SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Elbonix 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Elbonix is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Elbonix is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Elbonix 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

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used 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 population aged 6 to 17 years

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag 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 eltrombopag is 25 mg once daily

Monitoring and dose adjustment

After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), 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. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag 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 eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

* - For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
♦ - For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation

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

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. 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).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

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 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.
♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe aplastic anaemia

Initial dose regimen

Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have 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 eltrombopag (see section 5.1). The dose of eltrombopag 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 eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag 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 before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag 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 eltrombopag; 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 eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment

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

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

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

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag 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 eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

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

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

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

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

Paediatric population

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

<u>Method of administration</u>

Oral use.
The tablets should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or model for end stage liver disease (MELD) score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3 x ULN in patients with normal liver function, or ≥ 3 x baseline or > 5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

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

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

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤ 35 g/L) or with MELD score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35 g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1,439), 38 out of 955 subjects (4%) treated with eltrombopag and 6 out of 484 subjects (1%) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

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

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

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

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

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

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

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

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1,439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

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

Paediatric population

The above warnings and precautions for ITP also apply to the paediatric population.

Interference with laboratory tests

Eltrombopag is highly coloured and so has the potential to interfere with some laboratory tests. Serum discolouration and interference with total bilirubin and creatinine testing have been reported in patients taking Elbonix. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

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. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin

In vitro studies demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor) (see section 5.2). 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 ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag 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 due to chelation (see sections 4.2 and 5.2).

Food interaction

The administration of eltrombopag tablet or powder for oral suspension with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [< 50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolised through 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 plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Elbonix is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Elbonix is not recommended in women of childbearing potential not using contraception.

Breast-feeding

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

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 ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

In 4 controlled and 2 uncontrolled clinical studies, 530 chronic adult ITP patients were treated with eltrombopag. The mean duration of exposure to eltrombopag was 260 days. The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

In 2 controlled clinical studies, 171 chronic paediatric ITP patients were treated with eltrombopag. The median duration of exposure was 171 days. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥ 3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, diarrhoea, pyrexia, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, increased AST and rhinorrhoea.

In 2 controlled clinical studies 955 thrombocytopenic patients with HCV infection were treated with eltrombopag. The median duration of exposure was 183 days. The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28%) were treated for > 6 months and 9 patients (21%) were treated for > 1 year. The most important serious adverse reactions were febrile neutropenia and sepsis/infection. The most common adverse reactions occurring in at least 10% of patients included: headache, dizziness, insomnia, cough, dyspnoea, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, ecchymosis, arthralgia, muscle spasms, pain in extremity, fatigue, febrile neutropenia, and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=550), paediatric ITP studies (N=107), the HCV studies (N=955), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

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

ITP study population

Infections and infestations

Very common Nasopharyngitis♦, upper respiratory tract infection♦

Common Rhinitis♦

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

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

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

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

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

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

Psychiatric disorders

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

Nervous system disorders

Common Paraesthesia

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

Eye disorders

Common Dry eye

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

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

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

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Common Cough♦, Oropharyngeal pain♦, Rhinorrhoea♦

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

Gastrointestinal disorders

Common Nausea, Diarrhoea*, Mouth ulceration, Toothache♦
* Very common in paediatric ITP

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

Hepatobiliary disorders

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

Uncommon Cholestasis, Hepatic lesion, Hepatitis, Drug-induced liver injury

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

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, 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

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

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Common Pyrexia♦

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase 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 1to 17 years).

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

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

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous system disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure, Drug-induced liver injury

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion
Not known Skin discolouration, Skin hyperpigmentation

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous system disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, 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

Skin and subcutaneous tissue disorders

Very common	Ecchymosis
Common	Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular
Not known	Skin discolouration, Skin hyperpigmentation

Musculosketal and connective tissue disorders

Very common	Arthralgia, Muscle spasms, Pain in extremity
Common	Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common	Chromaturia

General disorders and administration site conditions

Very common	Fatigue, Febrile neutropenia, Pyrexia
Common	Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

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

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

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

In controlled studies in thrombocytopenic patients with HCV (n=1,439), 38 out of 955 subjects (4%) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

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

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

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

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

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

Double-blind placebo-controlled studies

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

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

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

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

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

a Logistic regression model adjusted for randomisation stratification variables

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

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

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

Table 5: Efficacy results from TRA100773B

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

a – Logistic regression model adjusted for randomisation stratification variables

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

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

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

Eltrombopag was administered to 302 ITP patients in the open-label extension study EXTEND (TRA105325), 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 platelet count was 19,000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on 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.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)

The safety and efficacy of eltrombopag in paediatric subjects has been investigated in two studies.

TRA115450 (PETIT2): The primary endpoint was a sustained response, defined as the proportion of subjects receiving eltrombopag, compared to placebo, achieving platelet counts ≥ 50,000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Subjects were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count < 30,000/µl. Ninety-two subjects were randomised by three age cohort strata (2:1) to eltrombopag (n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (40%) compared with placebo subjects (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p < 0.001) which was similar across the three age cohorts (Table 6).

Table 6: Sustained platelet response rates by age cohort in paediatric subjects with chronic ITP

	Eltrombopag n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag subjects required rescue treatment during the randomised period compared to placebo subjects (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of subjects in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag subjects reporting any bleeding was decreased to half of baseline (36 %). In comparison, at Week 12, 55% of placebo subjects reported any bleeding.

Subjects were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of subjects were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT): The primary endpoint was the proportion of subjects achieving platelet counts ≥ 50,000/µl at least once between weeks 1 and 6 of the randomised period. Subjects were refractory or relapsed to at least one prior ITP therapy with a platelet count < 30,000/µl (n=67). During the randomised period of the study, subjects were randomised by 3 age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (62%) compared with placebo subjects (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 7). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 7: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1,439/1,520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *p*-value < 0.05 for eltrombopag versus placebo

e 64% subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p=< 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% versus 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40% (17/43 patients; 95% CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had > 80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 8).

Table 8: Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

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

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

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 9.

Table 9 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95% CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

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). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the tablet formulation. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

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

Biotransformation

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 $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

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

Pharmacokinetic interactions

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

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended. The co-administration of 200 mg ciclosporin (a BCRP inhibitor) decreased the C_{max} and the AUC_{inf} of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the AUC_{inf} of eltrombopag by 39% and 24%, respectively.

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

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

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate fat and moderate calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (< 50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and 60% lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score $\geq$ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult patients. East Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric subjects with ITP are shown in Table 10.

Table 10 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric subjects with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.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). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

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

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from Days 4-32 (approximately equating to a 2-year old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in pediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in pediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP patients and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times or equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years old) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Elbonix 12.5 mg film-coated tablets
Tablet core Magnesium stearate Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

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

Elbonix 25 mg film-coated tablets
Tablet core Magnesium stearate Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

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

Elbonix 50 mg film-coated tablets
Tablet core Magnesium stearate Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

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

Elbonix 75 mg film-coated tablets
Tablet core Magnesium stearate Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Film-coated tablets

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT