

Ligand Partner GlaxoSmithKline Receives U.S. FDA Approval for Promacta®/Revolade™ For Use in Patients with Severe Aplastic Anemia

The third labeled indication for the drug

Represents a new first-in-class treatment option for SAA patient population with insufficient response to immunosuppressive therapy

SAN DIEGO-- **Ligand Pharmaceuticals Incorporated (NASDAQ: LGND)** announced that its partner GlaxoSmithKline (GSK) plc has received approval of a supplemental New Drug Application (sNDA) for the once-daily use of Promacta®/Revolade™ (eltrombopag) in patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST).¹ SAA is a blood disorder where the bone marrow fails to make enough red blood cells, white blood cells and platelets.² Eltrombopag, an oral thrombopoietin (TPO) receptor agonist, works by helping to induce proliferation and differentiation of bone marrow stem cells to increase production of blood cells.¹

Promacta gained Breakthrough Therapy designation status from the FDA in January 2014 and Priority Review in April 2014. Yesterday's approval by the FDA is based on results from an investigator-sponsored Phase II study (09-H-0154) conducted by the National Heart, Lung and Blood Institute (NHLBI) at the National Institutes of Health (NIH). The study demonstrated a hematologic response in SAA patients treated with eltrombopag who had an insufficient response to IST:¹

- Forty per cent (95% CI, 25, 56) of patients (N=17) experienced a hematologic response in at least one lineage – platelets, red blood cells (RBC), or white blood cells (ANC) – after Week 12.¹
 - In the extension phase, eight patients achieved a multi-lineage response; four of these patients subsequently tapered off treatment and maintained the response (median follow up 8.1 months, range 7.2-10.6 months).¹
- Ninety-one per cent of patients were platelet transfusion-dependent at baseline; the platelet transfusion-free period in responders ranged from eight to 1,096 days (median 200 days).¹
- Eighty-six per cent of patients were RBC-transfusion dependent at baseline; the RBC transfusion-free period in responders ranged from 15 to 1,082 days (median 208 days).¹

The most common adverse reactions ($\geq 20\%$) in the single-arm, open-label trial, in 43

patients with SAA who received Promacta were: nausea (33%), fatigue (28%), cough (23%), diarrhea (21%), and headache (21%). In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported, including five patients who had complex changes in chromosome 7. If new cytogenetic abnormalities are observed, discontinuation of Promacta should be considered.¹

About the NIH Study¹

In the single-arm, single-center, open-label Phase II 09-H-0154 study, eltrombopag was evaluated in 43 patients with SAA who have had an insufficient response to at least one prior IST and who had a platelet count $\leq 30 \times 10^9/L$. At baseline, the median platelet count was $20 \times 10^9/L$, hemoglobin was 8.4 g/dL, absolute neutrophil count (ANC) was $0.58 \times 10^9/L$, and absolute reticulocyte count was $24.3 \times 10^9/L$.

The treated population had a median age of 45 years (range 17 to 77 years) and 56% were male. The majority of patients (84%) received at least two prior immunosuppressive therapies.

Eltrombopag was administered at an initial dose of 50 mg once daily for two weeks and increased over two-week periods up to a maximum dose of 150 mg once daily. The primary endpoint was hematologic response which was initially assessed after 12 weeks of treatment with eltrombopag. Treatment was discontinued after 16 weeks if no hematologic response was observed. Additional efficacy assessments included median duration of response in months.

About Severe Aplastic Anemia (SAA)

SAA is a very rare but serious blood disorder where the bone marrow fails to make enough red blood cells, white blood cells, and platelets.² The exact cause of the disease is still unknown, but most cases of SAA are believed to be triggered by an autoimmune reaction where the body attacks blood-forming stem cells located in the bone marrow.³ As a result, patients with SAA are at risk for life-threatening infections or bleeding.² In the U.S., approximately 300 to 600 new cases of SAA are identified each year.²

Treatment of SAA is focused on increasing a patient's blood cell count; definitive care includes immunosuppressive therapy (IST) or hematopoietic stem cell transplantation.^{3,4} Supportive treatments – including blood transfusions, platelet transfusions that typically occur once a week, iron chelation therapy, and treatment of infections – help in the short term to relieve specific symptoms.⁵

Of patients treated with IST, one-quarter to one-third will not respond and 30-40 per cent of responders will relapse, causing symptoms to return.⁴ Approximately 40 per cent of SAA patients who don't respond to initial IST die from infection or bleeding within five years of their diagnosis.⁶

Currently, no established standard of care exists for SAA patients who have had an insufficient response to IST or are ineligible for hematopoietic stem cell transplantation.⁷

About Eltrombopag¹

Eltrombopag is marketed under the brand name Promacta® in the U.S. and Revolade™ in most ex-U.S. countries.

In addition to the approval of Promacta for SAA in the U.S., eltrombopag is indicated for the treatment of thrombocytopenia in patients with:

- chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
 - Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
 - Promacta should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
 - Safety and efficacy have not been established in combination with direct acting antiviral agents used without interferon for treatment of chronic hepatitis C.

Important Safety Information¹

The following Important Safety Information is based on the Highlights section of the Prescribing Information for Promacta. Please consult the full prescribing information for all the labelled safety information for Promacta. The revised full U.S. Prescribing Information, including Boxed Warning, will be available soon at

<https://www.gsksource.com/gskprm/htdocs/documents/PROMACTA-PI-MG-COMBINED.PDF>

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

In patients with chronic hepatitis C, Promacta in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (See Section 5.1 of the full Prescribing Information for additional information).

Hepatotoxicity:

Promacta can cause liver enzyme elevation, therefore, monitoring of liver function before and during therapy is required. If abnormalities are confirmed, monitoring of serum liver tests should continue until resolved or stabilized. Promacta should be discontinued if abnormalities are progressively increasing, persistent, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation. Hepatotoxicity may reoccur if Promacta is reinitiated.

Thrombotic/Thromboembolic Complications:

Thrombotic/thromboembolic complications may result from increases in platelet counts with Promacta. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and normal platelet counts. The potential for an increased risk of thromboembolism when administering Promacta to patients with known risk

factors for thromboembolism should be considered. To minimize the risk for thrombotic/thromboembolic complications, Promacta should not be used in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet counts.

Cataracts:

Cataracts have been reported in patients taking Promacta. A baseline ocular examination should be performed prior to administration of Promacta. During therapy with Promacta, regularly monitoring of patients for signs and symptoms of cataracts is required.

Drug Interactions:

Promacta must not be taken within four hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements.

Adverse Reactions:

The most common adverse reactions ($\geq 20\%$) in a single-arm, open-label trial in 43 patients with SAA who received Promacta were: nausea (33%), fatigue (28%), cough (23%), diarrhea (21%), and headache (21%). In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported, including five patients who had complex changes in chromosome 7. If new cytogenetic abnormalities are observed, discontinuation of Promacta should be considered.

The most common adverse reactions in three placebo-controlled clinical trials in chronic ITP patients ($\geq 3\%$ and greater than placebo) for Promacta versus placebo were: nausea (9% vs. 3%), diarrhea (9% vs. 7%), upper respiratory tract infection (7% vs. 6%), vomiting (6% vs. <1%), increased alanine aminotransferase (ALT) (5% vs. 3%), myalgia (5% vs. 2%), urinary tract infection (5% vs. 3%), oropharyngeal pain (4% vs. 3%), increased aspartate aminotransferase (AST) (4% vs. 2%), pharyngitis (4% vs. 2%), back pain (3% vs. 2%), influenza (3% vs. 2%), paresthesia (3% vs. 2%), and rash (3% vs. 2%).

The most common adverse reactions in two randomized, placebo-controlled clinical trials in thrombocytopenic patients with chronic hepatitis C ($\geq 10\%$ and greater than placebo) for Promacta versus placebo were: anemia (40% vs. 35%), pyrexia (30% vs. 24%), fatigue (28% vs. 23%), headache (21% vs. 20%), nausea (19% vs. 14%), diarrhea (19% vs. 11%), decreased appetite (18% vs. 14%), influenza-like illness (18% vs. 16%), asthenia (16% vs. 13%), insomnia (16% vs. 15%), cough (15% vs. 12%), pruritus (15% vs. 13%), chills (14% vs. 9%), myalgia (12% vs. 10%), alopecia (10% vs. 6%), and peripheral edema (10% vs. 5%).

Prior to the revised label being posted online, a copy of the label may be requested from GSK Media or Investor Relations.

About GSK

One of the world's leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit www.gsk.com.

About Ligand Pharmaceuticals

Ligand is a biopharmaceutical company with a business model that is based upon the concept of developing or acquiring royalty revenue generating assets and coupling them to a lean corporate cost structure. Ligand's goal is to produce a bottom line that supports a sustainably profitable business. By diversifying our 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 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 GlaxoSmithKline, Onyx Pharmaceuticals (a subsidiary of Amgen Inc.), Merck, Pfizer, Baxter International, Eli Lilly & Co. and Spectrum Pharmaceuticals. Please visit www.captisol.com for more information on Captisol. For more information on Ligand, please visit www.ligand.com. Follow Ligand on Twitter @Ligand_LGND.

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 eltrombopag, data analysis and evaluation of eltrombopag, utility or potential benefits to patients, the potential commercial market for eltrombopag and plans for continued development and further studies of eltrombopag. Actual events or results may differ from Ligand's expectations. For example, there can be no assurance that other trials or evaluations of eltrombopag will be favorable or that they will confirm results of previous studies, that data evaluation will be completed or demonstrate any hypothesis or endpoint, that eltrombopag will provide utility or benefits to certain patients, that any presentations will be favorably received, that eltrombopag will be useful, that marketing applications will be filed or, if filed, approved, or that clinical or commercial development of eltrombopag will be initiated, completed or successful or that our rights to eltrombopag will not be successfully challenged. 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 risk factors affecting Ligand can be found in prior press releases available at www.ligand.com as well as in 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. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

References

¹ GSK. Promacta Prescribing Information. 2014.

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⁵ Townsley DM, Desmond R, Dunbar CE, et al. "Pathophysiology and management of thrombocytopenia in bone marrow failure: possible clinical applications of TPO receptor agonists in aplastic anemia and myelodysplasia syndromes." *Int J Hematol*. 2013; 98(1):48-55.

⁶ Valdez JM, et al. "Decreased Infection-Related Mortality and Improved Survival in Severe Aplastic Anemia in the Past Two Decades." *Clinical Infectious Diseases*. 2011; 52(6):726-735.

⁷ Scheinberg P, Young NS. "How I treat acquired aplastic anemia." *Blood*. 2011.

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