

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Elbonix 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sl. No.	Name of Materials	Specification	Quantity per Capsule
01	Eltrombopag Olamine	INN	*63.800 mg (eqv to Regorafenib 50 mg)

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).

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.

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.

4.2 Posology and method of administration

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. 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 $\geq 50,000/\mu\text{l}$ should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts.

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.

Paediatric population aged 1 to 5 years

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

Monitoring and dose adjustment

Table 1 Dose adjustments of eltrombopag in ITP patients

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

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* - 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.

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.

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.

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.

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). 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/ μ l following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq$ 50,000/ μ l to $\leq$ 100,000/ μ l	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/ μ l to $\leq$ 150,000/ μ l	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments [♦] .
> 150,000/ μ l	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $\leq$ 100,000/ μ l, 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. 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. The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count $\geq$ 50,000/ μ l. 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/ μ l 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/ μ l to □ 150,000/ μ l	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/ μ l to □ 250,000/ μ l	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/ μ l	Stop eltrombopag; for at least one week. Once the platelet count is $\leq$ 100,000/ μ l, 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/ μ l, haemoglobin to < 9 g/dL or ANC < 0.5 $\times$ 10⁹/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.

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.

Hepatic impairment

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. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

Elderly

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 .

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.

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.

Method of administration

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).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 2.

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 ≤ 35 g/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.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening.

Hepatic decompensating (use with interferon)

Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

Patients should be closely monitored for signs and symptoms of TEE.

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. 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.

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.

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. 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.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken.

OATP1B1 and BCRP substrates

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

Cytochrome P450 substrates

No clinically significant interactions are expected when eltrombopag and CYP450 substrates are coadministered.

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.

Effects of other medicinal products on eltrombopag

Ciclosporin Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count. 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 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.

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-∞} 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.

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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.

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile

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.

Description of selected adverse reactions

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. 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.

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 .

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.

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.

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.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts $\geq$ 50,000- 400,000/ μ l, Mean (SD)	11.3 (9.46)	2.4 (5.95)

Patients with $\geq 75\%$ of assessments in the target range (50,000 to 400,000/ $\square$ l), n (%) <i>p</i> -value ^a	51 (38)	4 (7)
	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%) <i>p</i> -value ^a	106 (79)	56 (93)
	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%) <i>p</i> -value ^a	44 (33)	32 (53)
	0.002	
Requiring rescue therapy, n (%) <i>p</i> -value ^a	24 (18)	25 (40)
	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%) ^b <i>p</i> -value ^a	37 (59)	10 (32)
	0.016	

- Logistic regression model adjusted for randomisation stratification variables
- 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.

Chronic hepatitis C associated thrombocytopenia studies

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/ μ l in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts < 20,000/ μ l, < 50,000/ μ l and $\geq$ 50,000/ μ l respectively.

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 $\leq 30,000/\mu\text{l}$. 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 $\geq 50\%$, were excluded from participation.

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 $20,000/\mu\text{l}$ above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by $> 1.5\text{g/dL}$, 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 $> 0.5 \times 10^9/\text{L}$.

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- ∞) and C_{max} estimates for ITP patients are presented.

Table 5: Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	AUC(0- ∞) ^a , $\mu\text{g.h/ml}$	C _{max} ^a , $\mu\text{g/ml}$
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- ∞) 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.

Table 6 : Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	N	AUC(0-∞) (∫g.h/ml)	Cmax (∫g/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-∞) and Cmax 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. In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma AUC(0-∞) 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

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 2132 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.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a highcalcium, moderate fat and moderate calorie meal reduced plasma eltrombopag mean AUC_{0-∞} 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-∞} 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.

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-∞} 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

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. For patients with HCV initiate eltrombopag at a dose of 25 mg once daily.

Race

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-∞) values as compared to non-East Asian patients who were predominantly Caucasian.

Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55% higher plasma eltrombopag AUC(0- ∞) values as compared to patients of other races who were predominantly Caucasian .

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- ∞) 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- ∞) as compared to male patients.

Age

Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma eltrombopag AUC(0- ∞) as compared to younger patients .

6. PHARMACEUTICAL

PARTICULARS 6.1 List of excipients

Elbonix 50 mg film-coated tablets

Tablet core

Mannitol DC Grade
Pregelatinised Starch Glycolate
Magnesium Stearate
Colloidal Anhydrous Sillica (Aerosil 200)
Microcrystalline Cellulose (Avicel PH 102)

Tablet coating

Opadry II Blue (85G50642)
Opadry II White (85G68918)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

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

Aluminum blisters (Alu-Alu) in a carton containing 7,14, 21 or 28 or 30 film-coated tablets in HDPE Bottel.

Not all pack sizes may be marketed.

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

Beacon Pharmaceuticals Limited

9/B/2 Toyenbee Circular Road, Motijheel
Dhaka, Bangladesh

8. MARKETING AUTHORISATION NUMBER(S)

341-316-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01-06-2017

10. DATE OF REVISION OF THE TEXT

10.12.2018

BEACON PHARMACEUTICALS LIMITED
Bhaluka, Mymensingh, Bangladesh