FDA approves Novartis drug Promacta® for first-line SAA and grants Breakthrough Therapy designation for additional new indication

Nov 16, 2018

- - Promacta receives FDA approval for first-line treatment of severe aplastic anemia (SAA) and Breakthrough Therapy designation for low platelet counts in people exposed to radiation
- - Approval based on compelling benefit established through complete response rates among SAA patients when Promacta is added to standard immunosuppressive therapy relative to historic information on that therapy alone
- - Promacta is the first new treatment in decades for newly diagnosed SAA patients in the US; a decision by the European Medicines Agency is expected in 2019

EAST HANOVER, N.J., Nov. 16, 2018 /PRNewswire/ -- Novartis announced today that the US Food and Drug Administration (FDA) has expanded the label for Promacta® (eltrombopag) to include first-line treatment for adults and pediatric patients two years and older with SAA in combination with standard immunosuppressive therapy (IST).

Promacta, which is marketed as Revolade® in most countries outside the US, is an oral thrombopoietin receptor agonist (TPO-RA) that is already approved for SAA for patients who have had an insufficient response to IST. It is also approved for adults and children with chronic immune thrombocytopenia (ITP) who are refractory to other treatments, and for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection.

"Severe aplastic anemia can be a fatal diagnosis if left untreated, and many patients fail to respond to current initial treatment options," said Liz Barrett, CEO, Novartis Oncology. "Today's US approval for Promacta is an important step forward for people living with this challenging disease and shows how Novartis continues to reimagine care in areas where few treatment options exist."

The FDA's approval is based on Novartis' analysis of research sponsored by the National Heart, Lung and Blood Institute (NHLBI) Division of Intramural Research Program and conducted under a Cooperative Research and Development Agreement (CRADA). The study showed that 44% (95% CI 33, 55) of definitive IST-naive SAA patients achieved complete response at 6 months when treated with Promacta concurrently with standard IST, which was 27% higher than the complete response rate historically observed with the standard IST alone[1]. The overall response rate was 79% (95% CI 69, 87) at 6 months[2].

These high response rates have a significant clinical impact for patients with SAA who were not previously treated with standard IST. These results further build on the IST-refractory indication for patients with SAA which Promacta was granted in 2015, in which a subset of patients maintained stable counts and demonstrated restoration of bone marrow function following Promacta discontinuation[1,3].

The new data in IST-naïve SAA includes sustained response with a median duration of response of 24.3 months for patients receiving 6 months of Promacta in combination with horse anti-thymocyte globulin (h-ATG)

and cyclosporine (CsA) followed by maintenance CsA4.

In this study, the most common adverse reactions reported (incidence ≥5%) were abnormal liver function tests, rash, and skin discoloration including hyperpigmentation.

Severe aplastic anemia is a rare, life-threatening, acquired blood disorder in which a patient's bone marrow fails to produce enough red blood cells, white blood cells, and platelets[5]. As a result, people living with this serious disease may experience debilitating symptoms and complications, such as fatigue, trouble breathing, recurring infections, and abnormal bruising or bleeding that can limit their daily activities[2]. Historically, SAA was nearly uniformly a fatal diagnosis due to infection or hemorrhage resulting from the body's inability to produce new blood cells[4].

"Patients with SAA sometimes do not respond to the current treatment standard of IST," said Phillip Scheinberg, MD, Head, Division of Hematology, Hospital A Beneficência Portuguesa de São Paulo in Brazil, and previously with the Hematology Branch of the NHLBI. "With this approval, physicians now have an option to add Promacta to the standard IST in a regimen that has demonstrated significant overall and complete response rates upfront in SAA and reduce the numbers of those who are unresponsive to initial therapy."

Novartis submitted a Type II variation application for Revolade as a first-line SAA treatment to the European Medicines Agency in April 2018 and is expecting a decision in 2019.

Breakthrough Therapy for H-ARS
The FDA also granted Promacta Breakthrough Therapy designation as a counter measure for hematopoietic sub-syndrome of acute radiation syndrome (H-ARS).

Acute radiation syndrome, also known as radiation sickness, occurs after exposure to ionizing radiation and leads to many symptoms including thrombocytopenia. Thrombocytopenia is a reduction in platelet counts that increases the risk of hemorrhage[6]. Promacta was shown to decrease the risk of hemorrhage in patients with radiation sickness.

Research and development of Promacta for H-ARS is being conducted under contract with the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) for potential use following deliberate, natural, and emerging radio/nuclear threats, specifically to treat patients exposed to myelosuppressive doses of radiation.

FDA Breakthrough Therapy designation is for medicines that treat a serious or life-threatening disease or condition, and demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoint based on preliminary clinical evidence.

Promacta®/Revolade® (eltrombopag)
Eltrombopag, marketed as Promacta® in the US and Revolade® in countries outside the US, is approved in more than 90 countries worldwide for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to other treatments. It is also approved for the treatment of patients with severe aplastic anemia (SAA) as first-line therapy in the US (patients 2 years and older) and Japan, and in many other countries for patients who are refractory to other treatments. In more than 40 countries, Promacta/Revolade is indicate for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow them to initiate and maintain interferon-based therapy.
Promacta/Revolade 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 thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should only be used in patients with

ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

Important Safety Information
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).

PROMACTA is not for treatment of people with a precancerous condition called myelodysplastic syndromes (MDS). If you have MDS and receive PROMACTA, your MDS condition may worsen and become AML. If MDS worsens to become AML, you may die sooner from AML.

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 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 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 (SAA) 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.

The most common side effects of Promacta when used to treat adults and pediatric patients 2 years and older with SAA in combination with standard immunosuppressive therapy are: abnormal liver function tests, rash and skin discoloration including darkening of skin patches (hyperpigmentation).

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

Disclaimer
This press release contains 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; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, 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.

About Novartis
Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 1 billion people globally and we are finding innovative ways to expand access to our latest treatments. About 125,000 people of more than 140 nationalities work at Novartis around the world. Novartis Pharmaceuticals Corporation, a US affiliate of Novartis, is located in East Hanover, NJ. Find out more at www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References
1. Desmond, R. et al. Blood. 2014;123(12),1818-1825.
2. Novartis Data on File.
3. Olnes MJ et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367(1):11-19.
4. Townsley, D et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med 2017;376(16):1540-1550.
5. National Heart, Lung and Blood Institute (2018). Aplastic Anemia. Available at: https://www.nhlbi.nih.gov/node/80148. Accessed January 18, 2018.
6. Gorbunov NV, Sharma P. Protracted oxidative alterations in the mechanism of hematopoietic acute radiation syndrome. Antioxidants; 2015;4(1):134-52.

Novartis Media Relations
Central media line: +41 61 324 2200
E-mail: media.relations@novartis.com

Eric Althoff	Michael Billings
Novartis Global Media Relations	Benign Hematology Communications
+41 61 324 7999 (direct)	+1 862 778 8656 (direct)
+41 79 593 4202 (mobile)	+1 201 400 1854 (mobile)
eric.althoff@novartis.com	michael.billings@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Richard Pulik	+1 212 830 2448

Pierre-Michel Bringer +41 61 324 1065 Cory Twining +1 212 830 2417

Thomas Hungerbuehler +41 61 324 8425

Isabella Zinck +41 61 324 7188

SOURCE Novartis

List of links present in page

1. https://qa1.novartis.us/news/media-releases/fda-approves-novartis-drug-promacta-first-line-saa-and-grants-breakthrough-therapy-designation-additional-new-indication
2. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf
3. http://www.novartis.com/
4. http://twitter.com/novartis
5. http://www.novartis.com/news/media-library
6. mailto:media.relations@novartis.com
7. https://www.nhlbi.nih.gov/node/80148
8. mailto:media.relations@novartis.com
9. mailto:eric.althoff@novartis.com
10. mailto:michael.billings@novartis.com
11. mailto:investor.relations@novartis.com