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ADIS DRUG EVALUATION

Eltrombopag: A Review in Paediatric Chronic Immune Thrombocytopenia

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Abstract Eltrombopag (Promacta®; Revolade®) is an orally active thrombopoietin receptor agonist recently approved in the USA and the EU for use in paediatric patients aged ≥1 year with chronic immune thrombocytopenia (ITP) who have had an insufficient response or are refractory to other ITP treatments (e.g. corticosteroids, immunoglobulins or splenectomy). The efficacy of 7 or 13 weeks' therapy with oral eltrombopag (up to 75 mg/day) was compared with that of placebo in patients aged 1–17 years with previously treated chronic ITP in randomized, double-blind, multicentre phase II and III trials (PETIT and PETIT-2). In these trials, the platelet response rate (primary endpoint of PETIT) and the sustained platelet response rate (primary endpoint of PETIT-2) were significantly higher with eltrombopag than with placebo. A clinical benefit was shown by a reduction in the need for rescue therapy with eltrombopag versus placebo in both trials and a reduction of clinically significant bleeding in PETIT. During longer-term therapy (open-label treatment period for ≥24 weeks), eltrombopag maintained platelet counts above 50×10^9/L in the majority of patients and approximately one-half of patients were able to reduce or discontinue concurrent ITP drugs. Eltrombopag was generally well tolerated. Current evidence suggests that eltrombopag is a valuable addition to the limited treatment options available for the management of chronic ITP in paediatric patients with an inadequate response to first-line therapies.

Eltrombopag: clinical considerations in previously treated paediatric patients with chronic ITP
Oral thrombopoietin receptor agonist
Achieved a sustained platelet response rate of ≈40 % in PETIT-2
Reduced the need for rescue therapy in PETIT and PETIT-2 and reduced clinically significant bleeding in PETIT
Reduced the need for concomitant drugs for ITP in most patients during longer-term treatment
Generally well tolerated

1 Introduction

Immune thrombocytopenia (ITP; also known as idiopathic thrombocytopenic purpura) is an autoimmune haematological disorder [1, 2]. It is characterized by thrombocytopenia (a peripheral blood platelet count of $<100 \times 10^9$/L) and the potential for bleeding [1]. ITP in children is

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usually a benign condition that results in spontaneous remission within 6–12 months in the majority of children [2, 3]. However, approximately 5–10 % of paediatric patients with chronic ITP require some form of therapy directed at raising platelet levels [2]. The goal of treatment of chronic ITP is to maintain a platelet count that is adequate to prevent bleeding, rather than correcting the platelet count to normal levels [1–4].

First-line therapies include short-course corticosteroids (e.g. prednisone, prednisolone), intravenous immunoglobulin G and in some cases anti-D immunoglobulin [2–4]. Paediatric ITP patients who do not respond to first-line treatments or who experience adverse effects, have previously had limited treatment options [2]. Second-line therapies generally include rituximab, high-dose dexamethasone, immunosuppressant drugs (e.g. ciclosporin, azathioprine), danazol or splenectomy [3, 4]. However, cytotoxic drugs should be used with extreme caution in children and splenectomy is an invasive, irreversible procedure that may be associated with long-term complications (e.g. sepsis), highlighting the need for effective alternative therapies in these refractory patients [2–4].

Oral eltrombopag (Promacta®, Revolade®), a small-molecule thrombopoietin receptor agonist, is established in the treatment of adults with chronic ITP [5–7] and has recently been approved in the USA and the EU for the treatment of thrombocytopenia in paediatric patients aged ≥1 year with chronic ITP who have had an insufficient response [6] or are refractory [7] to other ITP treatments (e.g. corticosteroids, immunoglobulins or splenectomy). It is available as a tablet or powder for oral suspension (PfOS) formulation [6, 7]. This narrative review focuses on the efficacy and tolerability of eltrombopag in children and adolescents (aged 1–17 years) with chronic ITP not responsive to first-line therapies, and overviews its pharmacological properties. The use of eltrombopag in adults [5] and for other approved indications [8, 9] is reviewed elsewhere and is beyond the scope of this review.

2 Pharmacological Properties of Eltrombopag

The pharmacodynamic and pharmacokinetic properties of eltrombopag have been reviewed in detail previously [5, 8, 9]; therefore, this section briefly summarizes its key properties and focuses on data in paediatric patients where available.

2.1 Pharmacodynamic Profile

Oral eltrombopag interacts with the transmembrane domain of the thrombopoietin receptor and initiates signaling cascades to increase platelet production [10]. For instance, eltrombopag activates the Janus kinase/signal transducers and activators of transcription (JAK/STAT) and Ras-mitogen-activated protein kinase (MAPK) pathways that induce survival, proliferation and megakaryocyte differentiation activities in human bone marrow progenitors [10].

Eltrombopag showed high specificity for human and chimpanzee thrombopoietin receptors, and when combined with recombinant human thrombopoietin eltrombopag displayed an additive rather than antagonistic effect, suggesting that thrombopoietin and eltrombopag have different binding sites on the receptor [10]. In vitro, eltrombopag dose-dependently increased the differentiation of bone marrow CD34+ cells into CD41+ megakaryocytes and stimulated the proliferation of BAF3/hTpoR cells. Eltrombopag did not activate JAK/STAT signalling pathways in cells expressing other hematopoietic growth factor receptors (e.g. interleukin-3, erythropoietin, interferon-α) in vitro. Eltrombopag may also be associated with an increase in platelet life-span by the prevention of apoptosis in thrombopoietin-dependent cells [10].

Eltrombopag increases platelet counts in healthy adult volunteers [11] and in children [12, 13] and adults [14] with chronic ITP. In healthy adult volunteers, eltrombopag dose-dependently increased platelet counts; this returned to baseline levels after discontinuation, indicating that eltrombopag does not affect the ongoing rate of platelet destruction [11].

Eltrombopag had little or no effect on platelet function (platelet aggregation or activation), according to an in vitro study using platelet samples from healthy volunteers [15], a study in healthy volunteers (5–75 mg/day) [11], and in a study in patients with chronic ITP (patients received eltrombopag 50 or 75 mg/day) [16]. Furthermore, eltrombopag did not enhance the ability of adenosine diphosphate, collagen or the thrombin receptor-activating peptide to induce platelet aggregation [15, 16].

Therapeutic (50 mg/day) and supratherapeutic (150 mg/day) dosages of eltrombopag did not have a clinically significant effect on cardiac repolarization, according to results of a thorough corrected QT study in adult volunteers [17].

2.2 Pharmacokinetic Profile

The pharmacokinetics of oral eltrombopag in paediatric patients were best described by a two-compartment model with first-order absorption and first-order elimination [18]. Eltrombopag displays linear pharmacokinetics in adults, with dose-dependent increases in exposure seen with administration of eltrombopag 5–75 mg capsules to healthy volunteers [11], but were not fully linear above 150 mg [19]. Following once-daily administration of eltrombopag

20–75 mg capsules for 10 days in healthy adults, accumulation of eltrombopag was ≈40–50 % [11].

Eltrombopag is rapidly absorbed, with maximum plasma eltrombopag concentrations (C_{max}) reached (t_{max}) in 2–6 h [6, 7]. The absolute oral bioavailability of eltrombopag has not been established in humans. The oral absorption of drug-related material was estimated to be ≥52 % based on urinary and faecal excretion following a single dose of eltrombopag 75 mg in solution [6, 7].

In patients aged 12–17 years, steady-state geometric mean C_{max} was generally similar to that observed in adult patients following repeat administration of eltrombopag (normalized to 50 mg once daily) (6.80 vs. 7.03 μg/mL) [6]. Geometric mean C_{max} was ≈1.5-fold higher in patients aged 1–5 or 6–11 years receiving eltrombopag (normalized to 50 mg once daily) (11.6 and 10.3 μg/mL) than in adults. The geometric mean area under the plasma concentration–time curve (AUC) during the dosing interval (AUC_{τ}) of eltrombopag (normalized to 50 mg once daily) was also ≈1.5-fold higher in patients aged 1–5 or 6–11 years than in patients aged 12–17 years or adults (162 and 153 μg · h/mL vs. 103 and 101 μg · h/mL, respectively) [6]. Even though exposure to eltrombopag is numerically higher in paediatric patients aged 6–11 years than those aged 12–17 years or adults, a pharmacokinetic/pharmacodynamics model predicted that a 50 mg/day dosage (the recommended dose in adults) would still be a suitable starting dosage to achieve target platelet counts of $>50 \times 10^9$/L [18]. In patients aged 1–5 years a 25 mg/day dose is recommended (Sect. 5) [6, 7].

In a randomized, open-label, crossover, relative bioavailability study in adults, eltrombopag PfOS was associated with a 22 % higher AUC from time zero to infinity (AUC_{∞}) and 31 % higher C_{max} values than the tablet formulation when administered as a single 25 mg dose under fasting conditions [20]. The mean relative bioavailability of the PfOS formulation in patients with ITP aged 1–5 years was 29 % lower than the tablet formulation in patients with ITP aged 6–17 years [18]. The bioequivalence of the PfOS and tablet formulations in patients aged 1–5 years has not been specifically studied [18].

Administration of eltrombopag tablets with a high-fat, high-calcium breakfast reduced the eltrombopag AUC_{∞} by 59 % and C_{max} by 65 % compared with the fasting state in healthy adult volunteers [21]. Additionally, administration of a single 25 mg dose of the eltrombopag PfOS formulation with a high-calcium meal reduced plasma eltrombopag AUC_{∞} by 75 % and C_{max} by 79 % compared with the fasting state in adults, as well as delaying t_{max} by 1 h [20]. Administration of eltrombopag PfOS formulation 2 h before or 2 h after a high-calcium meal attenuated the food effect, but plasma eltrombopag exposure was decreased [20]. Eltrombopag should not be taken with food (Sect. 5) [6].

Based on a radiolabel study, the concentration of eltrombopag in blood cells is ≈50–79 % of that in plasma [6]. Eltrombopag is highly bound to plasma proteins in vitro (>99.9 %) [6, 7]. Eltrombopag is a substrate for breast cancer resistance protein (BCRP), but is not a substrate for P-glycoprotein or organic anion transporting polypeptide (OATP) 1B1 [6, 7].

Eltrombopag is extensively metabolized through oxidation [via cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C8], cleavage, and conjugation with glucuronic acid [via uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and UGT1A3], glutathione or cysteine [6, 7].

Faecal elimination predominates, with 59 % of a dose of eltrombopag excreted in faeces (20 % as unchanged drug) and 31 % in urine (0 % as unchanged drug) [6, 7]. The plasma elimination half-life of eltrombopag is ≈21–32 h in healthy volunteers [6, 7] and ≈26–35 h in adults with ITP [6]. The apparent clearance following oral administration increased with increasing body weight [6, 7], and was 0.612 L/h for a typical 70 kg, non-East/Southeast Asian male receiving the eltrombopag tablet formulation [18].

2.2.1 *Special Patient Populations and Potential Drug Interactions*

Hepatic impairment is associated with an increase in systemic exposure to eltrombopag [6, 7]. In adults, the AUC_{∞} of eltrombopag was 41 % higher in subjects with mild (Child-Pugh Class A) hepatic impairment and approximately twofold higher in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class B) hepatic impairment than in subjects with normal hepatic function, following a single 50 mg dose (Sect. 0).

Paediatric patients with ITP of East Asian descent (i.e. Japanese, Chinese, Taiwanese and Korean) had ≈43 % higher eltrombopag AUC_{τ} values than those not of East Asian descent (predominantly Caucasian) [6, 7]. Thus, the recommended starting dose is lower for East Asian patients (Sect. 5) [6, 7].

In vitro, eltrombopag is an inhibitor of CYP2C8 and CYP2C9, several UGT isoenzymes, BCRP and OATP1B1 [6, 7]. Exposure of the OATP1B1 and BCRP substrate rosuvastatin was increased by the coadministration of eltrombopag. Caution should be used when coadministering eltrombopag and substrates of OATP1B1 or BCRP. Clinically significant drug interactions have been reported between eltrombopag and antacids and other products containing polyvalent cations (reduced eltrombopag exposure) (Sect. 5) [6, 7].

3 Therapeutic Efficacy of Eltrombopag

The efficacy of oral eltrombopag in paediatric patients with previously treated persistent or chronic ITP was evaluated in a three-part, multicentre, phase II trial (PETIT) [12] and a two-part, multicentre, phase III trial (PETIT-2) [13]. The PETIT trial included a 24-week dose-finding phase ($n = 15$) and a 7-week randomized, double-blind, placebo-controlled phase ($n = 67$), which was followed by an open-label phase ($n = 64$) during which patients randomized to eltrombopag received an additional 17 weeks' therapy and those randomized to placebo received eltrombopag for 24 weeks [12]. PETIT-2 included a 13-week, randomized, double-blind, placebo-controlled period ($n = 92$) followed by a 24-week, open-label extension during which all patients received eltrombopag ($n = 87$) [13].

During the dose-finding phase of PETIT, the starting doses were conservative and multiple dose escalations occurred during the study period [12]. For instance, 14 of 15 subjects (93 %) needed ≥4 eltrombopag dose increases during the 24-week period [12]. At the end of the dose-finding phase, most (70 %) patients aged 6–17 years were receiving eltrombopag 75 mg daily (maximum allowed dose), and patients aged 1–5 were receiving a median of 66 mg daily (3 mg/kg) [12]. The 15 patients who were included in the dose-finding portion of PETIT did not progress into the double-blind phase [12]. Results from the dose-finding phase were used to establish starting dosages for the randomized phase of PETIT (Table 1); the dose-finding phase is not discussed further in this section [12].

PETIT and PETIT-2 included patients aged 1–17 years with a confirmed diagnosis of persistent or chronic ITP (duration of ≥6 months) [12] or chronic ITP (duration of >12 months) [13]; a platelet count $<30 \times 10^9$/L; had relapsed or refractory disease after at least one prior treatment for ITP; or were unable to continue other treatment for ITP [12, 13].

Patient demographics and baseline characteristics in the eltrombopag and placebo arms at the start of the randomized phase in each trial were well matched [12, 13]. At baseline in PETIT, 15 % of patients had persistent and 85 % had chronic ITP [12]. Additionally, 10 % of patients were receiving drugs for ITP at baseline, platelet counts of $\leq 15 \times 10^9$/L were observed in 51 % of patients and five patients (all in the eltrombopag treatment group) had undergone splenectomy [12]. In PETIT-2, 78 % of patients had previously received at least two treatments for ITP, four patients (all in the eltrombopag treatment group) had undergone splenectomy at baseline, and baseline platelet counts of $\leq 15 \times 10^9$/L were observed in 62 % of patients [13]. Numerically more patients in the eltrombopag treatment group were receiving drugs for ITP than those in the placebo group (21 vs. 3 %) [13]. Approximately one-third of patients were of East Asian ethnicity [13].

In the double-blind treatment periods, eligible patients were stratified according to age cohort (1–5, 6–11 and 12–17 years) and randomized to eltrombopag or placebo (Table 1) [12, 13]. The starting dosage of eltrombopag, as the PfOS formulation (patients aged 1–5 years) or a tablet (patients aged 6–17 years), was determined according to age, bodyweight and ethnicity (Table 1) [12, 13]. The eltrombopag dosage was adjusted based on platelet counts to a maximum dosage of 75 mg [12, 13] or 2 mg/kg [12] once daily. Patients were permitted to receive standard-of-care treatment during the study; however, any new drugs, increased doses of concomitant drugs, platelet transfusions, and splenectomies were considered rescue treatment [12, 13].

The primary endpoint was a platelet response (defined as a platelet count of $\geq 50 \times 10^9$/L without rescue therapy) at least once during days 8–43 in PETIT [12] and a platelet response for ≥6 weeks during weeks 5–12 in PETIT-2 [13].

3.1 Double-Blind Treatment Period

3.1.1 Effects on Platelets

Oral eltrombopag was significantly more effective than placebo in achieving the primary endpoint of a protocol-defined platelet response at least once during days 8–43 [12] or for ≥6 weeks during weeks 5–12 [13] in previously treated paediatric patients with persistent [12] or chronic [12, 13] ITP (Table 1). Furthermore, platelet responses with eltrombopag were achieved irrespective of age, with a platelet response rates of 60–63 % in PETIT [12] and 36–44 % in PETIT-2 [6] observed across the age cohorts (Table 1).

The numerically higher platelet response rate with placebo (80 %) than with eltrombopag (60 %) in patients aged 1–5 years in PETIT is thought to be a result of one-time responses in the placebo group (possibly due to infection), according to the study authors [12]. Of note, in PETIT-2 only the sustained responses were evaluated in the primary endpoint, and the 1–5 years age group had no responders with placebo (versus 36 % with eltrombopag) [12].

The secondary efficacy endpoint analyses demonstrated a benefit with eltrombopag over placebo with respect to the proportion of patients achieving a platelet response in ≥60 % of assessments between days 15–43 (weeks 2–6) in PETIT (Table 1) [12]. Additionally, a platelet response was achieved and maintained through week 6 in 13 patients in the eltrombopag arm (29 %) and in one patient in the placebo arm (5 %). According to a post hoc analysis, 24 %

Table 1 Efficacy of oral eltrombopag during the 7- [12] or 13-week [13] randomized, double-blind treatment periods of PETIT [12] and PETIT-2 [13] in patients aged 1–7 years with previously treated persistent or chronic immune thrombocytopenia

	ITT population		Response rate (% pts)		
	ELT[a]	PL	ELT[a]	PL	Odds ratio (95 % CI)
PETIT [12]					
Platelet response[b] any time during days 8–43[c]					
Overall	45	22	62	32	4.31 (1.39–13.34)*
Pts aged 1–5 years	10	5	60	80	
Pts aged 6–11 years	19	9	63	33	
Pts aged 12–17 years	16	8	63	0	
Sustained platelet response[b,d]	45	22	36	0	5.84 (1.18–28.90)**
PETIT-2 [6, 13]					
Sustained platelet response[b,d,c]					
Overall	64	29	41	3	18.0 (2.3–140.9)***
East Asian pts	20	10	35	0	NC
Pts aged 1–5 years	14	6	36	0	
Pts aged 6–11 years	26	13	42	0	
Pts aged 12–17 years	24	10	39	10	
Platelet response[b] any time during weeks 1–12	63	29	75	21	11.7 (4.0–34.5)****
Platelet response[b] any time during weeks 1–6	63	29	62	17	8.3 (2.7–25.1)***

ELT eltrombopag, *ITT* intent-to-treat, *NC* cannot be calculated, *PL* placebo, *pts* patient(s)

* $p < 0.05$, ** $p < 0.01$ vs. PL, *** $p < 0.001$ vs. PL, **** $p < 0.0001$ vs. PL

[a] Oral suspension formulation in children aged 1–5 years and a tablet formulation in those aged 6–17 years. In pts aged 1–5 years: starting dosage of 1.2 [13] or 1.5 [12] mg/kg once daily (0.8 mg/kg/day for East Asian pts); average ELT dosage 29.0 mg/day (mean) [12] and 26.7 mg/day (median) [13]. In pts aged 6-11 years: starting dosage of 50 once daily (25 mg/day for East Asian pts) in pts weighing ≥27 kg, and 25 [12] or 37.5 [13] mg once daily (12.5 mg/day for East Asian patients) in pts weighing <27 kg; average ELT dosage 47.3 mg/day (mean) [12] and 50.7 mg/day (median) [13]. In pts aged 12–17 years: starting dosage of 37.5 mg once daily [12] or 50 mg once daily (25 mg/day for East Asian pts) for pts weighing ≥27 kg and 37.5 mg/day (25 mg/day for East Asian pts) for pts weighing <27 kg [13]; average ELT dosage 44.8 mg/day (mean) [12] and 69.0 mg/day (median) [13]

[b] Platelet count of $\geq 50 \times 10^9$/L in the absence of rescue therapy

[c] Primary endpoint

[d] Platelet response in ≥60 % of assessments between days 15–43 (weeks 2–6) [12] or for ≥6 weeks from weeks 5–12 [13]

of patients in the eltrombopag group and no patients in the placebo group had a continuous response for >3 weeks. The median time to a platelet response in the eltrombopag group was 20, 12 and 19 days in patients aged 1–5, 6–11 and 12–17 years, respectively. The corresponding times in the placebo group were 33 and 8 days in patients aged 1–5 and 6–11 years (there were no placebo responders aged 12–17 years) [12].

In PETIT-2, eltrombopag was also significantly more effective than placebo with regard to a number of secondary endpoints, including the mean maximum period of continuous platelet response during the first 12 weeks (3.3 vs. 0.4 weeks; $p < 0.0001$) and the proportion of patients achieving a platelet response during the first 6 weeks (also consistent with the primary results of the PETIT trial) and 12 weeks (Table 1) [13].

The weighted mean platelet change, a measure of the magnitude of the platelet count response, was significantly higher in the eltrombopag group than placebo group during 12 weeks in the double-blind period (mean area under the curve 63.9 vs. 23.7; $p < 0.0001$). Furthermore, a repeated-measures analysis of platelet response during this time revealed that eltrombopag recipients had a higher likelihood of maintaining a response than placebo recipients [odds ratio (OR) 25.3; 95 % CI 8.2–78.7; $p < 0.0001$] [13].

3.1.2 *Effects on Bleeding Symptoms, Rescue Treatment and Health-Related Quality of Life*

In PETIT, patients receiving eltrombopag had a significantly lower risk of clinically significant bleeding (WHO grades 2–4) at any point during the double-blind period than placebo recipients according to a logistical regression model (27 vs. 59 % of patients) [OR 0.21; 95 % CI 0.06–0.72; $p = 0.013$] [12]. In PETIT-2, the incidence of clinically significant bleeding decreased from 25 % at

baseline to 5 % at week 12 in eltrombopag and from 21 to 7 % in placebo recipients [13]. Of patients with clinically significant bleeding in PETIT-2, three placebo recipients and no eltrombopag recipients reported WHO grade 3 bleeding, and no patients in either group had WHO grade 4 bleeding [13].

In PETIT, the incidence of any bleeding (WHO grades 1–4) was reduced from 78 % at baseline to 31 % at week 7 in the eltrombopag treatment group, and there was no reduction in the incidence of WHO grades 1–4 bleeding in the placebo group (82 % at both time points) [12]. At 12 weeks in PETIT-2, the incidence of any bleeding was 37 % in the eltrombopag group (71 % at baseline) and 55 % in the placebo group (69 % at baseline) [13].

In a pooled analysis of the PETIT and PETIT-2 trials ($n = 159$; data available as an abstract), patients receiving eltrombopag were significantly less likely to have any bleeding (OR 0.19; $p = 0.011$) or clinically significant bleeding (OR 0.29; $p = 0.007$) during the randomized period compared with those receiving placebo [22]. As with all pooled analyses, these data have their limitations and should be interpreted with caution.

Significantly fewer patients treated with eltrombopag than placebo initiated rescue therapy in PETIT (13 vs. 50 %; OR 0.1; 95 % CI 0.04–0.49; $p = 0.0020$) [12] or in PETIT-2 (19 vs. 24 %; OR 0.44; 95 % CI 0.2–0.9; $p = 0.032$) [13].

In terms of health-related quality of life, changes from baseline in mean Kids' ITP Tools questionnaire scores did not meet the criteria for a minimally important difference in eltrombopag or placebo recipients [12]. Of note, eltrombopag significantly improved health-related quality of life in adults with chronic ITP [23].

3.2 Open-Label Extension

Improvements in platelet counts were maintained during longer-term eltrombopag treatment in previously treated paediatric patients with persistent [12] or chronic [12, 13] ITP. A platelet response was achieved at least once during open-label treatment with eltrombopag in 81 % of patients in PETIT [12] and 80 % of patients in PETIT-2 [13]. The mean cumulative weeks of response (weeks 4–24) was 10.0 weeks and the mean maximum duration of continuous response (weeks 1–24) to eltrombopag was 8.6 weeks in PETIT-2 [13]. Furthermore, platelet responses were achieved irrespective of age [13]. In a pooled analysis ($n = 154$) of PETIT and PETIT-2, 52 and 38 % of patients receiving eltrombopag had a platelet response at least once for ≥50 % of assessments and ≥75 % of assessments, respectively [22]. Rescue therapy was initiated in 24 % of patients in PETIT [12] and 13 % of patients in PETIT-2 [13].

Patients were allowed to discontinue baseline ITP medications if appropriate based on their on-treatment platelet counts and decreased risk of bleeding during the open-label periods of both trials [12, 13]. Among 13 patients receiving other ITP therapies at the start of the PETIT extension study, six patients reduced ($n = 3$) or discontinued ($n = 3$) concomitant therapy (mainly corticosteroids) [12]. Among 15 patients receiving other ITP therapy at baseline of the open-label period in PETIT-2, eight patients reduced ($n = 1$) or discontinued ($n = 7$) concomitant therapy, mainly corticosteroids, without needing rescue therapy. An attempt to reduce or stop a concomitant drug was made in one patient; however, it was not successful and the patient required rescue medication [13].

In PETIT-2, the proportion of patients who experienced any bleeding events was 63 % at the start of the extension study and 24 % at the end, and clinically significant bleeding events were reported in 20 % of patients at the start and in 6 % at study end [13]. No grade 3 or 4 bleeding events were reported [13].

4 Tolerability of Eltrombopag

Oral eltrombopag was generally well tolerated in previously treated paediatric patients with persistent [12] or chronic [12, 13] ITP. During the randomized periods, the incidence of treatment-emergent adverse events in eltrombopag and placebo recipients was 82 versus 95 % in the PETIT trial [12] and 81 versus 72 % in the PETIT-2 trial [13]. In PETIT-2, two patients in the eltrombopag group (increased liver aminotransferases) and one in the placebo group (abdominal haemorrhage) withdrew because of adverse events during the double-blind period [13].

In a pooled analysis of the randomized phases of PETIT and PETIT-2, the most common treatment-emergent adverse events reported in eltrombopag recipients (incidence ≥10 % and greater than placebo) were upper respiratory tract infection and nasopharyngitis (Fig. 1) [6]. In the larger PETIT-2 trial, the most commonly reported drug-related adverse events were aminotransferase abnormalities (6 % of eltrombopag recipients vs. 0 % of placebo recipients) (Sect. 4.1) [13].

Serious adverse events occurred in 9 % of eltrombopag and 10 % of placebo recipients during the randomized phase of PETIT [12] and in 8 and 14 % during the randomized phase of PETIT-2 [13].

Most adverse events during the randomized periods were mild or moderate in severity [12, 13]. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 adverse events (eltrombopag vs. placebo) were reported in 11 versus 19 % of patients in PETIT [12] and in

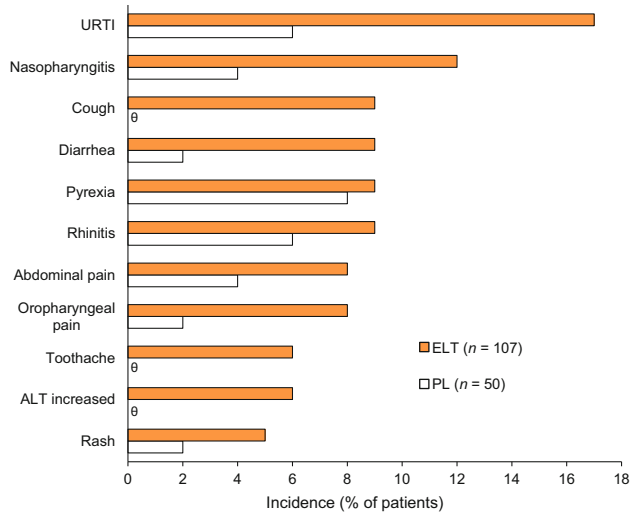

Fig. 1 Tolerability of oral eltrombopag in patients aged 1–17 years with previously treated persistent or chronic immune thrombocytopenia. Incidence (≥5 % of patients and more frequently than placebo) of adverse events in a pooled analysis of the 7- and 13-week randomized periods of the PETIT and PETIT-2 trials [6]. *ALT* alanine aminotransferase, *ELT* eltrombopag, *PL* placebo, *URTI* upper respiratory tract infection, *θ* indicates an incidence of 0

5 versus 28 % of patients in PETIT-2 [13]. Grade 4 adverse events were reported in two (5 %) eltrombopag recipients (neutropenia and febrile neutropenia) and one (5 %) placebo recipient (abdominal pain) in PETIT [12] and in no eltrombopag recipients and one (3 %) placebo recipient (grade 4 bleeding not assessed by WHO criteria) in PETIT-2 [13].

During the open-label extension period, 95 and 79 % of patients reported adverse events during the PETIT [12] and PETIT-2 [13] trials, respectively. Serious adverse events were reported in 12 % of patients in PETIT and 10 % of patients in PETIT-2 [12, 13]. In the PETIT-2 trial, eight (9 %) patients experienced grade 3 or 4 adverse events (one report of grade 4 neutropenia, which was judged to be unrelated to eltrombopag) [13].

In a retrospective case review ($n = 29$) of patients from PETIT and PETIT-2 as well as paediatric patients with chronic ITP who were treated with eltrombopag who did not participate in these trials (data available as an abstract), no new safety concerns were identified during long-term follow-up (median treatment duration 30 months) [24].

4.1 Adverse Events of Special Interest

Eltrombopag is associated with an elevation in liver enzymes or bilirubin in adult patients [6, 7]. In a pooled analysis of the randomized periods of both trials, 4.7 % of paediatric patients receiving eltrombopag had alanine aminotransferase (ALT) levels ≥3 × the upper limit of normal (ULN) compared with no placebo recipients [22]. During the extension studies, an additional seven patients were reported to have ALT levels ≥3 × ULN [22]. Hepatobiliary laboratory findings were typically mild, reversible and not accompanied by clinically significant symptoms that would suggest impaired liver function [12, 13].

In PETIT-2, 2 of 63 (3 %) eltrombopag recipients withdrew during the double-blind phase and 3 of 87 (3 %) eltrombopag recipients withdrew during the open-label phase because of hepatobiliary laboratory abnormalities [13]. Two patients (3 %) in PETIT had hepatobiliary laboratory abnormalities (grade 3 increases in ALT levels) that led to treatment discontinuation during the open-label period [12].

Eltrombopag is associated with an increased risk of the development or worsening of cataracts observed in patients with chronic hepatitis C and thrombocytopenia [6, 7], or chronic ITP [6]. No patient experienced new or worsening cataracts during PETIT [12]. However, cataract events were experienced by two patients in the eltrombopag group (both had received corticosteroids and one had pre-existing cataracts) during PETIT-2 [13]. Regular eye examinations are advised, especially when eltrombopag is used in combination with corticosteroids [6, 7].

The US prescribing information (PI) and the EU summary of product characteristics (SmPC) for eltrombopag contain warnings related to a potential risk of thrombotic or thromboembolic events [6, 7]. There were no reports of thromboembolic adverse events, malignancies or deaths in paediatric patients during either of the studies [12, 13].

Previous reports have suggested that thrombopoietin receptor agonists may increase the risk of reticulin fiber deposition within bone marrow [25]. Bone marrow biopsies were not performed in PETIT and PETIT-2; however, no evidence of bone marrow dysfunction was seen on peripheral smears or during laboratory evaluation [26]. In a retrospective case review of patients from PETIT and PETIT-2 as well as patients who did not participate in these trials [patients received eltrombopag ($n = 28$), romiplostim ($n = 5$) or both ($n = 10$)], an increase in reticulin grade (maximally grade 1 to 2) was seen in five of eight patients who received eltrombopag or romiplostim and had bone marrow biopsies before and during/after treatment [24]. Median treatment duration was 30 months (range 6–55 months) for eltrombopag and 13 months (range 1–32 months) for romiplostim. The median maintenance dosage was 0.94 mg/kg and 7.92 μg/kg in patients receiving eltrombopag and romiplostim, respectively [24].

5 Dosage and Administration of Eltrombopag

Oral eltrombopag tablets and PfOS are indicated in the USA [6] for the treatment of thrombocytopenia in patients aged ≥1 year with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. In the EU [7], oral eltrombopag tablets and PfOS are indicated for the treatment of patients with chronic ITP aged ≥1 year who are refractory to other treatments (e.g. corticosteroids or immunoglobulins). The EU SmPC also states that eltrombopag should not be used in patients with both ITP and hepatic impairment unless the expected benefit outweighs the increased risk of portal venous thrombosis [7].

In paediatric patients aged ≥6 years, the recommended eltrombopag initial dosage is 50 mg once daily, except in patients who are of East Asian ancestry or those who have hepatic impairment, in which case the recommended starting dosage is 25 mg once daily [6, 7]. The US PI recommends that an eltrombopag starting dosage of 12.5 mg once daily should be considered in patients of East Asian ancestry with hepatic impairment [6]; the EU SmPC recommends a starting dosage of 25 mg/day in these patients [7]. No dosage adjustment is necessary for patients with renal impairment [6, 7]. In patients aged 1–5 years, the recommended starting dosage is 25 mg once daily [6, 7].

When switching between the eltrombopag PfOS and eltrombopag tablets, platelet counts should be assessed weekly for two weeks [6, 7] and then monthly [6]. During therapy, the eltrombopag dosage should be adjusted as necessary (to a maximum of 75 mg/day) to maintain a platelet count of $\geq 50 \times 10^9$/L, using the lowest dosage of eltrombopag possible. Normalizing platelet counts is not the treatment goal [6, 7].

As eltrombopag chelates polyvalent cations, there should be a ≥2 h gap before or ≥4 h gap after eltrombopag administration and ingestion of other medications that contain divalent cations (e.g. antacids), calcium-rich foods (e.g. dairy products and calcium-fortified juices) or supplements containing polyvalent cations (e.g. iron, calcium, aluminum, magnesium, selenium and zinc) [6, 7]. The US PI states that eltrombopag should be given orally on an empty stomach (> 1 h before or >2 h after a meal) [6]. The eltrombopag tablets should not be crushed or mixed with food or liquids [6], and the oral suspension should be prepared with water only [6, 7].

Local manufacturer's prescribing information should be consulted for detailed information, including recommended dosage modifications according to platelet levels, monitoring requirements, precautions, warnings and use in special populations.

6 Current Status of Eltrombopag in the Management of Paediatric Chronic Immune Thrombocytopenia

Treatment of persistent (i.e. lasting for 3–12 months), and especially chronic (>12 months), ITP in children is contentious because data from randomized clinical trials are limited [3, 4]. Paediatric patients who do not respond to first-line treatments, or who experience adverse effects, have limited treatment options [2–4]. Thrombopoietin receptor agonists (e.g. eltrombopag, romiplostim) are used as second-line therapy in adults, and eltrombopag has recently been approved in the USA and the EU for the treatment of thrombocytopenia in paediatric patients aged ≥1 year with chronic ITP who have had an insufficient response [6] or are refractory [7] to other ITP treatments.

Eltrombopag stimulates platelet production (Sect. 2.1) and provides an alternative to the immunomodulatory therapies that are directed at reducing the rate of platelet destruction [2]. Well-designed clinical trials demonstrated the efficacy of oral eltrombopag at dosages ≤75 mg/day in the treatment of previously treated paediatric patients with chronic ITP. In PETIT, the percentage of patients who achieved a platelet response at least once between days 8 and 43 (primary endpoint) was significantly higher with eltrombopag than with placebo (Sect. 3.1). Furthermore, a sustained response (primary endpoint) was achieved by significantly more eltrombopag than placebo recipients in PETIT-2 (Sect. 3.1). The secondary efficacy endpoint analyses demonstrated a clinically meaningful benefit of eltrombopag versus placebo in terms of a decreased need for rescue medications or platelet transfusions in PETIT and PETIT-2, and a significant reduction in the incidence of clinically significant bleeding in PETIT. Efficacy was maintained during longer-term eltrombopag treatment, with most (≈80 %) patients achieving a platelet response at least once during the extension periods (Sect. 3.2). Importantly, ≈50 % of eltrombopag recipients were able to discontinue or reduce their concurrent ITP therapy.

A conservative approach to the initial dosing was used in both PETIT and PETIT-2 which may have resulted in lower platelet responses than if a higher eltrombopag starting dosage was used [12]. The study authors suggest that 15–20 % more patients may have responded during the double-blind phase if a higher starting dosage had been used [12]. Of interest, an ongoing trial is evaluating efficacy and safety of eltrombopag administered at escalated doses (up to 150 mg/day) in patients aged ≥12 years with chronic ITP (NCT01880047). According to preliminary results, one patient was considered a complete responder (two consecutive platelet counts >50,000 μL and increase from baseline >20,000 μL not attributable to rescue

therapy in the 8 weeks from initiating dose escalation) and two were considered partial responders (two consecutive platelet counts of >50,000 μL or increase from baseline >20,000 μL not attributable to rescue therapy by 8 weeks) out of the five adult patients who completed ≥8 weeks on active medication [27].

Eltrombopag was generally well tolerated in clinical trials in paediatric patients, with most adverse events being of grade 1–2 severity (Sect. 4). The most common drug-related adverse event was increased aminotransferase abnormalities in PETIT-2. Elevations in ALT generally resolved following eltrombopag discontinuation; however, regular liver function tests are recommended during treatment with eltrombopag [6, 7]. There is little evidence regarding the long-term risk of reticulin fibrosis in paediatric patients. At this time, it has been suggested that a bone marrow biopsy should be performed 1–1.5 years after initiation of treatment and then a second biopsy should be done 6–24 months later, depending on the results of the first biopsy [28].

Eltrombopag is not a curative therapy in chronic ITP and some patients may require ongoing therapy. Thus, confirmation of the long-term efficacy, tolerability, and safety of eltrombopag is just as crucial as the short-term findings. The long-term safety of eltrombopag in paediatric patients is currently being investigated in ongoing clinical trials (NCT02201290, NCT01957176). Platelet counts usually return to baseline once eltrombopag treatment is stopped (Sect. 2.1). However, it is also evident that some adult patients can maintain haemostatic platelet counts following discontinuation of thrombopoietin receptor agonists [29, 30]. A small retrospective case review of paediatric patients receiving eltrombopag or romiplostim also suggested that withdrawal of treatment without a negative effect may be possible in patients on stable treatment [24].

Besides eltrombopag, romiplostim is the only other thrombopoietin receptor agonist currently available for use in adults in the EU and USA [31, 32]. No head-to-head trials have been carried out comparing the efficacy of eltrombopag and romiplostim in adults or paediatric patients with chronic ITP. Two small, short-term (<15 weeks), randomized studies comparing romiplostim with placebo reported an increase in the platelet count to over 50×10^9/L in more than 80 % of children and adolescents [33, 34]. Well-designed comparative trials of eltrombopag and other second-line therapies would be of interest. According to a retrospective analysis of 51 adults with chronic ITP, eltrombopag (up to 75 mg/day) was effective in ≈80 % patients who had switched from romiplostim (up to 10 μg/kg/week) [35]. Response to eltrombopag correlated with the cause of romiplostim cessation, with only 25 % of patients who failed to respond to romiplostim responding to eltrombopag [35]. Additionally, romiplostim was successfully used in a 9-year-old girl who had chronic refractory ITP despite eltrombopag treatment [36]. Eltrombopag is administered orally, making it potentially more acceptable to paediatric patients than romiplostim, which requires weekly subcutaneous injections [6, 31, 32].

In conclusion, the thrombopoietin receptor agonist eltrombopag is an effective and generally well tolerated treatment for use in previously treated paediatric patients with chronic ITP. Oral eltrombopag was more effective than placebo in children and adolescents (aged 1–17 years) with chronic ITP not responsive to first-line therapies, in terms of the platelet response rate and the sustained platelet response rate. A clinical benefit was shown by a reduction in the need for rescue therapy with eltrombopag versus placebo in both trials and a reduction of clinically significant bleeding in PETIT. Longer-term treatment with eltrombopag maintained platelet counts above 50×10^9/L in the majority of patients and approximately one-half of patients were able to reduce or discontinue concurrent ITP drugs. Although additional long-term data would be useful, current evidence suggests that eltrombopag is an important addition to the limited treatment options available for the management of chronic ITP in paediatric patients with an inadequate response to first-line therapies.

Data Selection Sources: Relevant medical literature (including published and unpublished data) on eltrombopag was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 25 April 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Eltrombopag, SB-497115, Promacta, Revolade, immune thrombocytopenia, idiopathic thrombocytopenia, ITP, chronic, child, children, adolescent, infant, pediatric, paediatric.
Study selection: Studies in adolescents and paediatric patients with chronic immune (idiopathic) thrombocytopenia (ITP) who received eltrombopag. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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