

Overview: Promacta in Pediatric ITP PETIT and PETIT2 Clinical Trials

Promacta[®] (eltrombopag) has been approved by the US Food and Drug Administration (FDA) for the treatment of children six years and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. The approval is based on the PETIT and PETIT2 (eltrombopag in **PE**diatric patients with **Th**rombocytopenia from **ITP**) studies, which found treatment with Promacta significantly increased and sustained platelet counts among some pediatric patients with chronic ITP, and some patients taking concomitant ITP medications were able to reduce or discontinue their use of these medications, primarily corticosteroids. PETIT was a Phase II, three-part study and PETIT2 was a two-part study and the largest Phase III clinical trial in this patient population.

PETIT ^{1,2} NCT00908037			PETIT2 ^{3,4} NCT01520909		
Patient Population	<i>Enrolled 67 patients:</i> Randomized 52 patients (35 to Promacta and 17 to placebo) Between ages 1 and 17 with ITP of >6 months duration and a platelet count <30 Gi/L who received ≥1 prior treatment			<i>Enrolled 92 patients:</i> Randomized 72 patients (49 to Promacta and 23 to placebo) Between ages 1 and <18 with a confirmed diagnosis of cITP (duration >12 months) and platelet count <30 Gi/L at day 1	
Design	Part 1: Open-label dose-finding phase	Part 2: Randomized 2:1 to eltrombopag or placebo and stratified by age for 7 weeks (not in part 1)	Part 3: After Part 2, eltrombopag and placebo patients received 17 and 24 weeks of open label eltrombopag, respectively	Part 1: Eltrombopag vs placebo for 13 weeks (randomized period)	Part 2: All study participants received eltrombopag (through to week 24)
Endpoints	Primary: Proportion of randomized patients achieving platelet counts ≥50 Gi/L at least once, without rescue, between Weeks 1 and 6			Primary: Efficacy of eltrombopag, relative to placebo, in achieving platelet counts of ≥50 Gi/L for at least 6 out of 8 weeks between Weeks 5 to 12 of the randomized, double-blind period among patients with previously treated cITP for at least 12 months	
	Secondary: Platelet response, rescue treatment needs, duration of platelet count maintenance, pharmacokinetics, bleeding symptoms, adverse reaction and safety			Secondary: Platelet response, effect on concomitant ITP therapies, rescue treatment needs, bleeding symptoms, adverse reaction and safety	

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Primary Results	63% treated with eltrombopag achieved platelet counts ≥ 50 Gi/L at least once (without rescue) vs 18% on placebo ($p=0.0043$). Responses in individual cohorts were consistent with the overall response.	43% treated with eltrombopag achieved a statistically significant improvement in platelet counts and consistent platelet response for at least 6 of 8 weeks between Weeks 5 and 12 vs placebo (43% vs 4%, respectively, $p=0.0011$).
Secondary Results	Clinically meaningful benefit observed: <ul style="list-style-type: none"> Decreased need for rescue treatment (14% on eltrombopag vs 59% on placebo) Reduction or discontinuation of baseline ITP medications (36% [4/11] of open label patients) 	Clinically meaningful benefit observed: <ul style="list-style-type: none"> Decreased need for rescue treatment (18% on eltrombopag vs 22% on placebo) Reduction or discontinuation of baseline ITP medications (50% [5/10] of open label patients) over randomized and eltrombopag-only treatment periods
Safety Findings	Consistent with established profile for eltrombopag and no new safety concerns were observed. Most common adverse events (AEs) greater than or equal to 10% and greater than placebo: <ul style="list-style-type: none"> Upper respiratory tract infection Nasopharyngitis (common cold) Rhinitis (runny, stuffy nose) 	

About Promacta

Promacta is a prescription medicine used to treat adults and children 6 years of age and older with low blood platelet counts due to chronic immune (idiopathic) thrombocytopenia (ITP), when other medicines to treat ITP or surgery to remove the spleen have not worked well enough. Promacta is used to try to raise platelet counts in order to lower the risk for bleeding. Promacta should be used only in those whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. It is not known if Promacta is safe and effective in children younger than 6 years with ITP. The safety and efficacy profile of Promacta has not yet been established in countries outside the US in pediatric patients with chronic ITP. For various reasons, including the uncertainty of clinical trials, there is no guarantee that Promacta will become commercially available for pediatric patients with chronic ITP anywhere else in the world. Information about clinical trials for chronic ITP can be obtained by healthcare professionals at www.clinicaltrials.gov.

In addition to the approval of Promacta for chronic ITP in the US, it is approved to treat low blood platelet counts in people with chronic hepatitis C virus (HCV) infection before and during treatment with interferon. Promacta should only be used in people with chronic hepatitis C whose low blood platelet counts keep them from starting or continuing interferon-based therapy. It is not known if Promacta is safe and effective when used with other antiviral medicines that are approved to treat chronic hepatitis C.

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Promacta is a prescription medicine used to treat people with severe aplastic anemia (SAA) when other medicines to treat SAA have not worked well enough.

Promacta is not used to make a patient's platelet count normal.

Important Safety Information for Promacta® (eltrombopag)

Promacta can cause serious side effects, including liver problems, abnormal liver function tests, high platelet counts and higher risk for blood clots, and new or worsened cataracts (a clouding of the lens in the eye).

For patients who have chronic hepatitis C virus and take Promacta with interferon and ribavirin treatment, Promacta may increase the risk of liver problems. Patients should tell a healthcare provider right away if they have any of these signs and symptoms of liver problems including yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, unusual tiredness, right upper stomach area pain, confusion, swelling of the stomach area (abdomen).

A healthcare provider will order blood tests to check the liver before starting Promacta and during Promacta treatment. In some cases, treatment with Promacta may need to be stopped due to changes in liver function tests.

The risk of getting a blood clot is increased if the platelet count is too high during treatment with Promacta. The risk of getting a blood clot may also be increased during treatment with Promacta if platelet counts are normal or low. Some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes can cause severe problems or death. A healthcare provider will check blood platelet counts, and change the dose of Promacta or stop Promacta, if platelet counts get too high. Patients should tell a healthcare provider right away if they have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in the leg.

People with chronic liver disease may be at risk for a type of blood clot in the stomach area. Patients should tell a healthcare provider right away if they have stomach area pain that may be a symptom of this type of blood clot.

New or worsened cataracts have happened in people taking Promacta. A healthcare provider will check the patient's eyes before and during treatment with Promacta. Patients should tell a healthcare provider about any changes in eyesight while taking Promacta.

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Patients should tell a healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Promacta may affect the way certain medicines work. Certain medicines may keep Promacta from working correctly. Patients should take Promacta at least 4 hours before or 4 hours after taking products such as antacids used to treat stomach ulcers or heartburn and multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc, which may be found in mineral supplements. Patients should ask a healthcare provider if they are not sure if the medicine is one that is listed above.

Patients should avoid situations and medications that may increase the risk of bleeding while taking Promacta.

The most common side effects of Promacta when used to treat chronic ITP in adults are: nausea; diarrhea; upper respiratory tract infection (symptoms may include runny nose, stuffy nose, and sneezing); vomiting; muscle aches; urinary tract infection (symptoms may include frequent or urgent need to urinate, low fever in some people, pain or burning with urination); pain or swelling (inflammation) in the throat or mouth (oropharyngeal pain and pharyngitis); abnormal liver function tests; back pain; flu-like symptoms (influenza), including fever, headache, tiredness, cough, sore throat, and body aches; skin tingling, itching, or burning; and rash.

The most common side effects of Promacta in children 6 years and older when used to treat chronic ITP are: upper respiratory tract infections (symptoms may include runny nose, stuffy nose, and sneezing); pain or swelling (inflammation) in the nose and throat (nasopharyngitis); runny, stuffy nose (rhinitis); stomach (abdominal) pain; cough; pain or swelling (inflammation) in the throat or mouth; toothache; abnormal liver function tests; diarrhea; rash; vitamin D deficiency.

The most common side effects when Promacta is used in combination with other medicines to treat chronic HCV are: low red blood cell count (anemia); fever; tiredness; headache; nausea; diarrhea; decreased appetite; flu-like symptoms (influenza), including fever, headache, tiredness, cough, sore throat, and body aches; feeling weak; trouble sleeping; cough; itching; chills; muscle aches; hair loss; and swelling in the ankles, feet, and legs.

The most common side effects of Promacta when used to treat severe aplastic anemia are: nausea, feeling tired, cough, diarrhea, headache, pain in arms, legs, hands or feet, shortness of breath, fever, dizziness, pain in nose or throat, abdominal pain, bruising, muscle spasms, abnormal liver function tests, joint pain, and runny nose.

Laboratory tests may show abnormal changes to the cells in bone marrow.

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References

1. Bussel JB, Garcia de Miguel P, Despotovic J, et al. Eltrombopag treatment of childhood persistent and chronic immune thrombocytopenia: Final results of the PETIT study (TRA108062), a phase 2, placebo-controlled clinical trial. *Haematologica*. 2014;99(s1):263.
2. US National Institutes of Health. Clinicaltrials.gov Identifier: NCT00908037. Available at: <https://clinicaltrials.gov>. Accessed May 15, 2015.
3. Grainger JD, Locatelli F, Chotsampancharoen T, et al. Results from PETIT 2 (TRA115450): A randomized placebo-controlled trial of eltrombopag treatment in pediatric patients with chronic immune thrombocytopenia. *Haematologica*. 2014;99(s1):263.
4. US National Institutes of Health. Clinicaltrials.gov Identifier: NCT01520909. Available at: <https://clinicaltrials.gov>. Accessed May 15, 2015.