Clinical Data Backgrounder
Promacta® (eltrombopag) as an oral treatment for patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST)

About Severe Aplastic Anaemia (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. As a result, patients with SAA are at risk for life-threatening infections or bleeding.
- Treatment of SAA is focused on increasing a patient’s blood cell count; definitive care includes immunosuppressive therapy (IST) or hematopoietic stem cell transplantation. 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.
- Of patients treated with IST, one-quarter to one-third will not respond, and 30-40 per cent of responders relapse. Approximately 40 per cent of SAA patients unresponsive to initial IST die from infection or bleeding within five years of their diagnosis.

About GSK’s Promacta® (eltrombopag)
- On 26 August 2014, Promacta (eltrombopag), a thrombopoietin receptor (TPO-R) agonist, was approved for the treatment of patients with SAA who have had an insufficient response to IST.
- Promacta is the only once-daily oral TPO-R agonist.
- Promacta works by inducing proliferation and differentiation of bone marrow stem cells to increase production of blood cells.
- In addition to its use in SAA, Promacta is also 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.
  - Thrombocytopenia in patients with 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 infection.

For more information about Promacta, please see full U.S. Prescribing Information, including Boxed Warning, which will be available soon at https://www.gsksource.com/gskprm/htdocs/documents/PROMACTA-PI-MG-COMBINED.PDF.

Clinical Evidence Supporting the FDA Approval
- The U.S. Food and Drug Administration (FDA) approval is based on results from an investigator-sponsored Phase II study (09-H-0154) by the National Heart, Lung and Blood Institute (NHLBI) at the National Institutes of Health (NIH). Results from the study demonstrated a haematologic response in SAA patients treated with eltrombopag who have had an insufficient response to IST.
About the Phase II 09-H-0154 Study\(^1\)

- In the single-arm, single-centre, open-label Phase II study (09-H-0154), 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 \(\leq 30 \times 10^9/L\).
- The treated population had a median age of 45 years (range 17 to 77 years) and 56 per cent were male. At baseline, the median platelet count was \(20 \times 10^9/L\), haemoglobin 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 majority of patients (84%) received at least two prior immunosuppressive therapies.
  - Three patients had cytogenetic abnormalities at baseline.
- In the study, 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 haematologic response assessed after 12 weeks of treatment with eltrombopag. Haematologic response was defined as meeting one or more of the following criteria:
  - Platelet count increases to \(20 \times 10^9/L\) above baseline, or stable platelet counts with transfusion independence for a minimum of eight weeks.
  - Haemoglobin increase by \(>1.5g/dL\), or a reduction in \(\geq 4\) units of red blood cell (RBC) transfusions for eight consecutive weeks.
  - ANC increase of 100 per cent or an ANC increase \(>0.5 \times 10^9/L\).
- Treatment was discontinued after 16 weeks if no haematologic response was observed. Patients who responded continued therapy in an extension phase of the trial.

Phase II Study: 09-H-0154 Efficacy Results\(^1\)

- Forty per cent (95% CI, 25, 56) of patients (17/43) treated with eltrombopag experienced haematologic response, which was defined as single or multi-lineage response. Median duration of response was not reached (95% CI, 3.0, NR) due to few events (relapsed).
  - 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).
- 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).
- 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).

Phase II Study: 09-H-0154 Safety Results\(^1\)

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%), diarrhoea (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.

Important Safety Information\(^1\)

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](https://www.gsksource.com/gskprm/htdocs/documents/PROMACTA-PI-MG-COMBINED.PDF)
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 stabilised. 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 minimise the risk for thrombotic/thromboembolic complications, Promacta should not be used in an attempt to normalise 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 (≥20%) in a single-arm, open-label trial in 43 patients with SAA who received Promacta were: nausea (33%), fatigue (28%), cough (23%), diarrhoea (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 (≥3% and greater than placebo) for Promacta versus placebo were: nausea (9% vs. 3%), diarrhoea (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%), paraesthesia (3% vs. 2%), and rash (3% vs. 2%).

The most common adverse reactions in two randomised, placebo-controlled clinical trials in thrombocytopenic patients with chronic hepatitis C (≥10% and greater than placebo) for Promacta versus placebo were: anaemia (40% vs. 35%), pyrexia (30% vs. 24%), fatigue (28% vs. 23%), headache (21% vs. 20%), nausea (19% vs. 14%), diarrhoea (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 oedema (10% vs. 5%).

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).
Prior to the revised label being posted online, a copy of the label may be requested from one of the GSK Media or Investor Relations contacts listed in the “GSK enquiries” section at the end of the press release.


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.

References

1. GSK. Promacta Prescribing Information. 2014.