Eltrombopag for the Treatment of Chronic Immune (Idiopathic) Thrombocytopenic Purpura

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On November 20, 2008, the US Food and Drug Administration (FDA) granted accelerated approval for eltrombopag (Promacta Tablets, GlaxoSmithKline) for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulin therapy, or splenectomy.

Eltrombopag is a chemically synthesized thrombopoietin (TPO) receptor agonist for oral administration. The drug interacts with the transmembrane domain of the TPO receptor (also known as cMPL), leading to increased platelet production by megakaryocytes in the bone marrow.[1] The marketing approval was based upon demonstration of a favorable risk-to-benefit profile, where the major benefit pertained to demonstration of a clinically important increase in blood platelets among a population of patients with chronic ITP relatively refractory to prior therapies. Among this patient population, FDA regarded a durable platelet response as an established surrogate for clinical benefit. This determination was based upon the well-characterized pathophysiology of chronic ITP, including the etiologic role of severe thrombocytopenia in hemorrhage.[2]

Clinical and Regulatory Background

ITP is generally regarded as a disorder characterized by autoantibody-induced platelet destruction, thrombocytopenia, and “inappropriately” reduced platelet production.[3] Acute ITP occurs predominantly among children and is generally self-limited. Chronic ITP occurs mainly among adults, and spontaneous recovery is uncommon. The overall incidence of ITP among adults has been estimated to range from 1.6 to 6.6 per 100,000 persons/year of observation.[4] The frequency of death from hemorrhage in patients with platelet counts below 30 × 10^9/L has been estimated to range between 1.6% and 3.9% per patient-year, although this risk is importantly affected by age as well as the degree and duration of thrombocytopenia.[5] Intracranial hemorrhage is generally recognized as the most serious and life-threatening complication.[6,7]
The diagnosis of ITP is based mainly upon the detection of thrombocytopenia—the laboratory hallmark of the condition—and the exclusion of secondary causes of the thrombocytopenia. The major goal of chronic ITP therapy is to reduce the risk for hemorrhage. Hemorrhagic risk generally correlates with severity of thrombocytopenia; generally, medical treatment is initiated for platelet counts below \(30 \times 10^9/L\).[8] In the face of a hemostatic challenge such as surgery, platelet counts \(\geq 50 \times 10^9/L\) may be necessary to minimize hemorrhagic risk.

The therapy for most patients with chronic ITP predominantly consists of medications intended to increase platelet counts. Corticosteroids, generally the initial therapy, produce durable platelet responses in many patients. Other medications that have been shown to increase platelet counts, mostly for a relatively short period of time, consist of intravenous immunoglobulins (IVIG) and anti-D immunoglobulin.[9] Failure to respond sufficiently to these medications may result in the use of various other immunomodulatory medications (such as rituximab [Rituxan] or azathioprine) as well as the performance of splenectomy.[10] Splenectomy may result in a durable platelet response, although some patients remain refractory to the procedure. Few therapeutic options have proven beneficial in the refractory setting.

The thrombocytopenia in chronic ITP is thought to result primarily from enhanced platelet destruction. However, reduced platelet formation is also proposed as a contributor to the thrombocytopenia, as evidenced by “inappropriately” low TPO blood levels among patients with chronic ITP.[11] Additionally, in vitro studies have found evidence for deficient platelet production in patients with ITP.[12] Consequently, the development of TPO-receptor agonist molecules prompted manufacturers to explore the use of these molecules among patients with chronic ITP. In August 2008, FDA approved one of these molecules, romiplostim (Nplate), a biologic product for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[13,14]

The clinical development of eltrombopag was targeted toward two potential clinical uses of the drug among patients with relatively refractory chronic ITP: first, as “short-term,” episodic therapy for patients experiencing an acute hemorrhage risk, and second, as “long-term” therapy for patients at continuous risk for hemorrhage. Initial clinical studies showed that eltrombopag increased platelet counts in a dose-related manner among healthy subjects and patients with chronic ITP.[15] With the manufacturer’s initial focus on use of the drug among patients with chronic ITP, FDA designated eltrombopag as an orphan drug, based on the rarity of the condition (a condition affecting less than 200,000 Americans). In December 2007, the manufacturer submitted a New Drug Application (NDA) focused on approval of the drug for short-term treatment among previously treated patients with chronic ITP.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 67)</th>
<th>Eltrombopag, 50 mg (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>46 yr (18–85)</td>
<td>47 yr (19–84)</td>
</tr>
<tr>
<td>Female</td>
<td>64%</td>
<td>60%</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>42%</td>
<td>43%</td>
</tr>
<tr>
<td>≥ 2 prior treatments for ITP</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>Platelet count (\times 10^9/L), median</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Platelet count (\leq 15 \times 10^9/L)</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td>Platelet count (&gt; 15 \times 10^9/L)</td>
<td>54%</td>
<td>52%</td>
</tr>
</tbody>
</table>

ITP = immune thrombocytopenic purpura.
Following a detailed review of the clinical data and an FDA Advisory Committee recommendation, the FDA determined that in the studied population of patients with severe, relatively refractory chronic ITP, the drug was best used as maintenance therapy, rather than the initially proposed short-term therapy. Short-term use of the drug among these patients was associated with an excessive risk for serious hemorrhage following the drug's discontinuation. Data from the extension study of these patients indicated that eltrombopag therapy maintained platelet responses over a prolonged period of time. To further verify this long-term benefit, the drug was approved under the accelerated approval process. This process required the manufacturer to supply additional controlled clinical study data verifying the long-term benefits of the drug.

Eltrombopag was also approved with a Risk Evaluation and Mitigation Strategy (REMS). A REMS is an FDA-required risk management plan that utilizes tools beyond the approved package insert to mitigate serious risk(s). The Food and Drug Administration Act of 2007 provides the FDA with the authority to require a REMS if FDA determines that additional (beyond routine) postmarketing strategies are necessary to ensure that the benefits of a drug outweigh the risks. Serious safety concerns identified during the eltrombopag clinical development program consisted of risks for hepatic toxicity as well as hemorrhage and worsened thrombocytopenia (compared to baseline) upon the drug's discontinuation. Signals of potentially serious risks consisted of a risk for bone marrow reticulin formation leading to fibrosis, a risk for hematologic malignancy and progression of disease in patients with myelodysplastic syndromes (MDS), and a risk for thrombosis due to excessive platelet count increases. The nature and extent of these safety concerns prompted the need for the REMS.

### Table 2

**Disposition in Placebo-Controlled Studies of Ertomtobag**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo (n = 67)</th>
<th>Ertomtobag, 50 mg (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study</td>
<td>52 (78%)</td>
<td>69 (65%)</td>
</tr>
<tr>
<td>Discontinued prematurely from study drug</td>
<td>15 (22%)</td>
<td>37 (35%)</td>
</tr>
<tr>
<td>Reason for Study Drug Discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &gt; 200 × 10^9/L</td>
<td>2 (3%)</td>
<td>29 (27%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>5 (7%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>2 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Subject decision</td>
<td>2 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Major Clinical Studies

The major clinical data supporting eltrombopag approval were obtained from two double-blind, randomized, placebo-controlled clinical trials and a single-arm extension study.

**Placebo-Controlled Study Designs**

The major study features were similar for both of the placebo-controlled trials. Eligible patients were adults with a diagnosis of chronic ITP who had a platelet count < 30 × 10^9/L and who had either not responded to one or more prior therapies (including splenectomy) or who had relapsed within 3 months of the prior therapy. Neither study was specifically designed to assess eltrombopag's effects among patients who were undergoing hemostatic challenges, such as surgery.
Both studies were multicenter trials in which patients underwent a stratified randomization based on splenectomy status, use of concomitant ITP medications, and the baseline platelet count (> or ≤ 15 × 10^9/L). In Study 1, patients were randomized (1:1:1:1) to placebo or one of three eltrombopag dose regimens (30 mg, 50 mg, or 75 mg); in Study 2, patients were randomized (1:2) to placebo or eltrombopag, 50 mg. In Study 2, patients who had a platelet count < 50 × 10^9/L on or after day 22, were permitted to have the eltrombopag (or matching placebo) dose increased to 75 mg daily. Study medication was administered daily for 6 weeks, followed by a 6-week follow-up (“off-drug”) observation period. Patients were allowed to receive concomitant ITP medications, provided the dose had been stable for at least 1 month. During the active treatment period, patients who attained a platelet count > 200 × 10^9/L had the study drug discontinued but were evaluated over the subsequent 6 weeks. Efficacy and safety assessments were scheduled every week during the active treatment period and at 1, 2, 4, and 6 weeks during the post-treatment period. The primary endpoint in each study was a comparison of response rates, with a “response” defined as the attainment of a platelet count ≥ 50 × 10^9/L at any time during the active treatment period. During this period, patients for whom the study drug was discontinued because of a platelet count > 200 × 10^9/L were also assessed as having responded to the study drug. Secondary endpoints consisted mainly of various explorations of the platelet count responses as well as certain bleeding scale outcomes.

**Extension Study Design**

The extension study was a single-arm investigation that enrolled patients who had previously been enrolled in any eltrombopag clinical trial. Enrolled patients received individualized eltrombopag dose regimens to maintain a platelet response, coincident with attempts to decrease the dose or eliminate the need for any concomitant ITP medications. Patients were to receive eltrombopag over a prolonged period of time with regular evaluations for safety and the platelet count response.

**Results**

Eltrombopag was shown to increase platelets among most patients in both the placebo-controlled studies and the extension study. The efficacy results are initially discussed below, followed by a summary of the major safety results.

**Placebo-Controlled Studies**

Overall, 231 patients underwent randomization in the two placebo-controlled clinical studies. Baseline characteristics were similar within the arms of each of the studies, with the characteristics generally typical of a patient population with severe, relatively refractory chronic ITP.[16] For summary purposes, the baseline characteristics and disposition of the placebo and 50-mg eltrombopag cohorts are pooled in Tables 1 and 2, respectively. Within these cohorts, more patients who received eltrombopag had the study drug discontinued prematurely due to attainment of a platelet count > 200 × 10^9/L, compared to patients who received the placebo (27% vs 3%). Within both studies, patients receiving eltrombopag experienced increased platelet counts compared to the placebo groups (see Table 3 for the “efficacy population” of randomized patients who received at least one study drug dose and who had a baseline platelet count < 30 × 10^9/L). The eltrombopag platelet count response rate was similar among patients who had undergone splenectomy and those who had not undergone splenectomy—59% and 64%, respectively. Increases in platelet counts were detected 1 week following initiation of eltrombopag, and the maximum response was observed after 2 weeks of therapy. Within Study 1, patients generally experienced increases in platelet counts in proportion to the assigned eltrombopag dose regimen.
Within the two studies, seven patients experienced hemostatic challenges (four eltrombopag group patients and three placebo group patients). Only one patient (in the placebo group) received platelet and/or blood transfusions as a response to the bleeding challenge. Prior to the hemostatic challenge, “rescue” medications were given to two of the placebo group patients in order to increase platelet counts; none were administered to the eltrombopag group patients.

Bleeding was also assessed periodically during the two studies using bleeding scales.[17] However, the observed changes within these scales were within the lowest grades of bleeding (such as diminution of petechiae), and these incremental changes were of unclear clinical meaningfulness.

Extension Study
At the time of the NDA review, 109 patients had received eltrombopag in the extension study. Of these patients, 74 completed 3 months of therapy, 53 completed 6 months, and 3 patients completed 1 year of therapy. Overall, 80% of the enrolled patients achieved a platelet count > 50 × 10^9/L at least once during the study, and median platelet counts were > 50 × 10^9/L at the 3-, 6-, and 9-month follow-up evaluation time points. Most (54%) of the patients maintained platelet counts > 50 × 10^9/L for ≥ 10 continuous weeks while receiving eltrombopag. Reduction or discontinuation of baseline concomitant ITP medications was successful in 18 of 24 patients who underwent a dose reduction challenge. Fourteen of the patients were able to discontinue one or more of the baseline concomitant ITP medications.

Safety
Overall, 313 patients with chronic ITP were exposed to eltrombopag in the clinical development program. The drug was administered to 81 patients for at least 6 months and to 39 patients for at least 1 year. The major safety findings pertained to a risk for hepatotoxicity as well as a risk for serious hemorrhage and worsened thrombocytopenia (compared to baseline) following eltrombopag discontinuation.

In the controlled clinical studies, one patient experienced grade 4 (National Cancer Institute Common Terminology Criteria for Adverse Events toxicity scale) elevations in liver test values during eltrombopag therapy, worsening of underlying cardiopulmonary disease, and death. This patient had normal baseline liver tests but experienced marked increases in these values during eltrombopag therapy, coincident with worsening of his cardiopulmonary condition. No patients in the placebo groups experienced grade 4 liver test abnormalities. Overall, serum liver test abnormalities (predominantly grade 2 or less in severity) were reported in 10% and 8% of the eltrombopag and placebo groups, respectively. Seven patients treated with eltrombopag who experienced hepatobiliary laboratory test abnormalities in the placebo-controlled studies were re-exposed to eltrombopag in the extension study. Six of these patients again experienced liver test abnormalities (predominantly grade 1), resulting in eltrombopag discontinuation in one patient.

During the active treatment period of the controlled studies, only three patients experienced serious hemorrhages that required the use of rescue ITP medications (two in the eltrombopag group and one in a placebo group). However, five patients in the eltrombopag groups experienced these types of serious hemorrhages following discontinuation of the drug; none were experienced following
discontinuation of the placebo. All the serious hemorrhages were experienced within 32 days following eltrombopag discontinuation, and most were associated with platelet counts < 10 × 10⁹/L.

Signals of certain risks typical of TPO-receptor agonist products were evident in the eltrombopag development program. One risk pertained to reticulin fiber deposition in the bone marrow that may lead to fibrosis. In the extension study, seven patients had reticulin fiber deposition reported in bone marrow biopsies obtained during the study, including two patients who also had collagen fiber deposition. Baseline bone marrow biopsies were not available for these patients. None of the patients with the marrow fiber deposition experienced cytopenias, and none of the patients had eltrombopag discontinued.

Thrombosis, potentially related to excessive platelet count increases, is another risk associated with TPO-receptor agonist products. In the controlled studies, one thrombotic/thromboembolic complication was reported within the groups that received eltrombopag and none within the placebo groups. Seven patients experienced thrombotic/thromboembolic complications in the extension study.

The risk for hematologic malignancy, particularly among patients with myelodysplasia or other conditions predisposing to malignancy, was not evaluated in the eltrombopag clinical development program. Nevertheless, this signal was evidenced in the romiplostim development program, and this observation has implications for eltrombopag, based on the drug’s proposed mechanism of action. Defining the extent of this risk, if any, awaits further study.

Within the controlled clinical studies, the rate of serious adverse events was similar between the study groups (12% in the placebo group and 11% in the eltrombopag group). In general, the occurrence of specific adverse events was similar between the study groups. Table 4 summarizes the most common adverse reactions experienced by more than one patient receiving eltrombopag, with a higher rate in the eltrombopag group, compared to the placebo group. Adverse reactions reported in the extension study occurred in a pattern similar to those reported in the placebo-controlled studies.

**Discussion**

Data providing substantial evidence of eltrombopag efficacy and safety were obtained from two placebo-controlled clinical studies in which patients received eltrombopag for no more than 6 weeks and an extension study in which patients received prolonged eltrombopag therapy. Within the controlled studies, a platelet response—achievement of a platelet count ≥ 50 × 10⁹/L at any time during the active treatment period—was observed in 59% and 70% of the 50-mg eltrombopag group patients, compared to placebo group response rates of 16% and 11%, respectively. All studied patients had baseline platelet counts < 30 × 10⁹/L and most had previously received multiple ITP medications.

Following discontinuation of the study drug in these studies, serious hemorrhages requiring the use of rescue ITP medications occurred among five patients who had previously received eltrombopag but no patients who had previously received placebo. Most of the patients had developed severe thrombocytopenia (platelet counts < 10 × 10⁹/L) prior to the serious hemorrhagic episode. This imbalance in the occurrence of post-therapy serious hemorrhage suggests that, within this population of patients with severe, relatively refractory ITP, discontinuation of eltrombopag following no more than 6 weeks of therapy was associated with an important risk for hemorrhage. Consequently, the findings from the extension study were particularly important, to provide evidence of eltrombopag’s ability to maintain the desired platelet response.
The extension study provided prolonged eltrombopag exposure to patients who had previously enrolled in a shorter-duration eltrombopag trial. Consequently, the time of extension study enrollment and cumulative eltrombopag exposure varied among the enrolled patients, based upon the time of completion of the prior study’s follow-up period. Within the study, most of the 109 patients receiving eltrombopag maintained platelet counts in excess of $50 \times 10^9/L$ for at least $\geq 10$ continuous weeks of therapy. Median platelet counts were maintained in excess of $50 \times 10^9/L$ at the 3-, 6-, and 9-month follow-up time points. FDA regards achievement and maintenance of a platelet count $\geq 50 \times 10^9/L$ as evidence of a clinical benefit, based on the general understanding that hemorrhagic risks importantly correlate with platelet counts in patients with severe chronic ITP.[8,18] This assessment of benefit was supported during FDA’s advisory committee review of eltrombopag.

In addition to the risk for serious hemorrhage and worsened (compared to baseline) thrombocytopenia following discontinuation of eltrombopag, the other most notable eltrombopag safety finding was a risk for hepatotoxicity. Within the controlled clinical studies, one patient experienced grade 4 liver test abnormalities during eltrombopag therapy and ultimately died as an underlying cardiopulmonary condition worsened. No placebo group patients experienced grade 4 liver test abnormalities. A small imbalance in the rate of liver test abnormalities was also observed in the pooled data summary for the two controlled studies.

Other safety risk signals identified during FDA’s review pertained to those previously identified for TPO-receptor agonists, including a risk for bone marrow reticulin formation leading to fibrosis, a risk for hematologic malignancy and progression of disease among patients with myelodysplastic syndromes, as well as a risk for thrombosis due to excessive platelet count increases.

Coincident with the approval, the extent of the safety concerns for eltrombopag prompted FDA to require a boxed warning within the product label to describe the risk for hepatotoxicity as well as a Risk Evaluation and Mitigation Strategy. The REMS involves special procedures to promote informed risk-benefit decisions before initiating treatment and to require periodic monitoring of patients during eltrombopag therapy. For example, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin must be measured prior to the initiation of eltrombopag, every

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**Table 4**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Eltrombopag (n = 106)</th>
<th>Placebo (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
2 weeks during the dose-adjustment period, and monthly following establishment of a stable dose. The REMS program consists of a medication guide, a communication plan, and elements to assure the safe use of the drug. Specifically, these elements include the supply of eltrombopag via patient and prescriber participation in a program referred to as the PROMACTA CARES program.

For the PROMACTA CARES program, prescribers must register by attesting to understanding the risks associated with eltrombopag, safe use conditions, and program requirements. Institutional registration is also required if the institution is responsible for providing eltrombopag. Additionally, patients must enroll in the program to receive eltrombopag. Once a prescriber identifies a patient for eltrombopag therapy, the prescriber must complete an enrollment form and baseline questionnaire. Every 6 months throughout eltrombopag therapy, the prescriber must complete a form that documents certain adverse events and provides a verification of the appropriateness of continued eltrombopag therapy. Prescribers must report when eltrombopag is discontinued and the reason for the discontinuation.

Eltrombopag was approved under an accelerated approval program that required the manufacturer to supply clinical data verifying the efficacy and safety of the drug when administered over a prolonged period of time. At the time of eltrombopag approval, a randomized, double-blind, placebo-controlled study was ongoing to assess drug effects over a 6-month period. In addition to completing this investigation, the manufacturer was required to complete another study that examined the effect of eltrombopag administration during repetitive 6-week cycles of therapy. Postmarketing requirements also included modification of the extension study to continue in a manner that would provide additional data pertaining to the risk for bone marrow reticulin fiber deposition and possible fibrosis. Other studies were required to examine the effect of eltrombopag during pregnancy as well as the drug’s effects among lactating mothers and their breast-feeding infants.

Conclusion

Eltrombopag was the second TPO-receptor agonist approved by FDA. The drug was shown to have a favorable risk-to-benefit profile for the treatment of thrombocytopenia among patients with chronic ITP who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The clinical development program initially focused on the short-term treatment of patients with severe chronic ITP. However, the supplied data indicated that these patients were at risk for serious hemorrhage following eltrombopag discontinuation. The FDA relied on data from an extension study to verify that eltrombopag could maintain the desired platelet response over a prolonged period of time.

The drug was approved under an accelerated approval mechanism that requires the manufacturer to complete ongoing clinical studies that further assess eltrombopag safety and efficacy. Additionally, the approval was accompanied by a REMS intended to optimize the drug’s safe use. The product labeling included a boxed warning for the risk of hepatotoxicity and a description of the requirement for live test monitoring during the drug’s use. Together, these requirements should help optimize eltrombopag’s safe use among patients with chronic ITP who have few alternative therapies for the thrombocytopenia.


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