The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use

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ABSTRACT

On 11th March 2010, the European Commission issued a marketing authorization valid throughout the European Union for Revolade for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura. Revolade is an orphan medicinal product indicated for splenectomized patients with immune (idiopathic) thrombocytopenic purpura who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) and as second-line treatment for non-splenectomized patients where surgery is contraindicated. The active substance of Revolade is eltrombopag (ATC code B02BX05). Eltrombopag increases platelet production through activation of the thrombopoietin receptor. The recommended oral dose is 50 mg once daily to achieve and maintain a platelet count of the 50×10^9/L or more necessary to reduce or prevent the risk of bleeding. The benefit of Revolade is a durable response in maintaining platelet levels. The most common side effects include headache, nausea, hepatobiliary toxicity, diarrhea, fatigue, paresthesia, constipation, rash, pruritus, cataract, arthralgia and myalgia. The decision to grant the marketing authorization was based on the favorable recommendation of the Committee for Medicinal Products for Human Use of the European Medicines Agency. The objective of this paper is to describe the data submitted to the European Medicines Agency and to summarize the scientific review of the application. The detailed scientific assessment report and product information, including the summary of product characteristics, are available on the European Medicines Agency website (*www.ema.europa.eu*).

Key words: eltrombopag (Revolade), chronic immune (idiopathic) thrombocytopenic purpura, ITP, EMA, European Medicines Agency, CHMP, Committee for Medicinal Products for Human Use.

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Background

Chronic idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a low peripheral blood platelet count. The clinical hallmark of the disease is an increased, pathological tendency to bleed either spontaneously or after minimal trauma. Disease management decisions in patients with chronic ITP are based primarily on platelet count and severity of bleeding. The goal of treatment is to elevate platelet counts to a safe range (≥50×10^9/L to

Disclaimer: this publication is a summary of the European Public Assessment Report, the summary of product characteristics, and other product information available on the European Medicines Agency (EMA) website. Healthcare professionals and interested readers are referred to the EMA website for up-to-date information on this marketing authorization (www.ema.europa.eu). The authors remain solely responsible for the opinions expressed in this publication.

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400×10⁹/L) to minimize the risk of bleeding, not to normalize the platelet count. When first- and second-line therapies including intravenous immunoglobulins, corticosteroids, a variety of immunosuppressive drugs and elective splenectomy fail, patients are considered as having chronic refractory ITP. The percentage of patients with refractory ITP varies from 11% to 35% of adult chronic ITP patients.[1] Romiplostim (Nplate), a recombinant protein that increases platelet production through activation of the thrombopoietin receptor (TPO-R), and is administered once weekly as a subcutaneous injection, is currently authorized in the European Union (EU) for the treatment of refractory ITP.[2]

Glaxo Group Ltd. applied for a marketing authorization via the European Medicines Agency (EMA) centralized procedure for eltrombopag with the invented name Revolade. Eltrombopag has been designated as an orphan medicinal product in the EU. The review has been conducted by the Committee for Medicinal Products for Human Use (CHMP) of the EMA, which recommended the granting of the marketing authorization for eltrombopag based on a positive benefit-risk balance. The Committee for Medicinal Products for Human Use reached a positive Opinion on 17th December 2009. The approved therapeutic indication in the EU for Revolade is for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomized patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second-line treatment for adult non-splenectomized patients where surgery is contraindicated.

Revolade consists of film-coated tablets to be administered orally. Each film-coated tablet contains eltrombopag olamine, an orally bioavailable TPO-R agonist present in the form of the *bis*-monoethanolamine (olamine) salt (Figure 1). It is a crystalline solid, red/brown, sparingly soluble in water. It is thermally stable up to about 125°C. Revolade is presented as round, biconvex, white film-coated tablets of 25 or 50 mg.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. After initiating eltrombopag, the dose should be adjusted to achieve and maintain a platelet count of 50×10⁹/L or more as necessary to reduce the risk for bleeding. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc). Eltrombopag is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

This publication summarizes the assessment of the non-clinical and clinical data submitted until the CHMP Opinion on the initial marketing authorization application. Thereafter, the information on file, including the product information, is expected to be up-dated through submission of periodic safety up-date reports and scientific data pertinent to post-authorization commitments, as well through variation and extension applications of the marketing authorization. The up-dated scientific assessment reports and product information, including the summary of product characteristics (SmPC), are available on the EMA website.[3]

Non-clinical aspects

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag was shown to interact with the transmembrane domain of the human TPO-R and to initiate signaling cascades similar but not identical to that of endogenous TPO, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Comparison of eltrombopag potency with TPO potency in terms of EC_{50} (μM) showed that TPO was between 7 to 9 times more potent than eltrombopag in the $CD34^+$ megakaryocyte differentiation assay, as well as in the N2C-TPO proliferation assay. Eltrombopag showed a marked specificity for human and chimpanzee TPO-R. In chimpanzees, 5 daily doses of 10 mg/kg/day produced increases between 1.3-fold to 2.4-fold in platelet counts approximately one week after the last dose and returned to baseline values within two weeks. A similar trend was observed in reticulated platelet counts.

The selectivity of eltrombopag was assessed in a panel of standard *in vitro* radio-ligand binding and enzyme activity assays against 41 physiologically relevant receptors, enzymes and ion channels. Eltrombopag showed activity (defined as > 25% inhibition) on 4 targets: α_{2B}-receptor (38%, IC50= 15.5 μM), I_2-receptor (88%, IC50= 1.7 μM), estrogen-α-receptor (85%, IC_{50}= 0.3 μM) and estrogen-β-receptor (33%, IC_{50}= 1.9 μM).

In vitro studies showed hERG channel inhibition by eltrombopag. However, a QT study in healthy human subjects with daily doses of eltrombopag of 50 and 150 mg did not prolong the QT interval in comparison to placebo.

The toxicity of repeated oral doses of eltrombopag has been assessed in mice (5 studies), rats (6 studies), rabbits (2 studies) and dogs (4 studies) in studies of up to 13, 28, one and 52 weeks, respectively. In addition, repeat dose toxicity was assessed in 2-year carcinogenicity studies in mice. The principal toxicological findings associated with eltrombopag administration

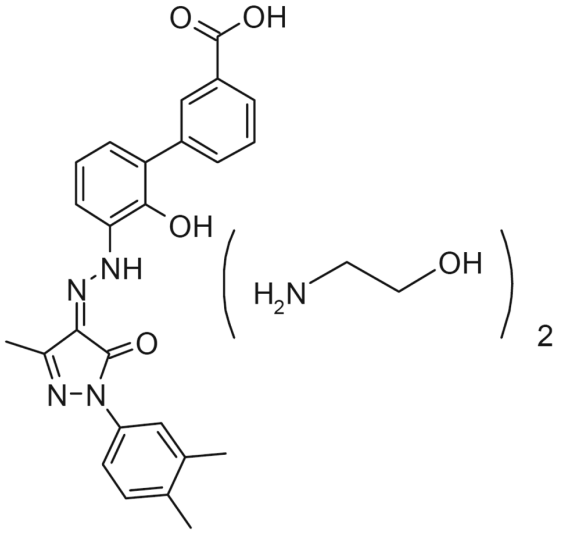

Figure 1. Structural formula of eltrombopag olamine.

included cataracts (mice and rats), renal toxicity (mice), and hepatotoxicity (mice, rats and dogs). Increased ossification (endosteal hyperostosis) and changes in the erythroid lineage related parameters (i.e. decreases in red cell mass, decreases in reticulocyte counts in rats and dogs) were also observed.

Treatment-related cataracts were observed in rodents and were dose and time-dependent. At 6 times or more the human clinical exposure based on AUC, cataracts were observed in mice after six weeks and rats after 28 weeks of dosing. At 4 times or more the human clinical exposure based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing (twice the human clinical exposure based on AUC). The clinical relevance of these findings is unknown. Routine monitoring of patients for cataracts is recommended.

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times, respectively, the human clinical exposure based on AUC. The clinical relevance of these findings is unknown. Patients with impaired renal function should use eltrombopag with caution and under close monitoring, for example, by testing serum creatinine and/or performing urine analysis.

Hepatocyte degeneration or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC. Eltrombopag can cause abnormal liver function in man (see "Clinical safety").

At poorly tolerated doses in rats and dogs (>10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short-term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and two years in mice or rats at maximally tolerated doses which were 4 to 2 times the maximum human clinical exposure based on AUC. Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not yet been established (see "Clinical safety").

Endosteal hyperostosis was observed in a 28-week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times the maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (two years) at 4 times the maximum human clinical exposure based on AUC. The potential for endosteal hyperostosis will be addressed through pharmacovigilance activities (see "Pharmacovigilance and risk management plan").

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

Eltrombopag did not affect female fertility, early embryonic development or embryo-fetal development in rats at doses up to 20 mg/kg/day (twice the human clinical exposure based on AUC). Also there was no effect on embryo-fetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.5 times the human clinical exposure based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced fetal body weight and gravid uterine weight in the female fertility study, a low incidence of supernumerary cervical ribs and reduced fetal body weight in the embryo-fetal development study. The potential risk for humans associated with the reproductive toxicity observed in animal studies is unknown. Revolade is not recommended during pregnancy and in women of childbearing potential not using contraception.

Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 h 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 suggested a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic

Table 1. Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP.

Eltrombopag dose, once daily	N	AUC(0-τ), μg.h/mL	C_{max}, 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)	12.65 (11.03, 14.49)

AUC(0-τ) and C_{max} based on population PK estimates.

index. Nevertheless, a potential risk of photoallergy could not be ruled out since no specific pre-clinical study was performed.

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population pharmacokinetic analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP subjects are presented (Table 1).

The final covariate model in the pharmacokinetic population analysis included the influence of body weight on CL/F, Vc/F, Q/F, and Vp/F, and influence of the disease (ITP *vs.* healthy), race (Asian *vs.* non-Asian), gender, and concomitant corticosteroids on CL/F. Mean (95% CI) apparent clearance was 33% (26%, 41%) lower in Asians compared to all other races, 26% (7%, 45%) lower in patients taking corticosteroids concomitantly, and 19% (7%, 31%) lower in females compared to males. Healthy subjects had a mean 17% (0%, 34%) higher CL/F than ITP patients. For the range of weights in the analysis (43-122 kg), eltrombopag CL/F, Vc/F, Q/F and Vp/F ranged from 26% lower to 41% higher values than for 70 kg individuals. Weight, gender, race (Asian *vs*. Non-Asian) and corticosteroid use were predictors of drug exposure in ITP patients; following the same dosing regimen, lighter subjects, women, subjects of Asian origin and corticosteroid users would have greater eltrombopag exposures. Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean).

Eltrombopag was absorbed with a peak concentration occurring 2-6 h after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations, such as dairy products and mineral supplements, significantly reduced eltrombopag exposure. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Eltrombopag was highly bound to human plasma proteins (> 99.9%), predominantly to albumin.

Absorbed eltrombopag was extensively metabolized. The predominant route of eltrombopag excretion was *via* feces (59%) with unchanged eltrombopag accounting for approximately 20% of the dose. Unchanged parent compound (eltrombopag) was not detected in urine but 31% of the dose was found in the urine as metabolites. The plasma elimination half-life of eltrombopag was approximately 21-32 h.

Eltrombopag was primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. Clinically significant drug interactions involving glucuronidation were not anticipated due to a limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Eltrombopag did not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data. No clinically significant interactions are expected when eltrombopag and CYP substrates, inducers, or inhibitors are co-administered.

In *in vitro* studies, eltrombopag was not a substrate for the organic anion transporter polypeptide, OATP1B1, but was an inhibitor of this transporter. Eltrombopag was also shown to be a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for five days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% CI: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions were also expected with other HMG-CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin; however, clinically significant interactions were not expected between eltrombopag and atorvastatin or fluvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken. Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

Eltrombopag chelates polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least 4 h apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation. Food low in calcium (< 50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soya milk, and unfortified grain did not have a significant impact on plasma eltrombopag exposure, regardless of calorie and fat content. Eltrombopag should be taken at least 4 h before or after any products such as antacids, dairy products or other calcium containing food products, or mineral supplements containing polyvalent cations.

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet counts should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

The Committee for Medicinal Products for Human Use also recommended that platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of immune (idiopathic) thrombocytopenic purpura in order to avoid platelet counts outside the recommended range.

Plasma eltrombopag $AUC_{0-\infty}$ was on average 32%, 36% and 60% lower in subjects with mild, moderate and severe renal impairment, respectively, compared with healthy subjects. No dose adjustment is necessary in patients with renal impairment. However, patients with impaired renal function should use eltrombopag with caution and should be closely monitored due to the renal tubular toxicity observed in rodents (see "Non-clinical aspects").

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. Administration of eltrombopag to patients with moderate to severe hepatic impairment should be undertaken with caution and should be closely monitored due to increased exposure to the medicinal product.

Clinical efficacy studies

Dose response study (TRA100773A)

The objective of the TRA100773A study was to determine the optimal dose of eltrombopag. TRA100773A compared 30, 50 and 75 mg doses of eltrombopag and placebo as oral tablets taker once daily for six weeks.[4] Adult patients with chronic ITP who had failed at least one previous therapy were included. A baseline platelet count below 30×10^9/L was required. The primary end point was the proportion of responders at day 43 (week 6 visit). Responders were defined as subjects whose platelet count reached 50×10^9/L or more at the day 43 visit or if they achieved a platelet count of more than 200×10^9/L prior to day 43. The study was stopped at the first interim analysis (29 patients on placebo, 30 patients on 30 mg, 30 patients on 50 mg and 28 patients on 75 mg; total 117 patients). A dose-dependent effect as assessed by the rate of responders (27.6%, 70.4% and 80.8% in the 30 mg, 50 mg, and 75 mg treatment groups, respectively) was observed, the results of the 2 higher doses being statistically significantly different from placebo (P<0.001). On the basis of these results, the applicant company selected 50 mg/d as the starting dose for phase III studies.

Phase III study TRA100773B

This was a double-blind, randomized, placebo-controlled study.[5] The study included patients diagnosed with chronic immune (idiopathic) thrombocytopenic purpura at least six months prior to screening with a platelet count of less than 30×10^9/L. In addition, subjects must have had either not responded to one or more prior therapies, or relapsed within three months of prior therapy. Subjects were allowed to receive ITP medications (corticosteroids, azathioprine, danazol, cyclosporine A or mycophenolate mofetil) during the study, provided that the dose had been stable for at least one month.

The doses for this study were eltrombopag 50 mg or matching placebo once daily for up to six weeks. Subjects with platelet counts less than 50×10^9/L on day 22 or after may have had their dose increased to eltrombopag 75 mg (or matching placebo). Subjects reaching a platelet count over 200×10^9/L were withdrawn from the study medication, but continued to attend follow-up visits.

The primary efficacy end point was a shift from a baseline platelet count of less than 30×10^9/L to 50×10^9/L or more after up to 42 days of dosing with the study medication. Subjects were classified as responders if they achieved a platelet count of 50×10^9/L or more at the day 43 visit. Subjects were also classified as responders if they responded strongly with a platelet count of more than 200×10^9/L and discontinued study medication prior to day 43. Subjects were randomized to treatment (eltrombopag 50 mg or placebo) in a 2:1 ratio. Randomization was stratified according to use or non-use of ITP medications at randomization, splenectomy status (refractory following splenectomy or non-splenectomized) and baseline platelet count (≤15×10^9/L or >15×10^9/L).

A total of 114 subjects were enrolled; 76 randomized to the eltrombopag treatment group, 38 randomized to placebo. Median age was 47 years in the eltrombopag arm and 51 years in the placebo group. There was a higher percentage of females in both groups (71% and 57% in the placebo and eltrombopag groups, respectively) and most patients were of white origin (61% and 70% in the placebo and eltrombopag groups, respectively).

Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving ITP medication at randomization. Similar percentages of subjects (34% and 37%, respectively) had had a prior splenectomy and baseline platelet counts of 15×10^9/L or under (48% and 50%, respectively). All subjects in both treatment groups had had at least one prior ITP therapy as determined by clinical review. Approximately 50% of subjects had received at least 3 prior treatments. A higher percentage of subjects in the eltrombopag treatment arm had had 3 or more and 4 or more prior therapies compared to placebo.

In the primary analysis of efficacy, a total of 59% of subjects on eltrombopag achieved a platelet count of 50×10^9/L or over on day 43, compared to 16% of subjects on placebo. The odds ratio for active/placebo treatment was 9.61 (95% CI: 3.31, 27.86, P<0.001). This effect of eltrombopag relative to placebo was significant across all subgroups regardless of baseline platelet count, use of concomitant ITP medication, or splenectomy status. A decrease in any bleeding (WHO grades 1 to 4) at day 43 was observed in secondary analyses in subjects treated with eltrombopag compared to placebo (39% *vs.* 60%, OR=0.27, P=0.029).

Study TRA102537 (RAISE)

This was a randomized, double-blind, placebo-controlled phase III study.[6] The selection criteria and treatments including concomitant treatments were similar to those of study TRA100773B (see above).

The primary end point was the odds of achieving a platelet count of 50×10^9/L or over and 400×10^9/L or under during the 6-month treatment period, for subjects receiving eltrombopag relative to placebo. Subjects were randomized 2:1 eltrombopag to placebo, and were stratified according to splenectomy status, baseline use or non-use of ITP medication, and baseline platelet count 15×10^9/L or below or greater than 15×10^9/L.

A total of 197 subjects were enrolled in the study, with 135 subjects randomized to the eltrombopag treatment group, and 62 subjects randomized to placebo. Median age was 52 years in the placebo arm and 47 years in the eltrombopag group. There was a higher percentage of females (69%) in both groups and most patients were of white origin (68% and 70% in the placebo and eltrombopag group, respectively).

Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving ITP medication at randomization. Similar percentages of subjects (34% and 37%, respectively) had had a prior splenectomy and baseline platelet counts of 15×10^9/L or below (48% and 50%, respectively). Median platelet counts at baseline were 16×10^9/L for both treatment groups. All subjects in both treatment groups had had at least one prior ITP therapy (including splenectomy) as determined by clinical review. Eighty-

one percent of placebo-treated subjects and 78% of eltrombopag-treated subjects had received at least 2 prior therapies, and more than 30% of subjects in each group had received 4 prior therapies or more.

In the primary efficacy analysis, the odds of responding over the six month treatment period were greater (OR=8.20, 99% CI: 3.59, 18.73, $P<0.001$) for eltrombopag-treated subjects compared to placebo-treated subjects. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after six weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the six month treatment period. This response was observed regardless of splenectomy status, baseline platelet count, and use of baseline ITP medications.

Secondary analyses showed that the observed baseline percentage of subjects with any bleeding (Grades 1 to 4) and clinically significant bleeding (Grades 2 to 4) was reduced by approximately 50% from day 15 to the end of treatment throughout the six month treatment period. Bleeding (Grades 1 to 4) was reported in 79% of the patients receiving eltrombopag *versus* 93% receiving placebo. Bleeding (Grades 2 to 4) was reported in 33% of the patients receiving eltrombopag *versus* 53% receiving placebo. At each time point in both treatment groups, more than half of the bleeding observed was Grade 1. Throughout the treatment period, clinically significant bleeding occurred infrequently, generally in less than 25% of subjects in the placebo group and in less than 15% of subjects in the eltrombopag group.

Clinical safety

The safety profile of eltrombopag had been evaluated in 26 completed or ongoing clinical studies in 1,616 eltrombopag-treated and 247 placebo-treated healthy volunteers and patients with ITP, hepatitis C, or chemotherapy-induced thrombocytopenia. The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg once daily. The duration of treatment with eltrombopag ranged from one day in healthy volunteers to up to 560 days in subjects with chronic ITP. Overall, eltrombopag was administered to 277 patients for at least six months and 202 patients for at least one year.

Drug-related adverse events in patients with ITP (updated cut-off date 10th December 2008, n=446) included adverse reactions observed during eltrombopag treatment such as headache (13%), nausea, increased alanine aminotransferase and increased aspartate aminotransferase (4%), diarrhea and fatigue (3%), paresthesia, constipation, rash, pruritus, increased blood bilirubin, cataract, arthralgia, myalgia and hyperbilirubinemia (2%), upper abdominal pain, alopecia, dry eye, peripheral edema, muscle spasm, bone pain, abnormal hepatic function and insomnia (1%). For a complete list of adverse drug reactions, see the summary of product characteristics (SmPC) and the European public assessment report.

Eltrombopag administration can cause abnormal liver function and in clinical studies with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed. However, findings were mostly mild (Grades 1 to 2), reversible, and not accompanied by clinically significant symptoms that would indicate impaired liver function. Across the 3 placebo-controlled studies, one patient in the placebo group and one patient in the eltrombopag group experienced a Grade 4 abnormality in liver tests. The summary of product characteristics advises monitoring and managing patients with hepatotoxicity and liver testing before initiation of treatment, every two weeks during the first three months, and every 4-6 weeks thereafter.

The rate of discontinuation due to adverse events (AE) in double blind trials was similar in both treatment groups, eltrombopag and placebo, although specific adverse events (e.g. thromboembolic complications) were numerically higher among eltrombopag patients. In the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% of both the eltrombopag and placebo groups. 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 four weeks following discontinuation of eltrombopag.

From all ITP studies, a total of 17 out of 446 (3.8%) patients experienced thromboembolic events (TEE) which included (in descending order of occurrence) deep vein thrombosis, pulmonary embolism, acute myocardial infarction, cerebral infarction, embolism. The risk of TEE has been found to be increased in patients with chronic liver disease treated with eltrombopag. Study TPL104054/ELEVATE in thrombocytopenic subjects with chronic liver disease was prematurely stopped by the Independent Data Monitoring Board for safety reasons. As of 20th August 2009, 6 of 261 (2.3%) subjects treated with eltrombopag 75 mg had experienced 7 TEEs. These consisted of 7 events in the portal venous system (4 portal vein thromboses, 3 mesenteric vein thromboses) in 6 subjects and one myocardial infarction. The median time to onset since the first dose of study medication was 22 days (range 15-53). None of the events occurred on-therapy, the median number of days since last dose was 9 days (range 1-38). Five of the 7 subjects experienced the TEE within two weeks of the last dose of study medication. Six of the cases occurred with platelet counts above 200×10^9/L.

The Committee for Medicinal Products for Human Use consulted an *ad hoc* expert group to provide advice on the significance of the events found. The group agreed that it was difficult to speculate on the possible mechanism for the observed TEE. A plausible explanation was the rapid increase in platelet counts observed in the liver impaired population due to the administration of a higher dose of eltrombopag (75 mg compared to 25 mg or 50 mg in the ITP population). However, information on whether the patients who experienced TEEs had received platelet transfusions in addition to drug treatment and the platelet counts achieved in the patients who had not had TEEs was not available. An enhancement of the pro-thrombotic state (hypercoagulability) due to an imbalance in coagulation factors or the presence of endothelial damage seen in liver disease may also have contributed to the TEEs. The TEEs observed in the ELEVATE study were considered to be

unlikely to be relevant to the ITP patient population because of the different pathophysiology of the two diseases, the different etiology of the thrombocytopenia and the different type and pattern of TEE observed in the two populations. The group expressed the need to include a strong warning in the summary of product characteristics highlighting the risk of TEE in patients with moderate and severe hepatic impairment. The *ad hoc* expert group considered that, especially for those patients undergoing invasive procedures, platelet transfusion remained a safer option. In line with the advice received, strong warnings highlighting the risks associated with moderate to severe liver impairment have been included in the summary of product characteristics (sections 4.2, 4.4 and 4.8).

The Committee for Medicinal Products for Human Use also considered that the lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated. In particular, in cases of platelet counts 50×10^9/L or over to 150×10^9/L or under, the lowest dose of eltrombopag and/or concomitant ITP treatment should be used to maintain platelet counts that avoid or reduce bleeding. In cases of a platelet count of more than 150×10^9/L to 250×10^9/L or under, the daily dose should be decreased and in cases of a platelet count of more than 250×10^9/L eltrombopag should be stopped with increased frequency of monitoring of platelet count and reinitiation of therapy at a reduced dose once the platelet count is 150×10^9/L or under.

The induction of reticulin formation and the potential development of bone marrow fibrosis was a serious safety concern during the review. There were limited data suggesting that eltrombopag was associated with reticulin formation in the bone marrow (collagen formation in 3 cases); however, whether this was a finding likely to have clinical consequences in the long term was considered to be still uncertain. Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphological abnormalities. Following identification of a stable dose of eltrombopag, the Committee for Medicinal Products for Human Use recommended that a complete blood count with white blood cell count and differential should be performed monthly. Peripheral blood smears should be examined for morphological abnormalities such as teardrop poikilocytes, nucleated red blood cells, immature white blood cells, dysplastic cells or cytopenia. If such abnormalities are new or worsening, treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis. 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.

For Mpl ligands, such as eltrombopag, there is a theoretical concern that they may stimulate the growth of hematopoietic malignancies, or increase progression of myelodysplastic syndromes to acute myelogenous leukemia. Five (1.2%) cases of malignancy in the eltrombopag group and one (1.4%) in the placebo group have been detected in all ITP studies. Among the 6 cases of malignancy observed in ITP studies, there were 2 cases of hematologic malignancy: one in the placebo group and one in the eltrombopag group.

In the double-blind RAISE study, patients had an ocular examination prior to study entry and after starting the study at months 3 and 6. The frequency of incident cases of cataract was similar for the eltrombopag group (4.5%) and the placebo group (4.9%). The frequency of cataract progression was slightly higher in the eltrombopag group compared with the placebo group. Prior to entry into the study, 25 patients had cataracts (13 placebo, 12 eltrombopag group) and during the study, 4 (33%) patients had a cataract progression in the eltrombopag group and 3 (23%) in the placebo group. The frequency of cataracts (incident/progression) was similar in open label studies (REPEAT 3%, EXTEND 5%). All patients who developed cataracts in ITP studies had had chronic treatment with corticosteroids.

No difference in the frequency of skin and subcutaneous adverse events was demonstrated between the eltrombopag and placebo groups in the controlled trials. The frequency reported in the open label studies was similar to the placebo controlled studies.

Pharmacovigilance and risk management plan

The marketing authorization application included a risk management and minimization plan. Identified safety concerns included hepatotoxicity, thromboembolic events, post-therapy recurrence of thrombocytopenia, potential for increase in bone marrow reticulin formation, hematologic malignancies, cataracts, renal tubular toxicity, phototoxicity, potential for hematologic changes, and potential for endosteal hyperostosis.

Pharmacovigilance activities will include targeted follow-up questionnaires, adjudication of reports of cataract, ongoing and planned studies (including: EXTEND TRA105325, Japanese study TRA108109, Japanese Extension TRA111433, Bone Marrow Study TRA112940 to assess serial bone marrow samples at baseline, 12 and 24 months, Sarcoma TRA105499, MDS Study, ENABLE1 TPL103922, ENABLE2 TPL108390, ENABLE ALL TPL108392, ELEVATE TPL104054, Sarcoma TRA105499, LENS TRA108132 observational study), pharmacogenetics studies, and registries (including: UK ITP Registry, PARC ITP Registry) and the USA risk evaluation and mitigation strategy (REMS).

Risk minimization activities include educational materials about the need to monitor and manage patients with hepatotoxicity, about thromboembolic events and related risk factors, posology and food interactions, the potential risk of bleeding after treatment has stopped, the potential for bone marrow reticulin fibre formation, the theoretical risk of hematologic malignancies with thrombopoietin receptor agonists and the risk of portal venous thrombosis in patients with moderate to severe hepatic impairment. The details of the educational program have to be agreed between the marketing authorization holder and each of the National Competent Authorities in the EU.

The safety and efficacy of eltrombopag in pediatric patients (< 18 years of age) has not been established. A pediatric study (PETIT) is being conducted to establish safety and efficacy in this population.

There are limited data on the use of eltrombopag in pregnant women and it is unknown whether eltrombopag/metabolites are excreted in human milk. Based on the animal studies, eltrombopag is likely to be secreted into milk; therefore, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or whether to continue or

abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Pharmacovigilance activities will include a targeted pregnancy follow-up questionnaire, a pregnancy registry in the USA, and a lactation study.

The efficacy and safety of eltrombopag have not been established for use in other thrombocytopenic conditions, including chemotherapy-induced thrombocytopenia and myelodysplastic syndromes.

Overall conclusions, risk benefit assessment and recommendations

The benefits of eltrombopag in terms of platelet counts have been established in several independent clinical trials on a short- and long-term basis. Once-daily oral eltrombopag administration increased platelet count in patients with chronic ITP unresponsive to at least one first-line therapy (corticosteroids or immunoglobulins). The effect of eltrombopag was superior to placebo in both splenectomized and non-splenectomized patients. In secondary analyses, eltrombopag was also consistently associated with a reduction in the risk of bleeding.

Eltrombopag dosing requirements must be individualized according to patient platelet counts. The objective of treatment with eltrombopag should not be to normalize platelet counts but to maintain platelet counts above the level for reduction of hemorrhagic risk (>50×10^9/L). The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

A number of risks and uncertainties have been identified. Identified risks included hepatobiliary laboratory abnormalities (including cholestasis, hepatic lesion, hepatitis in <1% of patients), thromboembolic events, which occurred in 3.8% of patients in 3 controlled and 2 uncontrolled clinical studies, and post-therapy recurrence of thrombocytopenia (transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% of patients). Potential risks included bone marrow reticulin formation, hematologic malignancies, renal toxicity, phototoxicity, cataracts, hematologic changes, and endosteal hyperostosis. However, the benefits observed were assessed as outweighing these risks. The applicant company has submitted a comprehensive risk management plan and has made the commitment to perform additional post-authorization studies.

In splenectomized patients refractory or intolerant to first-line therapies (corticosteroids and immunoglobulins), the benefits of eltrombopag outweighed the risks. However, considering the unknown risks, the benefit-risk balance could not be considered positive for non-splenectomized patients, for whom splenectomy is a therapeutic option that could potentially affect the course of the disease. Therefore, the indication for non-splenectomized patients has been restricted as second-line treatment only when surgery is contraindicated.

Authorship and Disclosures

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