

FDA Expands Use of Promacta® to Include Treatment of Children Ages 1 and Older with Chronic Immune Thrombocytopenia

- New oral suspension formulation, designed for younger children with rare blood disorder, is now approved
- For about one in four children with ITP, the condition persists for more than 12 months after diagnosis and is considered chronic^{1,2}
- Already approved for people 6 years of age and older with chronic ITP, Promacta is the only oral TPO-receptor agonist that may increase platelet production

SAN DIEGO-- **Ligand Pharmaceuticals Incorporated (NASDAQ: LGND)** today announces that the FDA has approved an expanded use for Promacta® (eltrombopag), a Novartis product, to include children 1 year of age and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. The updated label also includes a new oral suspension formulation of Promacta that is designed for younger children who may not be able to swallow tablets. Promacta was approved by the FDA as a tablet formulation in June 2015 for children 6 years of age and older and in 2008 for use in adult patients with the same condition.

ITP affects as many as 5 in 100,000 children each year³ and is characterized by a low platelet count⁴. Chronic ITP, defined as ongoing disease more than 12 months after diagnosis², occurs in 13–36% of children with immune thrombocytopenia¹. A small number of pediatric patients with chronic ITP may be at risk of significant bleeding⁵.

The label expansion of Promacta was based on data from two double-blind, placebo-controlled trials, including the largest Phase 3 clinical trial in this patient population. Treatment with Promacta significantly increased and sustained platelet counts among pediatric patients with chronic ITP with an insufficient response to prior chronic ITP therapies, and some patients taking concomitant ITP medications were able to reduce or discontinue their use of these medications, primarily corticosteroids. Promacta should be used only in those whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

Promacta is a once-daily oral thrombopoietin (TPO) receptor agonist that works by inducing stimulation and differentiation of megakaryocytes (large cells, found especially in bone marrow) from bone marrow stem cells to increase platelet production⁶.

About the PETIT and PETIT2 Clinical Trials

PETIT was a Phase 2, multi-center, three-part study to investigate the efficacy, safety and

tolerability of Promacta in pediatric patients (ages 1 to 17 years) with previously treated chronic ITP. Part 1 was an open label, dose finding study; Part 2 was double-blind and placebo-controlled, and Part 3 was an open-label extension. The primary endpoint, which was percentage of participants who achieved a platelet count ≥ 50 Gi/L without rescue therapy at least once between Weeks 1 and 6, was met by 62% and 32% of Promacta and placebo patients, respectively ($p=0.011$). The secondary efficacy endpoint analyses demonstrated clinically meaningful benefit in terms of decreased need for rescue treatment (13% of patients on Promacta compared to 50% of patients on placebo)⁷.

PETIT2 was a Phase 3, multi-center, two-part study to investigate the efficacy, safety and tolerability of Promacta in pediatric patients (ages 1 to 17 years) with previously treated chronic ITP. Part 1 was randomized, double-blind and placebo-controlled and Part 2 was an open-label extension. The primary endpoint, which was percentage of participants who achieved a platelet count ≥ 50 Gi/L without rescue therapy for at least six out of eight weeks between Weeks 5 and 12 of Part 1 of the study, was met by 41% of patients treated with Promacta and 3% of patients treated with placebo ($p<0.001$). This result was consistent across the age cohorts. The secondary efficacy endpoint analyses demonstrated clinically meaningful benefit in terms of decreased need for rescue treatment (19% of patients on Promacta compared to 24% of patients on placebo) during the randomized, double-blind period. Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. In the open label eltrombopag-only period, 15 of 87 patients were taking concomitant ITP medications at baseline. Of these 15 patients, 8 (53%) had a sustained reduction or permanent discontinuation of at least one baseline ITP medication (7 patients permanently discontinued and one patient had sustained reduction for ≥ 18 weeks)⁸.

In both studies, safety was consistent with the known safety profile of Promacta in chronic ITP in adults and the population under study. No new safety signals were detected. The most common adverse reactions in pediatric chronic ITP patients 1 year and older (greater than or equal to 10% and greater than placebo) were upper respiratory tract infection and nasopharyngitis^{7,8}.

About Chronic ITP

ITP is a blood disorder characterized by blood that does not clot as it should due to a low number of platelets. People who have ITP often have purple bruises or tiny red or purple dots on the skin. They also may have nosebleeds, bleeding from the gums during dental work, or other bleeding that's hard to stop. In most cases, an autoimmune response is thought to cause ITP in which a person's immune system attacks and destroys its own platelets⁴.

The two types of ITP are acute (temporary or short-term) and chronic (long-lasting). Acute ITP mainly occurs in children, often after a viral infection, and generally lasts less than 6 months. The platelet count returns to normal within 6 to 12 months and treatment may not be needed⁴. Chronic ITP, defined as ongoing disease more than 12 months after diagnosis², occurs in 13–36% of children with immune thrombocytopenia¹. A small number of pediatric patients with chronic ITP may be at risk of significant bleeding⁵.

The goal of treatment in chronic ITP for children is to maintain a safe platelet count that reduces the risk of bleeding⁴. The most commonly available and used therapies—corticosteroids and intravenous immunoglobulin (IVIG)—are associated with side effects that are often difficult to tolerate in a pediatric setting^{5,9,10}.

About Promacta

Promacta is marketed under the brand name Promacta[®] in the US and Revolade[®] in most countries outside the US.

Promacta is a prescription medicine used to treat adults and children 1 year 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 1 year with ITP. An application was submitted to the European Medicines Agency (EMA) earlier this year to include chronic ITP patients 1 year and older. This application includes chemistry, manufacturing and control (CMC) data supporting the new oral suspension formulation of Promacta.

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.

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.

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 2 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 1 year 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); cough; diarrhea; pyrexia; runny, stuffy nose (rhinitis); stomach (abdominal) pain; pain or swelling (inflammation) in the throat or mouth; toothache; abnormal liver function tests; rash; runny nose (rhinorrhea).

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.

Please see full Prescribing Information, including Boxed WARNING and Medication Guide, for Promacta®.

About Ligand Pharmaceuticals

Ligand is a biopharmaceutical company with a business model focused on developing or acquiring royalty generating assets and coupling them with a lean corporate cost structure. Ligand's goal is to produce a bottom line that supports a sustainably profitable business. By diversifying the portfolio of assets across numerous technology types, therapeutic areas, drug targets and industry partners, we offer investors an opportunity to invest in the increasingly complicated and unpredictable pharmaceutical industry. In comparison to its peers, we believe Ligand has assembled one of the largest and most diversified asset portfolios in the industry with the potential to generate revenue in the future. These therapies seek to address the unmet medical needs of patients for a broad spectrum of diseases including diabetes, hepatitis, muscle wasting, Alzheimer's disease, dyslipidemia, anemia, asthma and osteoporosis. Ligand's Captisol® platform technology is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Ligand has established multiple alliances with the world's leading pharmaceutical companies including; Novartis, Amgen, Merck, Pfizer, Baxter International and Eli Lilly.

Forward-Looking Statements

This news release contains forward-looking statements by Ligand that involve risks and uncertainties and reflect Ligand's judgment as of the date of this release. These forward-looking statements include comments regarding the size of the population affected by ITP and the side effects of Promacta. The failure to meet expectations with respect to any of the foregoing matters may reduce Ligand's stock price. Additional information concerning these and other important risk factors affecting Ligand (including Ligand's current reliance on revenues based on sales of Promacta® and Kyprolis®, and various risks to which Ligand's Captisol® cyclodextrin operations are subject) can be found in Ligand's prior press releases available at www.ligand.com as well as in Ligand's public periodic filings with the Securities and Exchange Commission, available at www.sec.gov. Ligand disclaims any intent or obligation to update these forward-looking statements beyond the date of this press release, except as required by law. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

References

1. George JN, Woolf SH, Raskob GE. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996;88(1):3-40.
2. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;12;113(11):2386-2393.
3. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. *Curr Opin Hematol*. 2007;14(5):515-519.
4. Immune Thrombocytopenia. US National Institutes of Health website. <http://www.nhlbi.nih.gov/book/export/html/4917>. Accessed August 5, 2015.
5. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207.
6. Full Prescribing Information.
7. Bussel JB, Garcia de Miguel P, Despotovic JM, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. *Lancet Haematol*. 2015; published online July 29, 2015.
8. Grainger JD, Locatelli F, Chotsampancharoen T, et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015; published online July 29, 2015.
9. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186.
10. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med*. 2002;346(13):995-1008.

View source version on businesswire.com:

<http://www.businesswire.com/news/home/20150824005801/en/>

Ligand Pharmaceuticals Incorporated

Todd Pettingill, (858) 550-7500

investors@ligand.com

or

LHA

Bruce Voss, (310) 691-7100

bvoss@lhai.com

Source: Ligand Pharmaceuticals Incorporated