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Novartis drug Promacta® shows long-term disease control for chronic/persistent immune thrombocytopenia (ITP)

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- - Nearly 70% of patients maintained platelet counts of ≥30×10[9]/L without rescue therapy for prolonged periods, reducing the overall risk of bleeding
- - More than one-third of patients permanently stopped one or more concomitant ITP medications (including corticosteroids, danazol, azathioprine)
- - Study establishes long-term safety profile for and demonstrates treatment benefit with Promacta

EAST HANOVER, N.J., Oct. 18, 2017 /PRNewswire/ -- Novartis today announced long-term study results supporting the positive safety and efficacy of Promacta (eltrombopag) in adults with chronic/persistent (enrolling patients that were 6 or more months from diagnosis) immune (idiopathic) thrombocytopenia (ITP) were published online in Blood. The EXTEND study found that a majority of patients maintained a substantial clinical response and many no longer needed concomitant ITP medications. The research evaluated patients for up to 8 years of continuous treatment (median exposure of 2.4 years)[1,2].

ITP is a rare and potentially serious blood disorder where the blood doesn't clot as it should due to a low number of platelets. As a result, patients with ITP experience bruising, bleeding and, in rare cases, serious hemorrhaging that can be fatal[3]. The goal of treatment in chronic/persistent ITP is to maintain a safe platelet count that reduces the risk of bleeding[1,3].

"The EXTEND data published in Blood validate Promacta as an important oral treatment option that, by often increasing platelet counts, significantly decreased bleeding rates and reduced the need for concurrent therapies in certain patients with chronic/persistent immune thrombocytopenia," said lead author James Bussel, M.D., professor emeritus of pediatrics at Weill Cornell Medicine. "With this information, physicians can better optimize long-term disease management for appropriate patients living with this chronic disease."

The efficacy results of EXTEND demonstrated that median platelet counts were elevated to ≥50×10^9/L within two weeks of Promacta treatment, with median platelet counts >50×10^9/L maintained for more than four years. Post-baseline, overall bleeding rates declined and the majority of bleeding that occurred during the study was Grade 1 or 2 according to the World Health Organization bleeding scale. Some patients (39%) were capable of reducing or permanently stopping one or more concomitant ITP medications without the need for rescue therapy, many of which sustained reduction for at least 24 weeks[1,2,4].

"We conducted this trial, the largest of its kind in adult patients, to ensure that clinicians have comprehensive data on hand as they work with their ITP patients to make treatment decisions," said Vas Narasimhan, M.D., Global Head Drug Development and Chief Medical Officer, Novartis. "The EXTEND results reinforce Promacta as a trusted treatment option that can be used over the long-term for those living with this chronic and rare disease."

Overall, the safety profile of Promacta was consistent with previous studies. The most common adverse

events were headache (28%), nasopharyngitis (25%) and upper respiratory tract infection (23%). During treatment on EXTEND, 6% of patients experienced thromboembolic events[1,2,4].

About the EXTEND Clinical Trial

EXTEND, an open-label extension study of four trials (TRA100773A, TRA100773B, TRA102537/RAISE and TRA108057/REPEAT) of Promacta, enrolled 302 adults with chronic/persistent ITP (6 or more months from diagnosis) who had received prior therapy for their ITP, and is the largest study of its kind. To qualify for the prior trials, patients must have had thrombocytopenia for at least 6 months (chronic ITP was previously defined as thrombocytopenia for 6 or more months).The objectives were to assess the safety and efficacy of long-term treatment with Promacta, including the proportion of patients achieving stable platelet counts during treatment with Promacta; maximum duration of platelet count elevation $\geq 50\times10^9$/L or $\geq 30\times10^9$/L during treatment with Promacta, and the effect of Promacta on reducing and/or sparing concomitant ITP therapies, while maintaining a platelet count $\geq 50\times10^9$/L[1,2].

The study allowed each patient to achieve an individualized dose and schedule of eltrombopag based upon their platelet counts in the desired range between 50 to 200 Gi/L. Therefore, patients who were enrolled in EXTEND must have completed the treatment and follow-up periods as defined in previous protocol and must have not experienced eltrombopag-related toxicity or other drug intolerance on prior eltrombopag study even if resolved. In addition, patients who discontinued from a previous study due to toxicity were not eligible unless they received placebo[1,2].

Promacta was started at a dose of 50 mg/day and titrated to 25-75 mg/day or less often based on platelet counts. Maintenance dosing continued after minimization of concomitant ITP medication and optimization of Promacta dosing. The overall median duration of exposure was 2.37 years (range, 2 days to 8.76 years) and mean average daily dose was 50.2 (range, 1–75) mg/day[1,2]. One hundred thirty five adult patients (45%) completed the study and 75 adult patients (25%) were treated for four or more years. Most patients were aged <65 years, female, and had platelet counts $<30\times10^9$/L at baseline. About one-third were using concomitant medications at baseline, and 53% had received three or more prior ITP therapies[1,2]. In addition, 91% (276/302) of patients achieved platelet counts $\geq 30\times10^9$/L without rescue treatment, and 86% (259/302) achieved platelet counts $\geq 50\times10^9$/L without rescue treatment[1,2,4].

Grade 3 and 4 adverse events (AEs) occurred in 26% and 6% of patients, respectively. Grade 3 cataracts occurred in four (1%) patients and Grade 3 pain in extremity in six (2%) patients. Grade 3 AEs occurring in three (<1%) patients each included diarrhea, headache, migraine, dyspnea, decreased platelet count, and menorrhagia; those occurring in five (2%) patients each included pneumonia, fatigue, back pain, increased alanine aminotransferase, increased aspartate aminotransferase, anemia, and hypertension. Grade 4 anemia and thrombocytopenia occurred in three (<1%) and four (1%) patients, respectively. All other Grade 4 events occurred in one patient each[1,2].

About Chronic/Persistent ITP

Chronic/persistent ITP is a rare and potentially serious blood disorder that is characterized by the improper functioning or destruction of platelets, which are blood cells that allow the blood to clot properly[3]. People who have ITP often have purple bruises or tiny red or purple dots on the skin[3]. They also display symptoms such as nosebleeds, bleeding from the gums during dental work, or other bleeding that is hard to stop[3]. The potential for drops in platelet counts may also cause emotional distress and may result in a hindered ability to do work or embarrassment due to visible symptoms[5].

ITP is classified by duration from diagnosis into: acute (0-3 months), persistent (3-12 months duration) and

chronic (>12 months duration). Chronic/persistent ITP is more likely to occur in adults, and women are affected two to three times more often than men[3].

The goal of treatment in chronic/persistent ITP is to maintain a safe platelet count that reduces the risk of bleeding. Treatment is determined by the severity of the symptoms. In most cases, drugs that alter the immune system's attack on the platelets are prescribed to help manage bleeding and bruising in adults.

About Eltrombopag

Eltrombopag, marketed as Promacta® in the United States and Revolade® in countries outside the US, is approved in more than 100 countries worldwide for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to other treatments, approved in over 45 countries worldwide for the treatment of patients with severe aplastic anemia (SAA) who are refractory to other treatments, and also approved in more than 50 countries for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow them to initiate and maintain interferon-based therapy. Eltrombopag is approved in the US and in the European Union for the treatment of thrombocytopenia in pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids and immunoglobulins.

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®.

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This press release contains forward-looking statements, including "forward-looking statements" within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of

existing clinical data; regulatory actions or delays or government regulation generally; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payer and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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James Bussel, M.D. has received research support payments for his service on an advisory board as well as participated in speakers' bureaus sponsored by Novartis Pharmaceuticals.

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