliter to ≤ 150.000/microliter	Eltrombopag and/or concomitant ITP treatment should be administered at the lowest dose necessary to achieve a thrombocyte count sufficient to prevent or reduce bleeding.
> 150.000/microliter to ≤ 250.000/microliter	The daily dose should be decreased in 25 mg increments. Wait 2 weeks to assess the effect of this change and any subsequent dose adjustments**
> 250.000/microliter	Discontinue eltrombopag treatment and increase thrombocyte monitoring frequency to twice weekly. When the thrombocyte count is ≤ 100.000/microliter, restart treatment by reducing the daily dose by 25 mg.

*In patients receiving 25 mg eltrombopag every other day, the dose is increased to 25 mg once daily.

**In patients receiving 25 mg eltrombopag once daily, consideration should be given to administering 12.5 mg once daily or, alternatively, 25 mg every other day.

Eltrombopag may be used in addition to other ITP products. To prevent excessive increases in thrombocyte counts during eltrombopag treatment, adjust the dose regimen of concomitant ITP products as medically appropriate.

Before making any further dose adjustments, wait at least two weeks to observe the effect of the previous dose adjustment on the patient's thrombocyte levels.

The standard eltrombopag dose adjustment (increase or decrease) is 25 mg once daily.

Discontinuation of treatment
If thrombocyte counts do not rise to a sufficient level to prevent clinically significant bleeding after 4 weeks of eltrombopag treatment at a daily dose of 75 mg, eltrombopag treatment should be discontinued.

Patients should be evaluated periodically on a clinical basis, and the decision to continue treatment should be made individually by the treating doctor. In patients who have not undergone splenectomy, this evaluation should include consideration of splenectomy. The recurrence of thrombocytopenia after discontinuation of treatment is possible (see section 4.4).

Method of administration:
Tablets should be taken orally. Eltrombopag should be administered at least 2 hours before or at least 4 hours after taking products containing antacids, dairy products (or other calcium-containing foods), or mineral supplements containing polyvalent cations (e.g., iron, calcium, magnesium, aluminum, selenium, and zinc) (see sections 4.5 and 5.2).

Additional information for special populations:
Kidney failure:
No dose adjustment is necessary in patients with kidney failure. Eltrombopag should be used with caution in patients with kidney failure, and these patients should be closely monitored (e.g., by serum creatinine testing and/or urinalysis) (see section 5.2).

Liver failure:
Eltrombopag should not be used in ITP patients with liver failure (Child-Pugh score ≥ 5) unless the expected benefit outweighs the risk of portal vein thrombosis (see section 4.4).

If eltrombopag use is necessary in ITP patients with liver failure, the starting dose should be 25 mg once daily. After initiation of eltrombopag in patients with hepatic failure, wait 3 weeks before increasing the dose.

In thrombocytopenic patients (thrombocyte count <50.000/microliter) with chronic liver disease without accompanying ITP, administration of eltrombopag at a dose of 75 mg once daily for two weeks as preparation for invasive procedures has been associated with an increased risk of thromboembolic events (TEEs) (see sections 4.4 and 4.8).

Paediatric population:
Due to limited efficacy and safety data, REVOPAG is not recommended for use in children under 1 year of age with chronic ITP.

Geriatric population:
Limited data are available on the use of eltrombopag in patients aged 65 years and older with ITP, and there is no clinical experience in patients over 85 years of age with ITP. In clinical studies with eltrombopag, no clinically significant differences in safety were observed between subjects aged 65 years and older and younger subjects. Although no differences in response between elderly and younger subjects have been identified in reported clinical experience, increased sensitivity in some elderly patients cannot be excluded (see section 5.2).

Patients of East/Southeast Asian Origin:
Eltrombopag treatment in adult and paediatric ITP patients of East/Southeast Asian origin should be initiated at a dose of 25 mg once daily (see section 5.2).

Monitoring of the patient's thrombocyte count should continue, and standard criteria should be followed for subsequent dose adjustments.

4.3. Contraindications
REVOPAG is contraindicated in patients with 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 may cause abnormal liver function and severe hepatotoxicity, which can be life-threatening (see section 4.8).

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels should be measured before starting eltrombopag treatment, every 2 weeks during the dose adjustment phase, and monthly after a stable dose has been established. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin levels increase, fractionation should be checked. Abnormal serum liver tests should be rechecked within 3 to 5 days for evaluation. If abnormalities are confirmed, abnormal serum liver tests should be monitored until they resolve, stabilize, or return to baseline values. Eltrombopag should be discontinued if ALT levels increase (in patients with normal liver function, if ALT

exceeds ≥3 times the upper limit of normal [x ULN], or in patients with elevated transaminases prior to treatment, if ALT reaches ≥3 times baseline or >5 x ULN, [whichever is lower]) and if any of the following conditions apply:

- the increase is progressive, or
- it lasts ≥ 4 weeks or,
- it is accompanied by an increase in direct bilirubin levels, or
- clinical symptoms of liver injury or evidence of hepatic decompensation are present.

Eltrombopag should be used with caution in patients with liver disease. In ITP patients with hepatic failure, treatment should be initiated at a lower starting dose. Close monitoring is required when eltrombopag is administered to patients with hepatic failure (see section 4.2).

Hepatic decompensation (in combination with interferon):
Liver decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤35 g/L) or a baseline model for end-stage liver disease (MELD) score ≥10.

Thrombotic/thromboembolic complications:
An increased risk of TEO was identified in patients with chronic liver disease who received eltrombopag 75 mg once daily for two weeks as preparation for invasive procedures. 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced TEO (all in the portal venous system) and 2 of 145 (1%) subjects in the placebo group experienced TEO (one in the portal venous system, one myocardial infarction). Five of the 6 eltrombopag-treated patients who developed thrombotic complications had thrombocyte counts above 200.000/microliter and experienced the event within 30 days after the last dose of eltrombopag.
Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In ITP clinical trials of eltrombopag, thromboembolic events have been observed at both low and normal thrombocyte counts. Caution should be exercised when using eltrombopag in patients with known risk factors for thrombosis, including but not limited to hereditary (e.g., Factor V Leiden) or acquired risk factors (e.g., ATIII deficiency, antiphospholipid syndrome), older age, prolonged immobilisation, malignancy, contraceptive or hormone replacement therapy, surgery/trauma, obesity, and smoking. Thrombocyte counts should be closely monitored, and if counts exceed target levels, dose reduction or interruption of eltrombopag treatment should be considered (see section 4.2). The risk-benefit balance should be considered in patients at risk for thromboembolic events (TEO) of any etiology.
No cases of TEO were identified in a clinical study of refractory SAA, but the risk for these events cannot be excluded because the number of patients exposed in this patient population was limited.

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

Bleeding after discontinuation of eltrombopag treatment:
Recurrence of thrombocytopenia is possible in patients with ITP after discontinuation of treatment with eltrombopag. In most patients, thrombocyte counts return to baseline levels within two weeks after stopping eltrombopag, which may increase the risk of bleeding and, in some cases, lead to bleeding events. This risk is elevated if eltrombopag is discontinued while the patient is receiving anticoagulant or antithrombocyte therapy. When eltrombopag is discontinued, re-initiation of ITP treatment according to current clinical guidelines is recommended. Additional medical management may include discontinuation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet supplementation. Thrombocyte counts should be monitored weekly for 4 weeks following discontinuation of eltrombopag.

Risk of bone marrow reticulin formation and bone marrow fibrosis:
Eltrombopag may increase the risk of development or progression of reticulin fiber formation within the bone marrow. As with other thrombopoietin receptor (TPO-R) agonists, the clinical significance of this finding has not yet been established.

Before initiating eltrombopag treatment, a peripheral blood sample should be closely examined to establish a baseline for cellular morphological abnormalities. After a stable dose of eltrombopag has been established, a complete blood count (CBC) with white blood cell differential (WBC) should be performed monthly. If immature or dysplastic cells are observed, peripheral blood samples should be evaluated for new or worsening morphological abnormalities (e.g., teardrop-shaped and nucleated red blood cells, immature leukocytes) or cytopenias. If new morphological abnormalities or cytopenias develop in patient, or if existing findings worsen, eltrombopag treatment should be discontinued and a bone marrow biopsy, including staining for fibrosis, should be considered.

Progression of Existing Myelodysplastic Syndrome (MDS):
There is a theoretical concern that TPO-R agonists may stimulate the progression of existing hematologic malignancies such as MDS. TPO-R agonists are growth factors that promote the expansion, differentiation, and thrombocyte production of thrombopoietic progenitor cells. The TPO-R is predominantly expressed on cells of the myeloid lineage.

In clinical trials of TPO-R agonists in patients with MDS, transient increases in blast cell counts have been observed, and cases of progression from MDS to acute myeloid leukaemia (AML) have been reported. In adults and elderly patients, the diagnosis of ITP should be confirmed by excluding other clinical conditions associated with thrombocytopenia, particularly MDS.

During the course of disease and treatment, bone marrow aspiration and biopsy should be considered, especially in patients over the age of 60, those with systemic symptoms, or those with abnormal signs such as increased peripheral blasts.
The safety and efficacy of eltrombopag for the treatment of thrombocytopenia due to MDS have not been established. Eltrombopag should not be used for the treatment of MDS-related thrombocytopenia outside of clinical studies.

Ocular changes:
Cataracts have been observed in toxicology studies with eltrombopag in rodents (see section 5.3). Hemorrhages may occur on the retinal (preretinal) surface, beneath the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring is recommended for patients.

QT/QTc prolongation:
In a QTc study conducted in healthy volunteers at a dose of 150 mg/day, eltrombopag did not show any clinically significant effect on cardiac repolarization. Prolongation of the QTc interval has been reported in clinical studies in ITP patients, but the clinical significance of this finding is unknown.

Loss of response to eltrombopag:
If there is a loss of response or failure to maintain a thrombocyte response during treatment with eltrombopag within the recommended dose range, potential causes including increased bone marrow reticulin formation should be investigated.
Paediatric population:
The above warnings and precautions related to ITP also apply to the paediatric population.

Interference with laboratory tests:
Eltrombopag has a dark color and has the potential to interfere with some laboratory tests. Interactions have been reported with total bilirubin and creatinine assays in patients receiving eltrombopag, accompanied by discoloration in serum. If laboratory test results are inconsistent with clinical observations, re-testing using an alternative method may help determine the validity of the results.

4.5. Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products
HMG-CoA Reductase Inhibitors:
In a study where 39 healthy adult subjects received eltrombopag 75 mg once daily for 5 days along with a single dose of 10 mg rosuvastatin a substrate of OATP1B1 and BCRP, the C_{max} of rosuvastatin increased by 103% (90% CI: 82%, 126%) and $AUC_{0-\infty}$ increased by %55 (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors including pravastatin, simvastatin, atorvastatin, fluvastatin, and lovastatin. When co-administered with eltrombopag, a lower statin dose should be considered, and patients should be carefully monitored for statin's adverse effects (see section 5.2).

OATP1B1 and BCRP substrats:
Caution is advised when administering substrates of OATP1B1 (e.g., methotrexate) and BCRP (e.g., topotecan and methotrexate) concomitantly with eltrombopag (see section 5.2).

Cytochrome P450 substrates:
Studies using human liver microsomes have shown that eltrombopag (up to 100 µM) does not exhibit *in vitro* inhibition of CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11, but it showed inhibitory effects on CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as probe substrates. In a clinical study involving 24 healthy male volunteers administered eltrombopag 75 mg once daily for 7 days, no inhibition or induction of the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) was observed. Clinically relevant interactions between eltrombopag and CYP450 substrates are not expected (see section 5.2).

Effects of other drugs on eltrombopag
Cyclosporine:
A decrease in eltrombopag exposure was observed with concomitant administration of 200 mg and 600 mg of cyclosporine (BCRP inhibitor). Co-administration of 200 mg cyclosporine decreased eltrombopag Cmax and $AUC_{0-\infty}$ by 25% and 18%, respectively. Co-administration of 600 mg cyclosporine decreased eltrombopag Cmax and $AUC_{0-\infty}$ by 39% and 24%, respectively. Dose adjustment of eltrombopag based on thrombocyte counts is allowed during treatment (see section 4.2). When used concomitantly with cyclosporine, thrombocyte counts should be monitored at least weekly for 2–3 weeks. Dose increases of eltrombopag may be necessary based on thrombocyte counts.

Polyvalent cations (chelation):
Eltrombopag forms chelates with multivalent cations such as iron, calcium, magnesium, aluminum, selenium, and zinc. Co-administration of a single 75 mg dose of eltrombopag with an antacid containing multivalent cations (1524 mg aluminum hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). To avoid clinically significant reductions in eltrombopag absorption due to chelation, eltrombopag should be administered at least 2 hours before or 4 hours after other products containing multivalent cations such as antacids, dairy products, or mineral supplements (see section 4.2).

Lopinavir/ritonavir:
Co-administration of eltrombopag with lopinavir/ritonavir may reduce eltrombopag plasma concentrations. A study in 40 healthy volunteers showed that co-administration of a single 100 mg dose of eltrombopag and a repeat-dose twice-daily regimen of lopinavir/ritonavir 400/100 mg resulted in a 17% decrease in eltrombopag plasma $AUC_{0-\infty}$ (90% CI: 6.6%; 26.6%). Therefore, caution should be exercised if eltrombopag and lopinavir/ritonavir are co-

administered. Platelet counts should be closely monitored to ensure appropriate maintenance of eltrombopag dosage when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers:
Eltrombopag is metabolized via multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect eltrombopag plasma concentrations; however, medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g., fluvoxamine) or decrease (e.g., rifampicin) eltrombopag concentrations.

Medicinal products for ITP treatment:
In clinical studies, eltrombopag has been used concomitantly with corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin in the treatment of ITP. Platelet counts should be monitored when eltrombopag and other drugs used in the treatment of ITP are used in combination to prevent platelet counts from exceeding the recommended range (see section 4.2).

Interaction with food
Co-administration of eltrombopag tablets with foods high in calcium (e.g., meals containing dairy products) significantly decreases plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or a low-calcium meal [<50 mg calcium] does not result in clinically relevant effect in plasma eltrombopag exposure (see section 4.2).

A single 50 mg eltrombopag in tablet form administered with a standard high-calorie, high-fat breakfast containing dairy products reduced plasma eltrombopag average $AUC_{0-\infty}$ by 59% and mean C_{max} 65%.

A single 25 mg dose of eltrombopag as oral suspension powder administered with a high-calcium, moderate-fat, moderate-calorie meal decreased average plasma eltrombopag $AUC_{0-\infty}$ by 75% and mean C_{max} 79%. When administered 2 hours before a high-calcium meal, this reduction in exposure was less pronounced (average $AUC_{0-\infty}$ decresed by 20% and mean C_{max} by 14%).

Low-calcium (<50 mg calcium) foods such as fruit, lean ham, beef, additive-free fruit juice (without added calcium, magnesium or iron), additive-free soy milk, and additive-freegrains, regardless of calorie and fat content, did not significantly affect plasma eltrombopag exposure (see sections 4.2 and 4.5).

Additional information on special populations
There are no available data.

Pediatric population:
There are no available data.

4.6. Pregnancy and lactation

General recommendations
Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)
REVOPAG is not recommended for women of childbearing potential who are not using contraception. Women of childbearing potential must use effective contraception during treatment.

Pregnancy
There are no adequate data from the use of eltrombopag in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

The use of REVOPAG during pregnancy is not recommended.

Lactation
It is unknown whether eltrombopag or its metabolites are excreted in human milk. Animal studies have shown that eltrombopag is likely to be excreted in milk (see section 5.3), therefore a risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from eltrombopag therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the nursing mother.

Reproductive ability/Fertility
Fertility was not affected in male and female rats at exposures similar to those in humans. However, it cannot be said with certainty that there is no risk to humans (see section 5.3).

4.7. Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. When assessing a patient's ability to perform tasks that require judgment, motor or cognitive skills, the patient's clinical condition and the adverse reaction profile of eltrombopag, including dizziness and decreased attention, should be taken into account.

4.8. Undesirable effects

Summary of the safety profile:
Immune thrombocytopenia in adult and paediatric patients
The safety of eltrombopag was assessed using data from the completed open-label (n=360) studies TRA108057 (REPEAT), TRA105325 (EXTEND), and TRA112940 in adult patients

(n=763), in addition to pooled double-blind, placebo-controlled studies TRA100773A and B, TRA102537 (RAISE), and TRA113765, in which 403 patients received eltrombopag and 179 patients received placebo (see Section 5.1). Patients received the study drug for up to 8 years (in the EXTEND study). The most serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions, reported in ≥10% of patients, included nausea, diarrhoea, increased alanine aminotransferase, and back pain.

The safety of eltrombopag in previously treated paediatric patients (aged 1 to 17 years) with ITP has been demonstrated in two studies (n=171) (see section 5.1). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomised, placebo-controlled study. Patients were randomised in a 2:1 ratio and received eltrombopag (n=63) or placebo (n=29) for up to 13 weeks during the randomised phase of the study. PETIT (TRA108062) was a three-part, open-label and double-blind, randomised, placebo-controlled study with non-overlapping patient cohorts. Patients were randomised in a 2:1 ratio and received eltrombopag (n=44) or placebo (n=21) for up to 7 weeks. The adverse reaction profile was generally similar to that observed in adults, with the addition of a few adverse reactions marked with *. In paediatric patients aged 1 year and older with ITP, the most common adverse reactions (≥3% and occurring more frequently than with placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache, and rhinorrhoea.

Severe aplastic anaemia in adult patients

The safety of eltrombopag in severe aplastic anaemia was evaluated in a single-arm, open-label study (N=43); in this study, 11 patients (26%) being treated for >6 months, and 7 patients (16%) for >1 year (see section 5.1). The most common adverse reactions occurring in at least 10% of patients included: headache, dizziness, cough, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, increased transaminases, arthralgia, pain in extremities, muscle spasms, fatigue, and pyrexia.

List of adverse reactions:

Adverse reactions considered by investigator to be treatment-related [studies for adult ITP (N=763), studies for pediatric ITP (N=171), studies for SAA (N=43), and post-marketing reports] are listed below by MedDRA body organ system classification and frequency.

Tabulated list of adverse reactions

Adverse reactions from adult ITP studies (N=763), pediatric ITP studies (N=171), SAA studies (N=43), and postmarketing reports are listed below by MedDRA system organ class and frequency. Within each system organ class, adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, for each adverse drug reaction, the corresponding frequency category is based on the following convention:

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), unknown (cannot be estimated from available data).

ITP study population:

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

Benign and malignant neoplasms (including 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, presence of myelocytes, increased thrombocyte count, increased haemoglobin

Immune system disorders

Uncommon:	Hypersensitivity

Metabolism and nutrition disorders

Common:	Hypokalemia, decreased appetite, increased blood uric acid level
Uncommon:	Anorexia, gout, hypocalcemia

Psychiatric disorders

Common:	Sleep disorder, depression
Uncommon:	Apathy, mood swings, frequent crying

Nervous system disorders

Common:	Paresthesia, hypoesthesia, somnolence, migraine
Uncommon:	Tremor, balance disorder, dysesthesia, hemiparesis, migraine with aura, peripheral neuropathy, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache

Eye disorders

Common:	Dry eye, blurred vision, eye pain, decreased visual acuity
Uncommon:	Lenticular opacities, astigmatism, cortical cataract, increased lacrimation, retinal hemorrhage, retinal pigment epitheliopathy, visual

failure, abnormal visual acuity tests, blepharitis, keratoconjunctivitis sicca

Ear and internal ear disorders

Common: Ear pain, vertigo

Cardiac disorders

Uncommon: Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, QT prolongation on electrocardiogram

Vascular disorders

Common: Deep vein thrombosis, hematoma, hot flush

Uncommon: Embolism, superficial thrombophlebitis, facial flushing

Respiratory, thoracic and mediastinal disorders

Very common: Cough*

Common: Oropharyngeal pain*, rhinorrhea*

Uncommon: Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal cracking, sinus disorder, sleep apnea syndrome

Gastrointestinal disorders

Very common: Nausea, diarrhea*

Common: Mouth ulceration, toothache*, vomiting, abdominal pain×, oral hemorrhage, flatulence

Uncommon: Dry mouth, glossodynia, abdominal tenderness, discolored stool, food poisoning, frequent bowel movements, hematemesis, oral discomfort

Hepatobiliary disorders

Very common: Increased alanine aminotransferase**

Common: Increased aspartate aminotransferase**, hyperbilirubinemia, abnormal hepatic function

Uncommon: Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury

Skin and subcutaneous tissue disorders

Common: Rash, alopecia, hyperhidrosis, generalized pruritus, petechiae

Uncommon: Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discoloration, skin exfoliation

Musculoskeletal disorders, connective tissue and bone diseases

Very common: Back pain

Common: Myalgia, muscle spasm, bone pain, musculoskeletal pain

Uncommon: Muscle weakness

Kidney and urinary disorders
Common: Proteinuria, increased blood creatinine, thrombotic microangiopathy with kidney failure***
Uncommon: Kidney failure, leukocyturia, lupus nephritis, nocturia, increased blood urea, increased urine protein/creatinine ratio

Reproductive system and breast disorders
Common: Menorrhagia

General disorders and administration site conditions
Common: Pyrexia×, chest pain, asthenia
Uncommon: Hot flush, hemorrhage at venipuncture site, irritability, inflammation at wound sites, fracture, foreign body sensation

Investigations
Common: Increased blood alkaline phosphatase
Uncommon: Increased blood albumin, increased total protein, decreased blood albumin, increased urine pH

Injury and poisoning
Uncommon: Sunburn

*Additional adverse reactions observed in pediatric studies (ages 1 to 17)
× Very common in pediatric ITP
**Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously at low frequency
***Acute kidney injury and kidney failure terms grouped preferentially

SAA study population:

Blood and lymphatic system disorders
Common: Neutropenia, splenic infarction

Metabolism and nutrition disorders
Common: Iron overload, decreased appetite, hypoglycemia, increased appetite

Psychiatric disorders
Common: Anxiety, depression

Nervous system disorders

Very common: Headache, dizziness
Common: Syncope

Eye disorders
Common: Dry eye, cataract, yellowing of sclera, blurred vision, visual failure, vitreous floaters

Respiratory, thoracic and mediastinal disorders
Very common: Cough, oropharyngeal pain, rhinorrhea
Common: Epistaxis

Gastrointestinal disorders
Very common: Diarrhea, nausea, gingival bleeding, abdominal pain
Common: Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, discolored stool, tongue swelling, gastrointestinal motility disorder, flatulence

Hepatobiliary disorders
Very common: Increased transaminases
Common: Increased blood bilirubin (hyperbilirubinemia), jaundice
Unknown: Drug-induced liver injury*

Skin and subcutaneous tissue disorders
Common: Petechiae, rash, pruritus, urticaria, skin lesion, macular rash
Unknown: Skin discoloration, skin hyperpigmentation

Musculoskeletal disorders, connective tissue and bone diseases
Very common: Joint pain, limb pain, muscle spasms
Common: Back pain, muscle pain, bone pain

Kidney and urinary disorders
Common: Chromaturia

General disorders and administration site conditions
Very common: Fatigue, pyrexia, chills
Common: Asthenia, peripheral edema, fracture

Investigations
Common: Increased blood creatine phosphokinase

*Cases of drug-induced liver injury have been reported in patients with ITP.

Selected adverse reactions explanations

Thrombotic/thromboembolic events (TEOs)

In adult chronic ITP patients receiving eltrombopag in 3 controlled and 2 uncontrolled clinical studies (n=446), a total of 19 TEOs occurred in 17 patients and included (in descending order) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), and embolism (n=1) (see Section 4.4).

In a placebo-controlled study (n=288, safety population) following 2 weeks of treatment in preparation for an invasive procedure, 6 of 143 (4%) patients with chronic liver disease receiving eltrombopag experienced 7 thromboembolic events in the portal venous system and 2 of 145 (1%) subjects in the placebo group experienced 3 TEOs. 5 of 6 patients treated with eltrombopag experienced TEOs with platelet counts>200,000/mikroliter.

Except for patients with thrombocyte counts ≥ 200.000/microliter, no specific risk factors were identified in patients who experienced TEO.

Hepatotoxicity

In controlled clinical trials in chronic ITP, elevations in serum ALT, AST, and bilirubin have been observed with eltrombopag treatment (see section 4.4).

These findings were mostly mild (Grade 1–2), reversible, and not associated with clinically significant symptoms of liver dysfunction. Across three placebo-controlled studies in adult patients with chronic ITP, Grade 4 liver test abnormalities were reported in one patient each from the eltrombopag and placebo groups. In two placebo-controlled studies in pediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 x ULN was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In the single-arm phase II monotherapy study of SAA refractory to treatment, concomitant ALT or AST > 3 x ULN with total (indirect) bilirubin > 1.5 x ULN was reported in 5% of patients. Total bilirubin > 1.5 x ULN occurred in 14% of patients.

Thrombocytopenia following discontinuation of treatment

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

Increased bone marrow reticulin

Throughout the program, no clinically significant bone marrow abnormalities or evidence of clinical findings indicative of bone marrow dysfunction were observed in any of the subjects. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see Section 4.4).

Cytogenetic abnormalities
In a phase II clinical trial of SAA patients who did not respond to eltrombopag treatment with a starting dose of 50 mg/day (increased to a maximum of 150 mg/day every 2 weeks) (ELT112523), the incidence of new cytogenetic abnormalities was 17.1% in adult patients [7/41 (changes in chromosome 7 were detected in 4 of them)]. The median time to detection of a cytogenetic abnormality was 2.9 months.

In a phase II clinical trial (ELT116826) conducted in SAA patients who did not respond to treatment with eltrombopag at a dose of 150 mg/day (with ethnic or age-related modifications as indicated), the incidence of new cytogenetic abnormalities was 22.6% in adult patients [7/31 (3 of whom had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients developed cytogenetic abnormalities by month 3, and one by month 6 of treatment.

Haematological malignancies
In a single-arm, open-label SAA study, three out of three (7%) patients were diagnosed with MDS after treatment with eltrombopag. In two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) patients were diagnosed with MDS or AML.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

In the event of overdose, thrombocyte counts may increase excessively and may lead to thrombotic/thromboembolic complications. In case of overdose, oral administration of a metal cation-containing preparation such as calcium, aluminium or magnesium preparations should be considered to chelate eltrombopag and thereby limit its absorption. Thrombocyte counts should be closely monitored. Eltrombopag therapy should be restarted according to the recommended dosing and administration guidelines (see section 4.2).

A case of overdose with 5000 mg of eltrombopag was reported in one subject in ITP clinical trials. Reported adverse reactions included mild rash, transient bradycardia, elevations in ALT and AST, and fatigue. Liver enzymes measured between Days 2 and 18 post-ingestion showed AST at 1.6 × ULN, ALT at 3.9 × ULN, and total bilirubin at 2.4 × ULN. Thrombocyte counts were 672.000/microliter on Day 18 post-ingestion, with a maximum thrombocyte count of 929.000/microliter. All events resolved without sequelae following treatment.

Since eltrombopag is not significantly excreted via the kidney route and is highly bound to plasma proteins, haemodialysis is not expected to be an effective method for enhancing eltrombopag elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics
ATC code: B02BX05

Mechanism of action

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

Clinical efficacy and safety

Clinical studies

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

The safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP were evaluated in two Phase III, randomized, double-blind, placebo-controlled studies (RAISE [TRA102537] and [TRA100773B]) and two open-label studies (REPEAT [TRA108057] and EXTEND [TRA105325]). Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and to 202 patients for at least 1 year.

Double-Blind, Placebo-Controlled Studies

RAISE: 197 ITP patients were randomized 2:1 to receive eltrombopag (n=135) or placebo (n=62), with randomization stratified by splenectomy status, baseline ITP medication use, and baseline thrombocyte count. The dose of eltrombopag was adjusted during the 6-month treatment period based on individual thrombocyte counts. All patients initiated treatment with a dose of 50 mg eltrombopag. Between Day 29 and the end of treatment, 15% to 28% of patients in the eltrombopag group were maintained on a dose of ≤25 mg, while 29% to 53% received the 75 mg dose.

In addition, patients were allowed to reduce doses of concomitant ITP medications and to receive rescue therapy as per local standard practice. More than half of the patients in each treatment group had received ≥3 prior ITP therapies, and 36% had undergone splenectomy.

Median baseline thrombocyte counts were 16.000/microliter in both treatment groups. In the eltrombopag group, median thrombocyte counts remained above 50.000/microliter at all study visits starting from Day 15, while in the placebo group, median counts remained below 30.000/microliter throughout the study.

Thrombocyte count responses in the range of 50.000–400.000/microliter without rescue therapy were achieved in a significantly higher proportion of patients in the eltrombopag group during the 6-month treatment period ($p < 0.001$). After 6 weeks of treatment, 54% of patients in the eltrombopag group and 13% in the placebo group achieved this response. This response was maintained throughout the study, with 52% and 16% of patients in the eltrombopag and placebo groups, respectively, maintaining this response at the end of the 6-month treatment period.

Table 3: Secondary efficacy outcomes in the RAISE Study

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Cumulative number of weeks with thrombocyte count ≥ 50.000-400.000/microliter, Average (SS)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments within target range (50.000 ila 400.000/microliter), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients experiencing bleeding at any time during the 6-month period (WHO Grade 1-4), n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients experiencing bleeding at any time during the 6-month (WHO Grade 2-4), n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Patients requiring rescue treatment, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients previously treated for ITP (n)	63	31
Patients who discontinued or reduced their initial treatment, n (%)[b]	37 (59)	10 (32)
P-value [a]	0.016	

a - Logistic regression model adjusted for randomization stratification variables
b - In the eltrombopag group, 21 out of 63 patients (33%) who were using 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 Grade 1-4), and more than 20% reported clinically significant bleeding (WHO Grade 2-

4). The proportion of patients reporting any bleeding (Grade 1-4) and clinically significant bleeding (Grade 2-4) in the eltrombopag group decreased by approximately 50% from day 15 through the end of the 6-month treatment period compared to baseline.

TRA100773B: In the TRA100773B study, the primary efficacy endpoint was defined as the proportion of ITP patients who responded by increasing their thrombocyte count from <30.000/microliter at baseline to ≥ 50.000/microliter on day 43. Patients who discontinued treatment early due to thrombocyte counts >200.000/microliter were considered responders, while patients who discontinued treatment for any other reason were considered non-responders in terms of thrombocyte count. A total of 114 subjects previously treated for chronic ITP were randomized 2:1 to receive eltrombopag (n=76) or placebo (n=38).

Table 4: Efficacy Results in the TRA100773B Study

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Number eligible for efficacy analysis, n	73	37
Patients with thrombocyte count ≥ 50.000/microliter olan hastalar up to dosing day 42 (compared to baseline count <30.000/microliter), n (%)	43 (59)	6 (16)
P-value [a]	< 0.001	
Key secondary endpoints		
Patients assessed for bleeding on day 43, n	51	30
Bleeding (WHO Grade 1-4), n (%)	20 (39)	18 (60)
P-value [a]	0.029	

a - Logistic regression model adjusted for randomization stratification variables

Both in RAISE and TRA100773B studies, the response to eltrombopag compared to placebo was similar regardless of prior ITP medication use, splenectomy status, and baseline thrombocyte count at randomization (≤ 15.000/microliter, >15.000/microliter).

In the subgroup of ITP patients with baseline thrombocyte counts ≤ 15.000/microliter in the RAISE and TRA100773B studies, median thrombocyte counts did not reach the target level (> 50.000/microliter); however, a response was achieved after 6 weeks of treatment in 43% of patients receiving eltrombopag in both studies. Additionally, in the RAISE study, 42% of patients with baseline thrombocyte counts ≤ 15.000/microliter who received eltrombopag treatment achieved a response at the end of 6 months. Between Day 29 and the end of treatment, 42% to 60% of patients treated with eltrombopag in the RAISE study received a 75 mg dose.

Open-label uncontrolled studies:
REPEAT (TRA108057): his open-label, multiple-dose study (three 6-week cycles followed by a 4-week drug-free period) demonstrated no loss of response with episodic use of multiple eltrombopag cycles.
EXTEND (TRA105325): In this open-label extension study, eltrombopag was administered to 302 patients. Treatment duration completion rates were as follows: 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years, and 18 completed 6 years. The median baseline thrombocyte count before eltrombopag administration was 19,000/µl. Median thrombocyte counts at years 1, 2, 3, 4, 5, 6, and 7 of the study were 85,000/µL, 85,000/µL, 105,000/µL, 64,000/µL, 75,000/µL, 119,000/µL, and 76,000/µL, respectively.
No studies comparing eltrombopag with other treatment options (e.g., splenectomy) have been conducted. The long-term safety of eltrombopag should be considered before starting treatment.

Pediatric population (1 to 17 years old)
The safety and efficacy of eltrombopag in pediatric patients have been investigated in two studies.

TRA115450 (PETIT2): The primary endpoint was defined as the proportion of patients treated with eltrombopag who achieved a sustained response, reaching thrombocyte counts ≥ 50.000/microliter for at least 6 of 8 weeks between weeks 5 and 12 of the double-blind randomized period versus placebo. Volunteers had a diagnosis of chronic ITP for at least 1 year prior and either did not respond to at least one previous ITP treatment, relapsed during treatment, or were unable to continue other ITP treatments for medical reasons, with thrombocyte counts <30.000/microliter. Ninety-two volunteers were randomized (2:1) by three age groups to eltrombopag (n=63) or placebo (n=29). Eltrombopag dosing was adjusted individually based on thrombocyte counts.

Overall, a statistically significantly greater proportion of patients treated with eltrombopag (40%) compared to placebo (3%) achieved the primary endpoint (Odds ratio: 18.0 [95 GA % 2.3; 140.9] p <0.001), with similar results across the three age groups (see Table 5).

Table 5: Sustained thrombocyte response by age group in paediatric patients with chronic ITP

	Eltrombopag n/N (%) [95% GA]	Placebo n/N (%) [95% GA]
Group 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]

Group 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Group 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

During the randomized period, significantly fewer patients in the eltrombopag group required rescue therapy compared to placebo (19% [12/63] karşısında 24% [7/29], p=0.032).

At baseline, 71% of patients in the eltrombopag group and 69% of patients in the placebo group reported any bleeding (WHO Grade 1–4). By Week 12, the proportion of eltrombopag patients reporting any bleeding was halved compared to baseline (36%), whereas 55% of placebo patients reported bleeding at Week 12.

Patients were only allowed to reduce or discontinue their initial ITP therapy during the open-label phase of the study. 53% of patients (8/15) were able to reduce (n=1) or discontinue (n=7) their initial ITP therapy, mostly corticosteroids, without requiring rescue therapy.

TRA108062 (PETIT): The primary endpoint was defined as the proportion of patients who achieved a thrombocyte count ≥ 50.000/microliter at least once between Weeks 1 and 6 of the randomized period. Patients (n=67) had thrombocyte counts < 30.000/microliter and had either not responded to at least one previous ITP therapy or had relapsed during treatment. During the randomized phase, patients were assigned to eltrombopag (n=45) or placebo (n=22) in a 2:1 ratio, stratified by three age groups. The eltrombopag dose was adjusted individually based on thrombocyte counts.

Overall, a statistically significantly greater proportion of eltrombopag patients (62%) achieved the primary endpoint compared to placebo patients (32%) (Odds ratio: 4.3 [95% GA: 1.4; 13.3] p=0.011).

In the PETIT 2 study, a sustained response was observed in 50% of initial responders for 20 out of 24 weeks; in the PETIT study, a sustained response was observed in 15 out of 24 weeks.

5.2. Pharmacokinetic properties

General properties

Plasma eltrombopag concentration–time data obtained from 88 patients in the TRA100773A and TRA100773B studies were combined with data obtained from 111 healthy adult subjects in a PK analysis. Plasma eltrombopag $EAA_{0-\tau}$ and C_{max} estimates for ITP patients are presented in Table 6.

Table 6: Geometric average (95% confidence interval) of steady-state plasma eltrombopag pharmacokinetic parameters in adult ITP patients

Eltrombopag dose once daily	N	AUC $_{(0-\tau)}$[a], microgram.s/mL	C_{max}[a], microgram/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; 14.5)

a –$EAA_{0-\tau}$ ve C_{max} derived from population PK post-hoc calculations

Absorption:
Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The concomitant administration of antacids, dairy products, and other products containing polyvalent cations such as mineral supplements significantly reduces eltrombopag exposure (see Section 4.2). The absolute oral bioavailability of eltrombopag in humans is unknown. Based on urinary excretion and metabolites eliminated in feces, it has been estimated that at least 52% of a single 75 mg eltrombopag solution dose is orally absorbed.

Distribution:
Eltrombopag is highly bound to plasma proteins in humans, primarily to albumin (>99.9%). Eltrombopag is a substrate for BCRP but not a substrate for P-glycoprotein or OATP1B1.

Biotransformation:
Eltrombopag is mainly metabolized via hydrolysis, oxidation, and conjugation pathways involving glucuronic acid, glutathione, or cysteine. In a radiolabeled human study, eltrombopag accounted for approximately 64% of plasma radiocarbon $EAA_{0-\infty}$. Minor metabolites formed through glucuronidation and oxidation were also detected. In vitro studies suggest that CYP1A2 and CYP2C8 enzymes are responsible for the oxidative metabolism of eltrombopag. The enzymes uridine diphosphoglucuronosyltransferase (UGT) 1A1 and UGT1A3 are identified as responsible for glucuronidation, while gut bacteria in the lower gastrointestinal tract are thought to play a role in hydrolysis.

Elimination:
Absorbed eltrombopag is extensively metabolized. The main elimination route is feces (59%), with 31% of the dose recovered as metabolites in urine. Unchanged eltrombopag is not detected in urine. Approximately 20% of the dose is excreted unchanged in feces. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours.

Pharmacokinetic interactions
A study with radiolabeled eltrombopag in humans showed glucuronidation plays a minor role in eltrombopag metabolism. Studies with human liver microsomes identified UGT1A1 and UGT1A3 as enzymes responsible for glucuronidation. Eltrombopag inhibits some UGT enzymes *in vitro*. However, due to the limited contribution of individual UGT enzymes to eltrombopag glucuronidation, clinically significant drug interactions involving glucuronidation are not expected.

About 21% of eltrombopag is subject to oxidative metabolism. CYP1A2 and CYP2C8 have been identified as enzymes responsible for eltrombopag oxidation in human liver microsome studies. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see Section 4.5).

In vitro studies have shown that eltrombopag is an inhibitor of OATP1B1 and BCRP transporters and that eltrombopag increases the exposure of rosuvastatin, a substrate of OATP1B1 and BCRP, in a clinical drug interaction study (see Section 4.5). Dose reduction of statins by 50% is recommended during eltrombopag treatment.

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

İn vitro studies have also shown that eltrombopag is not a substrate of the organic anion transporting polypeptide OATP1B1 but is an inhibitor of this transporter (IC_{50} value 2.7 µM (1.2 µg/ml). Additionally, *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC_{50} value of 2.7 µM (1.2 µg/ml)).

Linearity/Non-linearity:
The absolute oral bioavailability of eltrombopag after administration to humans has not been demonstrated. Based on urinary excretion and metabolites eliminated in feces, the oral bioavailability of drug-related material following a single 75 mg eltrombopag solution dose is estimated to be at least 52%.

Patient Characteristics
Kidney failure:
The pharmacokinetics of eltrombopag have been studied in adult subjects with kidney failure after administration of eltrombopag. Following a single 50 mg dose, the eltrombopag $EAA_{0-\infty}$ values were 32% to 36% lower in subjects with mild to moderate kidney failure compared to healthy volunteers, and 60% lower in subjects with severe kidney failure. There is significant overlap in exposure and notable variability between patients with kidney failure and healthy volunteers. Unbound (active) eltrombopag concentrations have not been measured for this highly protein-bound medicinal product. Eltrombopag should be used with caution in patients with kidney failure, and such patients should be closely monitored, for example with serum creatinine testing and/or urinalysis (see Section 4.2). The efficacy and safety of eltrombopag have not been established in patients with moderate or severe kidney failure or with hepatic failure.

Liver failure:
The pharmacokinetics of eltrombopag have been studied in adult subjects with hepatic failure after eltrombopag administration. Following a single 50 mg dose, eltrombopag $EAA_{0-\infty}$ values

were 41% higher in subjects with mild hepatic failure and 80% to 93% higher in subjects with moderate to severe hepatic failure compared to healthy volunteers. There is significant overlap in exposure and notable variability between patients with hepatic failure and healthy volunteers. Unbound (active) eltrombopag concentrations have not been measured for this highly protein-bound medicinal product.

Therefore, eltrombopag should not be used in ITP patients with hepatic failure (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal vein thrombosis (see Sections 4.2 ve 4.4).

Race:
The effect of East Asian race on eltrombopag pharmacokinetics was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 ITP patients (18 East Asians). According to population pharmacokinetic analysis calculations, plasma eltrombopag $EAA_{(0-\tau)}$ values in East Asian ITP patients were approximately 49% higher compared to non-East Asian patients, who were predominantly of Caucasian descent (see Section 4.2).

Gender:
The effect of gender on eltrombopag pharmacokinetics was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 ITP patients (57 females). According to the population pharmacokinetic analysis calculations, eltrombopag $EAA_{(0-\tau)}$ values in female ITP patients were approximately 23% higher than in male patients, without adjustment for body weight differences.

Pediatric Population (Ages 1-17):
Eltrombopag pharmacokinetics were evaluated in 168 pediatric ITP patients who received once-daily dosing in two studies (TRA108062/PETIT and TRA115450/PETIT-2). After oral administration (CL/P) plasma eltrombopag apparent clearance increased proportionally with body weight. The effects of race and gender on calculated plasma eltrombopag CL/F values were consistent between pediatric and adult patients. Plasma eltrombopag $EAA_{(0-\tau)}$ values in East/Southeast Asian pediatric ITP patients were 43% higher than in non-Asian patients. Plasma eltrombopag $EAA_{(0-\tau)}$ values in pediatric female patients were 25% higher compared to male patients.

Pharmacokinetic parameters of eltrombopag in pediatric ITP patients are shown in Table 7.

Table 7: Geometric average (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in pediatric patients with ITP (once daily 50 mg dosing regimen)

Age	C_{max} (µm/ml)	$AUC_{(0-\tau)}$ (µm.hr/ml)
12 to 17 years (n=62)	6.8 (6.17; 7.5)	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 are presented as geometric average (95% CI). $AUC_{(0-\tau)}$ and C_{max}, are based on population pharmacokinetic (PK) post-hoc calculations.

5.3. Preclinical safety data

Güvenlilik farmakolojisi ve tekrarlanan doz toksisitesi

Eltrombopag does not stimulate thrombocyte production in rats, mice or dogs due to its specificity for the TPO receptor. Therefore, data from these animals do not fully model potential adverse effects related to eltrombopag pharmacology in humans, including reproductive and carcinogenicity studies.

Treatment-related cataracts have been observed in rodents and are dose- and time-dependent. Cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing at exposures ≥ 6 times human clinical exposure at 75 mg/day in ITP patients based on AUC. At exposures ≥ 4 times human clinical exposure at 75 mg/day, cataracts were observed after 13 weeks in mice and 39 weeks in rats. Ocular opacities were observed in pre-weaning rat pups dosed from Days 4 to 32 (approximately equivalent to a 2-year-old human at the end of the dosing period) at non-tolerated doses, 9 times the maximum human clinical exposure in pediatric ITP patients at 75 mg/day based on AUC (histology not performed). However, at tolerated doses corresponding to 5 times the human clinical exposure in pediatric ITP patients based on AUC, no cataracts were observed in juvenile rats. Cataracts were not observed in adult dogs after 52 weeks of dosing (2 times the human clinical exposure in adult or pediatric ITP patients at 75 mg/day based on AUC).

Kidney tubular toxicity was observed in mice and rats in studies up to 14 days at exposures generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice dosed at 25, 75, and 150 mg/kg/day. These effects were less severe at lower doses and characterized by various regenerative changes. The lowest dose exposure corresponded to approximately 1.2 or 0.8 times the human clinical exposure at 75 mg/day in adult or pediatric ITP patients based on AUC. No renal effects were observed after 28 weeks in rats or 52 weeks in dogs at doses 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in pediatric ITP patients at 75 mg/day based on AUC.

At doses associated with morbidity and mortality or poorly tolerated doses in mice, rats, and dogs, hepatocyte degeneration and/or necrosis accompanied by increases in serum liver enzymes were frequently observed. No hepatic effects were observed after chronic dosing in rats (28 weeks) and dogs (52 weeks) at exposures approximately 4 or 2 times human clinical exposure at 75 mg/kg in adult ITP patients or 3 or 2 times in pediatric ITP patients based on AUC.

Decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (in rats only) were observed in short-term studies in rats and dogs at poorly tolerated doses (>10 or 7 times the maximum human clinical exposure in adult or pediatric ITP patients based on AUC). There were no significant effects on erythrocyte mass or reticulocyte counts in adult or pediatric ITP patients at 75 mg/kg daily after dosing for 28 weeks in rats, 52 weeks in dogs, and up to 2 years in mice or rats at maximum tolerated doses that were 2 to 4 times the maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28-week toxicity study in rats at an intolerable dose of 60 mg/kg/day (6 or 4 times the clinical exposure in humans with adult or pediatric ITP at 75 mg/day based on AUC). No bone changes were observed in mice or rats after lifetime exposure (2 years) at 4 or 2 times the human clinical exposure in adult or pediatric ITP patients at 75 mg/day based on AUC.

Carcinogenicity and Mutagenicity

Eltrombopag is not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (4 or 2 times the human clinical exposure based on AUC in adult or paediatric ITP patients, respectively). Eltrombopag was neither mutagenic nor clastogenic in bacterial mutation assays or two *in vivo* tests in rats (micronucleus and unscheduled DNA synthesis), where exposures corresponded to approximately 10 or 8 times human clinical exposure at 75 mg/day in adult or pediatric ITP patients based on C_{max}). Eltrombopag was marginally positive in an *in vitro* mouse lymphoma assay (mutation frequency <3-fold increase). These *in vitro* and *in vivo* findings suggest eltrombopag does not pose a genotoxic risk in humans.

Reproductive Toxicity

Eltrombopag doses up to 20 mg/kg/day in rats (2 times the human clinical exposure at 75 mg/day in adult and adolescent [12-17 years] ITP patients based on AUC) did not affect female fertility, early embryo development, or embryofetal development.

In rabbits, doses up to 150 mg/kg/day (0.3 to 0.5 times human clinical exposure in ITP patients based on AUC) showed no embryofetal developmental effects. However, maternal toxic doses of 60 mg/kg/day in rats (6-times the human clinical exposure in ITP patients at 75 mg/day based on AUC) were associated with embryo lethality (increased pre- and post-implantation loss), decreased fetal body weight and gravid uterine weight in female fertility studies, and

reduced cervical rib incidence and decreased fetal body weight in embryofetal development studies. Eltrombopag should not be used during pregnancy unless the expected benefits outweigh the potential risks to the fetus (see Section 4.6). Eltrombopag did not affect male fertility at the highest dose of 40 mg/kg/day tested in rats (3 times the human clinical exposure in ITP patients based on AUC). In a prenatal and postnatal development study in rats, no adverse effects on pregnancy, parturition, or lactation were observed in F0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day), and no effects on growth, development, neurobehavior, or reproductive function were observed in offspring (F1). Eltrombopag was detected in plasma of all F1 rat pups during a 22-hour sampling period after administration to F0 dams, indicating likely exposure eltrombopag in rats likely occurred through lactation.

Phototoxicity

In vitro studies suggest a potential phototoxicity risk for eltrombopag, but no cutaneous phototoxicity (at exposures 10 or 7 times human clinical exposure in adult or pediatric ITP patients at 75 mg/day based on AUC) or ocular toxicity (≥ 4 times human clinical exposure in adult or pediatric ITP patients at 75 mg/day based on AUC) was observed in rodents. Furthermore, a clinical pharmacology study in 36 subjects showed no evidence of increased photosensitivity after 75 mg dosing. This assessment was made using a delayed phototoxicity index. However, since no specific non-clinical study was conducted, the potential for photoallergy risk cannot be excluded.

Juvenile Term Animal Studies

Ocular opacities were observed in pre-weaning rats at intolerated doses. At tolerated doses, no ocular opacities were observed (see "Safety Pharmacology and Repeat-Dose Toxicity" section above). Considering exposure margins based on EAA values, the risk of cataracts associated with eltrombopag in pediatric patients cannot be excluded. There is no evidence suggesting a higher toxicity risk for eltrombopag in pediatric ITP patients compared to adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose (PH 101)
Mannitol (Type 50C)
Povidone K30
Microcrystalline cellulose (PH 112)
Sodium starch glycolate
Magnesium stearate
Opadry 13B28444 White Film Coating
HPMC 2910 / Hypromellose
Titanium dioxide
Macrogol/PEG
Polysorbate 80

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 30°C.

6.5. Nature and contents of the container
For our product, the primary packaging material consists of transparent PVC-Aclar and aluminum foil blisters. The blisters are packed inside cartons. Each carton contains blister packs with 14 film-coated tablets and is provided together with the package leaflet.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah.
Basın Ekspres Cad. No:1 34303
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10. DATE OF REVISION OF THE SPC