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Eltrombopag

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Contents

Abstract

▲ Eltrombopag, an orally administered, small-molecule non-peptide thrombopoietin receptor agonist, selectively binds to the transmembrane domain of the thrombopoietin receptor on the surface of platelets, megakaryocytes and megakaryocyte precursor cells. The drug acts via the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway to activate megakaryocyte proliferation and differentiation in bone marrow progenitor cells, similar to those observed with endogenous thrombopoietin.

▲ Platelet counts are increased as a result of eltrombopag therapy, and the drug has shown good clinical efficacy in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP) in randomized, double-blind, placebo-controlled, multicentre, phase II dose-finding and phase III trials.

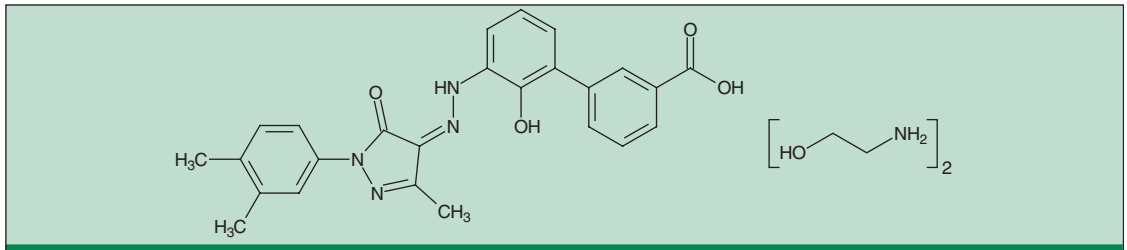
▲ After 6 weeks of therapy in the phase III trial, eltrombopag 50 mg/day was associated with a significantly higher response rate (proportion of patients with a platelet count of ≥50 000 cells/μL at day 43; primary endpoint) than placebo in adult patients with chronic ITP.

▲ In addition, the proportion of patients with ITP achieving a platelet count of >200 000 cells/μL and discontinuing treatment due to protocol-defined treatment-cessation criteria, was ≈8-fold higher with eltrombopag than with placebo.

▲ Eltrombopag therapy for 6 weeks also significantly decreased the incidence of WHO-defined bleeding compared with placebo.

▲ Eltrombopag was generally well tolerated in clinical trials, with an adverse events profile that did not differ significantly from that with placebo.

Features and properties of eltrombopag (Promacta®)	
Indication	
Chronic immune (idiopathic) thrombocytopenic purpura (ITP) in adults with an insufficient response to treatment with corticosteroids, immunoglobulins or splenectomy	
Mechanism of action	
Synthetic non-peptide thrombopoietin receptor agonist	
Dosage and administration	
Dosage	Initial dosage: 50 mg/day
	Maximum dosage: 75 mg/day
Frequency	Once daily
Route of administration	Oral
Pharmacokinetic profile (in adult patients with ITP receiving 50 mg/day)	
Time to maximum plasma concentration	2–6 h
Mean area under the plasma concentration-time curve over a dosage interval	91.9 μg • h/mL
Plasma elimination half-life	26–35 h
Most common adverse events (incidence ≥4% and more frequent than with placebo)	
Nausea, vomiting and menorrhagia	



Chronic immune (idiopathic) thrombocytopenic purpura (ITP), also known as immune or autoimmune thrombocytopenia, is an autoimmune haematological disorder characterized by a low platelet count that has persisted for more than 6 months[1] and mucocutaneous bleeding.[1,2] Symptoms range from mild bruising and mucosal bleeding to haemorrhage from any site in the body; intracranial haemorrhage is the most serious of these.[2] The annual incidence of adult chronic ITP in the US in 2003 was approximately 58–66 new cases per million population,[2] and an informal estimate, based on an analysis of data from a large US claim database between 2002 and 2006, suggests a prevalence of 236 adult cases per million population.[3]

Most patients with ITP never experience serious bleeding, even with severe thrombocytopenia,[4] and many are asymptomatic.[2] Consequently, there is a trend towards lower levels of therapeutic intervention.[2,4] However, patients who have severe, symptomatic disease or disease that is treatment refractory show significant morbidity,[2] and treatment remains necessary for these patients.

The goal of ITP treatment is to increase platelet count and decrease the risk of serious haemorrhage.[1] Historically, the underlying cause of ITP was believed to be accelerated platelet destruction.[5] Treatment options have focused on slowing platelet destruction by suppressing platelet autoantibody production or inhibiting macrophage-mediated platelet destruction, and include glucocorticoids (e.g. prednisone), intravenous immunoglobulin, splenectomy and, in treatment-refractory disease, immunomodulatory agents, such as danazol or azathioprine.[5,6] These treatments are not always effective, or at best have only a transient effect, and treatment-related adverse events often restrict further use.[5]

Impaired platelet production may also be a potential disease mechanism for ITP.[1,5] As a result, growth factor and growth factor analogue stimulation of megakaryopoiesis, such as with recombinant thrombopoietic growth factors, has also been investigated.[1,7,8] Although these agents increased platelet counts, some (e.g. pegylated recombinant human megakaryocyte growth and development factor, a recombinant thrombopoietin) were associated with autoantibodies that crossreact with and neutralize endogenous thrombopoietin, leading to severe thrombocytopenia.[8] Therefore, research into other agents, including non-peptide thrombopoietin receptor agonists that activate the thrombopoietin receptor at different sites to thrombopoietin, was initiated.[8]

This article provides an overview of the pharmacological properties of the non-peptide thrombopoietin receptor agonist eltrombopag (Promacta®), and reviews the clinical efficacy and tolerability of the drug in adult patients with chronic ITP. Medical literature on the use of eltrombopag in adults with chronic ITP was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- Eltrombopag is an orally bioavailable, low molecular weight, synthetic nonpeptide thrombopoietin receptor agonist.[9] Eltrombopag selectively binds to

the transmembrane domain of the thrombopoietin receptor present on the surface of platelets, megakaryocytes and megakaryocyte precursor cells,[9] and acts via the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signalling pathway.[9] Responses to eltrombopag are similar to those observed with endogenous thrombopoietin (stimulation of transcription through STAT-based and megakaryocyte-specific promotors).[9] Thus, it has a positive effect on the proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.[9]

- Eltrombopag showed specificity *in vitro* for human and chimpanzee thrombopoietin receptors and no activity against cell lines that did not express the thrombopoietin receptor.[9] Eltrombopag showed activity in human and chimpanzee, but not cynomolgus or murine, cells by activating STAT5, demonstrating activation of the thrombopoietin receptor.[9] Eltrombopag was inactive against cell lines against which various cytokines (e.g. interleukin-3, erythropoietin, interferon-α) were active.[9]
- *In vitro* studies have demonstrated that eltrombopag has a proliferation effect similar to that seen with thrombopoietin on megakaryocytic cells expressing the thrombopoietin receptor.[9] For example, eltrombopag stimulated proliferation of BAF3/Tpo-R cells (concentration that produces a 50% effective response [EC_{50}] 30 nmol/L) and CD41+ cells (marker of megakaryocyte differentiation; EC_{50} 100 nmol/L) in human bone marrow cell lines. Eltrombopag was at least as effective as thrombopoietin in stimulating proliferation of CD41+ cells.[9]
- *In vitro* and *ex vivo* studies using platelet samples from healthy volunteers and patients with chronic ITP have shown that eltrombopag has no effect on platelet aggregation or activation,[10-12] and platelet function with eltrombopag did not differ from that with placebo.[11] These studies also showed that eltrombopag did not enhance or antagonize agonist-induced platelet aggregation.[10,12]
- Platelet counts in healthy volunteers receiving eltrombopag 5–75 mg/day for 10 days in a randomized, single-blind, placebo-controlled, phase I study showed a dose-dependent increase.[11] Increases were evident from day 8 of treatment, with peak platelet counts occurring at day 16.[11] Platelet counts returned to baseline values by day 22 (12 days after the last dose of eltrombopag).[11] There was no evidence of rebound thrombocytopenia after ceasing eltrombopag treatment.[11] Effects on platelet counts in the phase II[13] and III[14] studies are discussed in section 3.
- The phase II study showed that thrombopoietin levels were within the normal range at baseline and were unaffected by eltrombopag therapy.[13]
- Eltrombopag appears to have no clinically significant effect on corrected QT (QT_c) interval, following a thorough QT/QT_c interval study in healthy adult volunteers.[15]

2. Pharmacokinetic Profile

This section is based on a single-blind, placebo-controlled, phase I study in 73 healthy male volunteers receiving oral eltrombopag 5–75 mg/day for 10 days[11] and additional information from the US prescribing information.[15] Few published pharmacokinetic data for the recommended 50 mg/day dosage are available; 75 mg/day, the recommended dosage for non-responders, is focused on as an alternative dosage whenever possible.

Absorption and Distribution

- A population-based pharmacokinetic model suggests that a two-compartment model with dual sequential first-order absorption and lag-time best describes the pharmacokinetic profile of oral eltrombopag.[15]
- Eltrombopag is rapidly absorbed after oral administration, with peak plasma concentrations (C_{max}) achieved within 2–6 hours of administration in patients with ITP.[15] The pharmacokinetics of eltrombopag were dose proportional over a dose range of 5–75 mg.[11]
- Based on a two-compartment model, area under the concentration-time curve (AUC) over a dosage interval (AUC_τ) values after administration of eltrombopag 50 or 75 mg once daily in adult patients

with ITP were estimated to be 91.9 and 146 μg • h/mL.[15] A 75 mg single solution dose of eltrombopag was associated with ≥52% oral absorption of drug-related material.[15]

• *In vitro* studies suggest that eltrombopag is highly bound to human plasma proteins (>99%); eltrombopag in blood cells makes up 50–79% of the plasma concentration.[15]

• Eltrombopag pharmacokinetics are altered when the drug is administered with polyvalent cations. Coadministration of eltrombopag and a metal cation-containing antacid was associated with a significant decrease in systemic exposure (70%) to eltrombopag.[15]

• Similarly, in a separate study, a high-calcium, high-fat breakfast increased time to maximum concentration by 1 hour[15] and decreased C_{max} and AUC from time zero to infinity (AUC_{∞}) values by 65% and 59%.[15] The calcium content of the meal may have contributed to these changes. The fat content of the meals had no significant effect on eltrombopag C_{max} or AUC_{∞} values when the calcium content was low.[15]

Metabolism and Elimination

• *In vitro* studies indicate that eltrombopag is metabolized in the liver.[15] Although the glutathione conjugation pathways predominate, these have not yet been fully characterized. Cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C8 are responsible for minor oxidative metabolism, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and UGT1A3 are responsible for glucuronidation.[15]

• The plasma elimination half-life of eltrombopag in patients with ITP was approximately 26–35 hours.[15] Eltrombopag is eliminated in the faeces and via the kidneys. Faecal elimination predominates; 59% of a dose of eltrombopag is excreted in faeces (20% as unchanged drug) and 31% in urine (0% as unchanged drug).[15]

Potential Drug Interactions

• No clinical studies as yet have investigated the effects of agents that are strong inducers or inhibitors of CYP1A2, CYP2C8, UGT1A1 or UGT1A3 on eltrombopag metabolism.[15]
• A clinical study in healthy volunteers showed that eltrombopag is not an inhibitor of, and does not induce, CYP isoenzymes.[15] *In vitro* studies suggest that eltrombopag may be an inhibitor of UGT isoenzymes.[15]
• Eltrombopag is not a substrate for P-glycoprotein or organic anion transporting polypeptide (OATP) 1B1.[15] However, clinical and preclinical studies showed inhibition of OATP1B1 by eltrombopag.[15] Increased systemic exposure to rosuvastatin (an OATP1B1 substrate) was seen in healthy volunteers receiving concurrent eltrombopag and rosuvastatin (a 2-fold increase in plasma rosuvastatin C_{max} and a 1.5-fold increase in AUC_{∞}), suggesting the necessity of a lower rosuvastatin dosage when given concomitantly with eltrombopag.[15]

Special Populations

• Patient ethnicity may affect the pharmacokinetics of eltrombopag.[15] Systemic exposure to the drug may be increased in individuals of East-Asian descent (based on estimations from a population-based pharmacokinetic model); as a consequence, an initial dose decrease to 25 mg/day is recommended in these patients. The pharmacodynamic response to eltrombopag was qualitatively similar to non-Asian subjects in this model, although the absolute response was somewhat greater.
• Although some studies have shown a slightly higher systemic exposure to eltrombopag in African -American individuals, the effects of African-American ethnicity on the pharmacokinetics of eltrombopag have not been established.[15]
• As might be expected with an agent that is metabolized in the liver, systemic exposure to eltrombopag is increased in patients with mild or moderate to severe hepatic impairment (41% and 80–93% increases in AUC_{∞}, respectively) compared with healthy individuals.[15] Consequently, the

initial eltrombopag dosage should be reduced to 25 mg/day in patients with moderate or severe hepatic impairment.

- Safety and efficacy of eltrombopag in patients with varying degrees of renal function have not been established and close monitoring of safety and platelet response is recommended for patients with renal impairment.[15]

3. Therapeutic Efficacy

The therapeutic efficacy of eltrombopag in patients with chronic ITP has been examined in two trials of 6 weeks' duration,[13,14] one intermittent therapy trial[16] and an extension study[17] of patients who had completed a previous eltrombopag study.[13,14,16,18] Long-term results are also available from a 6-month study.[18]

6-Week Trials

The efficacy of eltrombopag in the treatment (single cycle of ≤6 weeks) of chronic ITP was investigated in two fully published, randomized, double-blind, placebo-controlled, multicentre studies. One was a phase II dose-finding study of eltrombopag 30, 50 or 75 mg/day or placebo in 118 patients[13] and the other was a phase III study of eltrombopag 50 mg/day or placebo in 114 patients.[14] Pooled data from the phase II and III trials were only available as abstracts[19-22] and have been supplemented by data from the US prescribing information.[15]

Adult patients were eligible for either study if they had a 6-month or longer history of ITP had either not responded to at least one prior therapy, including splenectomy, or had relapsed within 3 months of previous therapy and had a platelet count of <30 000 cells/μL.[13,14] Patients were followed up for an additional 6 weeks after completing treatment. Concomitant ITP medications could be continued if the dosage had been stable for at least 1 month.[13,14] In the phase III trial, patients who had not responded to eltrombopag 50 mg/day after 3 weeks of treatment could have their dosage increased to 75 mg/day for the remaining 3 weeks.[14] Within each treatment arm, patients were stratified according to use of concomitant ITP therapy, platelet count (≤15 000 or >15 000 cells/μL) and splenectomy status.[13,14]

In both studies, if a patient reached platelet counts of >200 000 cells/μL, treatment was discontinued for that patient to reduce the risk of thrombocytosis.[13,14] However, patients continued to be followed up over the full trial duration.

The primary efficacy endpoint in both studies was the response rate (the proportion of patients with a platelet count of ≥50 000 cells/μL) after 6 weeks of treatment.[13,14] Secondary endpoints differed between the trials; however, both assessed the incidence and severity of bleeding events (rated using the WHO Bleeding Scale) [descriptive analyses only] and health-related quality of life (HR-QOL). The proportion of patients with a platelet count of >200 000 cells/μL was also assessed in both studies.[13,14]

Exploratory analyses of eltrombopag 50 mg/day versus placebo, based on pooled data from the phase III trial, and the 50 mg/day and placebo arms of the phase II trial, evaluated the response to eltrombopag by splenectomy status[21] and severity of bleeding.[19]

The median platelet count at baseline was 17 000–18 000 cells/μL for all randomized patients (normal range 150 000–400 000 cells/μL) in a pooled analysis of the phase II and III trials; at baseline, 43% of patients had undergone splenectomy, 39% used concomitant ITP therapies and 47% had a platelet count of ≤15 000 cells/μL.[20]

- A 6-week dose-finding study established that the optimal starting dosage of eltrombopag in adult patients with chronic ITP was 50 mg/day. Significantly more eltrombopag 50 (n = 30) or 75 mg/day (n = 28) than placebo (n = 29) recipients were responders (70% and 81% vs 11%; both $p < 0.001$ vs placebo).[13] Recipients of eltrombopag 30 mg/day (n = 30) did not significantly differ from placebo recipients in response rate (28% vs 11%).[13] The median platelet counts at endpoint with eltrombopag 50 or 75 mg/day were 128 000 and 183 000 cells/μL compared with 16 000 cells/μL with placebo.[13]

- The proportion of patients with platelet counts of >200 000 cells/μL during the study were ≈9-fold and ≈12-fold higher among recipients of eltrombopag 50 and 75 mg/day than placebo (37% and 50% vs 4% [statistical analyses not reported]).[13]
- Eltrombopag showed efficacy in increasing platelet count in patients with chronic ITP in the phase III study (figure 1). Significantly more eltrombopag 50 mg/day (n = 73) than placebo (n = 37) recipients demonstrated a response (59% vs 16%; $p < 0.0001$) [primary endpoint].[14] In addition, ≈8-fold more eltrombopag than placebo recipients had platelet counts >200 000 cells/μL[14] (figure 1) and ceased treatment during the study (statistical analyses not reported). The eltrombopag dosage was increased to 75 mg/day on or after day 22 of the study in 34 eltrombopag recipients because of no response to a 50 mg/day dosage; of these, 10 patients (29%) responded to treatment.[14]
- Response to treatment was not affected by stratification factors (the presence of concomitant ITP medication,[14] baseline platelet count[14] or splenectomy status[14,21]).

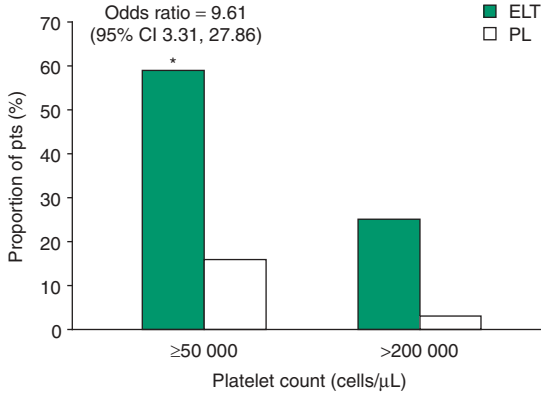


Fig. 1. Efficacy of eltrombopag (ELT) in adult patients (pts) with chronic immune (idiopathic) thrombocytopenic purpura. Proportion of pts demonstrating a response (platelet count ≥50 000 cells/μL; primary endpoint) or platelet count >200 000 cells/μL after 6 weeks of treatment with ELT 50 mg/day (n = 73) or placebo (PL; n = 37) in a randomized, double-blind, multicentre, phase III study.[14] The ELT dosage was increased to 75 mg/day on or after day 22 of the study in 34 ELT recipients because of no response to a 50 mg/day dosage. * $p < 0.0001$ vs PL.

- The odds of any bleeding in the phase III study were significantly lower among eltrombopag recipients than among placebo recipients on day 43 (odds ratio 0.27; 95% CI 0.09, 0.88; $p = 0.029$).[14] No clinically significant bleeding (WHO grade 2–4) occurred while patients had platelet counts ≥50 000 cells/μL.[14]
- Severe bleeding events during the 6 weeks of treatment and 6 weeks of follow-up were infrequent (9 of 231 patients) according to a combined analysis, and occurred only in patients who did not respond to or discontinued treatment with eltrombopag, or who received placebo.[19]
- In general, HR-QOL assessed using the Short Form-36 questionnaire did not significantly change from baseline in eltrombopag or placebo recipients in either study.[13,14]
- In most patients in the phase II[13] and phase III[14] trials, platelet count returned to baseline levels within 2 weeks of stopping eltrombopag therapy; however, two patients demonstrated a prolonged platelet count elevation (>100 000 cells/μL after 85 days).[22]
- Within 4 weeks of treatment cessation, 11% of eltrombopag and 13% of placebo recipients in the phase III study had platelet counts <10 000 cells/mL and ≥10 000 cells/mL less than their baseline count.[14]
- Transient decreases in platelet counts to values below baseline were observed in 10% and 6% of eltrombopag and placebo recipients following treatment discontinuation in the controlled clinical trials.[15]

Intermittent Treatment

Intermittent treatment of chronic ITP with eltrombopag has been investigated in a phase II, noncomparative study (REPEAT [Repeat Exposure to Eltrombopag in Adults with Idiopathic Thrombocytopenic Purpura]).[16]

REPEAT enrolled patients with previously treated chronic ITP and baseline platelet counts of 20 000–50 000 cells/μL (n = 66).[16] Patients received eltrombopag 50 mg/day for three cycles (up to 6 weeks of treatment followed by an off-therapy

period of up to 4 weeks). A response to treatment was defined as a platelet count of ≥50 000 cells/μL that was at least twice the baseline count at day 43 of the treatment cycle, or early treatment discontinuation due to platelet counts >200 000 cells/μL. Patients who did not respond in cycle 1 did not continue in the study. The primary endpoint of REPEAT was consistency between cycles (i.e. the proportion of patients who showed a response in cycle 1 who also responded in cycles 2 or 3).[16]

- A total of 80% of patients responded in cycle 1 of the REPEAT study and were thus permitted to continue in the study.[16] Consistency in eltrombopag response between cycles was demonstrated in patients who received further cycles of eltrombopag: a total of 87% of cycle 1 responders also responded in cycle 2 or 3.[16] Median platelet counts remained above 79 000 cells/μL after day 8 in all three cycles and <20% of patients experienced any bleeding in each cycle.

Long-Term Treatment

Results of a 6-month, randomized, double-blind, placebo-controlled, phase III study of eltrombopag (RAISE [RAndomized placebo-controlled ITP Study with Eltrombopag])[18] and an ongoing, noncomparative study (EXTEND [Eltrombopag eXTENded Dosing])[17] are available as abstracts.

RAISE included adult patients with chronic ITP who had platelet counts of <30 000 cells/μL and who had been previously treated for ITP.[18] A total of 197 patients were randomized to individualized treatment with eltrombopag (initial dosage 50 mg/day, then adjusted according to individual response) [n = 135] or placebo (n = 62). The primary endpoint for RAISE was the odds of responding (i.e. achieving a platelet count of 50 000–400 000 cells/μL) during the treatment period.[18]

EXTEND enrolled patients with chronic ITP who had previously completed an eltrombopag trial (including the pivotal 6-week trials,[13,14] the REPEAT trial[23] and RAISE[18]).[17] Patients received individualized dosages (initial dosage 50 mg/day, adjusted to 25–75 mg/day depending on platelet count). A total of 207 patients had evaluable data available; median duration of therapy was 91.5 days.[17]

- In EXTEND, platelet counts of ≥50 000 cells/μL were seen in 79% of eltrombopag patients at least once during the study, and similar results were observed among patients regardless of whether they received concomitant ITP medication at baseline or whether they had undergone a splenectomy.[17] Preliminary results from the RAISE study are consistent with these findings; recipients of eltrombopag were ≈8 times more likely to respond during the treatment period than those receiving placebo (odds ratio 8.2; 99% CI 3.59, 18.73; $p < 0.001$).[18]

4. Tolerability

Tolerability data for eltrombopag are available from the clinical trials discussed in section 3. This section focuses mainly on 6-week data from the phase III trial,[14] supplemented by data from the phase II trial[13] and pooled analyses of these trials.[15,20,21] Results of the intermittent REPEAT trial are briefly discussed.[15,16] Some data are available only as abstracts.[16,20,21]

- Eltrombopag was generally well tolerated in clinical trials in patients with chronic ITP.[13,14,24] Adverse events were reported by 59% of eltrombopag (n = 76) and 37% of placebo (n = 38) recipients in the 6-week phase III trial.[14] Combined analysis of the 6-week phase II and III trials (106 eltrombopag and 67 placebo recipients) indicated that few eltrombopag 50 mg/day or placebo recipients discontinued treatment because of adverse events (5% vs 7%).[20] The incidence of serious adverse events also did not differ between eltrombopag and placebo recipients (11% vs 12%).[20]
- The most common adverse events in the 6-week phase III trial that occurred more frequently with eltrombopag 50 mg/day than with placebo were gastrointestinal in nature (figure 2).[14]
- Data from the placebo-controlled clinical trials demonstrate that the most common adverse events (in ≥4% of eltrombopag 50 mg/day recipients [n = 106) and numerically more common than in placebo recipients [n = 67]) were nausea (6% and

4% of eltrombopag and placebo recipients), vomiting (4% and 3%) and menorrhagia (4% and 1%).[15]

- Eltrombopag may be associated with hepatotoxicity. The US prescribing information includes a boxed warning about this risk (see section 5 for further details).[15] The overall rate of serum liver test abnormalities in the controlled clinical trials was 10% and 8% of eltrombopag and placebo recipients; these were predominantly grade 2 or less in severity. Few patients (1% and 3%) discontinued treatment due to hepatobiliary abnormalities.[15]
- Cataract development or progression, deemed a risk in preclinical studies, was reported in 5% of eltrombopag recipients and 3% of placebo recipients in a pooled analysis.[15]
- Pooled analyses demonstrated that splenectomy status was not associated with any clinically meaningful difference in the incidence of the most common adverse events between eltrombopag and placebo recipients.[21]
- The most common serious adverse event was haemorrhage; most haemorrhagic events occurred after eltrombopag discontinuation.[15] There were no deaths that were deemed treatment-related in the 6-week phase II or phase III studies.[13,14]
- Less than 50% of 66 patients undergoing intermittent administration of eltrombopag 50 mg/day in the REPEAT study reported adverse events in any cycle.[16] Headache was the most common adverse event in these patients (21% of patients).
- Thrombopoietin receptor agonists increase the risk for developing or progressing reticulin fibre deposition in bone marrow. As a consequence, eltrombopag recipients should, prior to eltrombopag initiation, have peripheral blood smears to establish a baseline level of cellular morphological abnormalities.[15] Once a stable dosage of eltrombopag has been identified, monthly peripheral blood smears and complete blood counts should be taken to test for new or worsening morphological abnormalities or cytopenias. If these develop, eltrombopag treatment should be discontinued and a bone marrow biopsy (including staining for fibrosis) should be considered.[15]

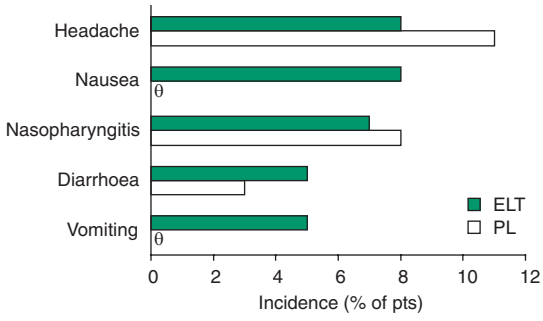


Fig. 2. Tolerability of eltrombopag (ELT) in adult patients (pts) with chronic immune (idiopathic) thrombocytopenic purpura. Incidence of adverse events reported in ≥5% of ELT recipients over 6 weeks of treatment with ELT 50 mg/day (n = 76) or placebo (PL; n = 38) in a randomized, double-blind, multicentre, phase III study.[14,24] The ELT dosage was increased to 75 mg/day on or after day 22 of the study in 34 ELT recipients because of no response to a 50 mg/day dosage.[14] θ = 0% incidence.

5. Dosage and Administration

The recommended starting dosage of eltrombopag is 50 mg/day, with a maximum dosage of 75 mg/day, for adults with chronic ITP who have experienced an insufficient response to corticosteroids, immunoglobulins or splenectomy.[15] The dosage should be adjusted to achieve and maintain a platelet count of ≥50 000 cells/μL. Patients of East-Asian descent should receive a 25 mg/day starting dosage.

Eltrombopag is to be given on an empty stomach (1 hour before or 2 hours after a meal), and there should be a 4-hour interval between eltrombopag administration and the administration of another medication, food or supplements that contain polyvalent cations (e.g. calcium, iron).[15] Treatment should be discontinued if the platelet count does not increase to a level that avoids clinically important bleeding after 4 weeks at the maximum dosage.

The US prescribing information includes a boxed warning for a risk of hepatotoxicity.[15] Liver function tests should be administered before and at regular intervals during eltrombopag treatment. Treatment should be discontinued if ALT levels increase to ≥3 times the upper limit of normal and are progressive, or persistent for at least 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for

hepatic decompensation.[15] Reinitiating eltrombopag treatment in these situations is not recommended.

If the potential benefit of reinstating eltrombopag treatment is considered to outweigh the hepatotoxicity risk, proceed with caution and monitor hepatic function closely. Caution should also be exercised when treating patients with moderate or severe hepatic insufficiency; these patients should receive a 25 mg/day starting dosage.[15]

The manufacturer's prescribing information should be consulted for detailed information on dosage and administration.

6. Eltrombopag: Current Status

Eltrombopag currently has orphan drug status in the US and is indicated for use as therapy in previously treated adult patients with chronic ITP.[25] Eltrombopag has shown clinical efficacy in two well designed, 6-week trials (including a phase III study) in adult patients with chronic ITP and appears to be generally well tolerated in the short term. Fully published results from the REPEAT, RAISE and EXTEND trials are awaited. Eltrombopag is also being evaluated in thrombocytopenia associated with liver disease[26-28] and in patients with solid tumours undergoing chemotherapy.[29]

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