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HEALTH TECHNOLOGY BRIEFING
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Avatrombopag in addition to standard of care for chronic immune thrombocytopenia

NIHRIO ID	28852	**NICE ID**	10377
Developer/Company	Swedish Orphan Biovitrum AB	**UKPS ID**	654946

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Avatrombopag is currently in clinical development for the treatment of chronic immune thrombocytopenia (ITP) in patients who have had an insufficient response to previous treatment. ITP is an auto-immune disease that arises when the body's immune system attacks platelet cells resulting in a decreased number of platelets (platelet count). Platelets help blood to clot following damage to a blood vessel wall so if there is a decreased number of platelets there is an increased risk of frequent bleeding or severe bleeding. This results in the symptoms associated with ITP such as petechial (pin prick rash of blood spots), bruising, nosebleeds, gum bleeds, fatigue and heavy periods.

Avatrombopag is given as an oral tablet and works by mimicking the action of a hormone called thrombopoietin (TPO) which is responsible for causing pre-curser cells to mature into platelets. Avatrombopag binds to TPO receptors resulting in increased platelet production and increased platelet count. Results from clinical studies have demonstrated that avatrombopag is safe and efficacious. If licensed, avatrombopag could offer an additional treatment option for patients with chronic ITP who have had limited response to previous therapy.

PROPOSED INDICATION

For the treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.[1]

TECHNOLOGY

DESCRIPTION

Avatrombopag (Doptelet) is an orally-administered small molecule thrombopoietin (TPO) receptor agonist.[2] TPO is a glycoprotein hormone that acts as one of the main regulators of platelet production and activation.[2] TPO receptor agonists are a class of platelet growth factors that mimic the action of endogenous TPO on megakaryocytes and megakaryocyte precursors, promoting their growth and differentiation and increasing platelet production.[3] Avatrombopag partially mimics the biological effects of TPO by promoting the differentiation of CD34+ cells to megakaryocytes to increase platelet number but not platelet activation.[2,4,5] Unlike other TPO agonists which may block TPO binding, avatrombopag works synergistically with TPO to increase platelet count.[2]

Avatrombopag in combination with standard of care is in clinical development for the treatment of chronic ITP in patients who have had an insufficient response to previous treatment. In the phase III clinical trial (NCT01438840) patients are given avatrombopag for 26 weeks. Participants will be given a starting dose of 20mg avatrombopag and the dose will be titrated up to a maximum dose of 40mg or titrated down to a minimum dose of 5mg depending on their response.[1]

INNOVATION AND/OR ADVANTAGES

Avatrombopag is different from other TPO receptor agonists in that it does not have a boxed safety warning for hepatotoxicity, is administered with food, and does not have any dietary restrictions. Furthermore, it does not interact with polyvalent cations (calcium, magnesium, iron, selenium, zinc, etc.) in foods, mineral supplements, or antacids that could reduce systemic exposure and efficacy.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avatrombopag currently has Marketing Authorisation in the EU/UK for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.[7]

The very common adverse effects, occurring in ≥ 10% of people, include: headache, contusion, thromboembolic events, epistaxis, upper respiratory tract infection, nasopharyngitis, arthralgia, gingival bleeding and petechiae.[8]

Avatrombopag is currently in phase II clinical development for:[9]

- Thrombocytopenia after donor hematopoietic stem cell transplant
- Chronic hepatitis C virus related thrombocytopenia

Avatrombopag is currently in phase III clinical development for:[10]

- Treatment of adults scheduled for a surgical procedure

- Treatment of chemotherapy induced thrombocytopenia
- Chronic liver diseases and thrombocytopenia

PATIENT GROUP

DISEASE BACKGROUND

Immune thrombocytopenia (ITP), also called idiopathic thrombocytopenia, is an autoimmune bleeding disorder characterized by abnormally low levels of blood cells called platelets (thrombocytopenia) due to the body's immune system mistaking the platelets as being foreign and destroying them.[11,12] Platelets are specialized blood cells that stick together (clot) to seal small breaks on blood vessel walls to stop bleeding.[13,14] ITP can follow a virus, vaccination or certain medications, but for most people the cause is unknown.[11]

There is currently no definitive laboratory test to diagnose ITP. However, a normal platelet count ranges from approximately 150,000 to 400,000 per microliter of blood and if someone has a platelet count lower than 100,000 per microliter of blood with no other reason for low platelets they may have ITP.[13] If the platelet count remains low after 12 months this is called chronic ITP.[11]

Without enough platelets, bleeding can occur inside the body (internal bleeding), underneath, or from the skin (external bleeding).[14] A greater reduction in platelet numbers is often associated with more frequent bleeding episodes and an increased risk of severe bleeding.[12] Common symptoms of ITP are petechial (pin prick rash of blood spots), bruising, nosebleeds, gum bleeds, black mouth blisters, fatigue and heavy periods.[11] In severe cases, individuals may have gastrointestinal bleeding or blood in the urine or stool or heavy and prolonged menstrual bleeding. In very rare instances, bleeding inside the skull (intracranial haemorrhage) can occur, which can be life threatening.[12]

CLINICAL NEED AND BURDEN OF DISEASE

The UK incidence of adult ITP is estimated to be between 1.6 to 3.9 per 100,000 adults per year, with around 3,000-4,000 people being affected at any one time in England and Wales.[15] Women are two to three times more likely than men to develop chronic ITP.[14]

According to the 2018-19 Hospital Episodes Statistics data in England, in 2018-19, there were 14,994 finished consultant episodes (FCE) for idiopathic thrombocytopenia (ICD-10 code D69.3) resulting in 13,876 admissions and 8,943 FCE bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for ITP, treatment is used to raise the platelet count to counteract symptoms.[11] Treatment of ITP is based on platelet count and bleeding symptoms.[17] If the clinical presentation is not that of a life-threatening bleeding, corticosteroids are considered the standard initial treatment. Intravenous immunoglobulins (IVIG) are recommended for patients with critical bleeding and for those unresponsive to corticosteroids or for whom corticosteroids are contraindicated.[18] Patients with life-threatening bleeding, regardless of

platelet count, can be considered for combination therapy with corticosteroids, intravenous immunoglobulin and platelet transfusion.[17]

CURRENT TREATMENT OPTIONS

First line (rescue) treatment options:[19]
- Prednisolone
- IVIG

Second line treatment options:[19]
- Rituximab
- Splenectomy

Third line treatment options:[19]
- Eltrombopag
- Romiplostim

PLACE OF TECHNOLOGY

If licensed, avatrombopag will offer an additional treatment option for patients with chronic ITP who have had an insufficient response to previous treatment.

CLINICAL TRIAL INFORMATION

Trial	**AMENDMENT 02**, NCT01438840; A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial With an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard of Care for the Treatment of Thrombocytopenia in Adults With Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenia Purpura) **Phase: III** - Completed **Locations:** EU (not incl. UK), South Africa, Singapore, Australia and New Zealand
Trial design	Randomized, Double-blind, Placebo-controlled, Parallel Assignment
Population	N=49 participants; adults aged 18 years and older; diagnosed with chronic ITP according to the American Society for Hematology/British Committee for Standards in Hematology guidelines; participants who previously received one or more ITP therapies
Intervention(s)	Avatrombopag (oral administration) Starting dose of 20mg and the dose will be titrated up to a maximum dose of 40mg or down to a minimum dose of 5mg depending on the patients' response to the drug.
Comparator(s)	Placebo
Outcome(s)	Number of Weeks With Platelet Count Greater Than or Equal to $50x10^9/L$ During 6-Month Treatment Period [Time Frame: Week 1 to Week 26] See trial record for full list of outcomes

Results (efficacy)	Avatrombopag was shown to be superior to placebo as measured by the cumulative number of weeks of platelet response (platelet count ≥50 x 10^9/l) over 6 months (26 weeks) of once-daily treatment. Avatrombopag treatment resulted in a median of 12.4 cumulative weeks of platelet response during the core study and was also shown to be superior to placebo (0 weeks), with a greater platelet response rate in avatrombopag-treated patients at day 8 (65.6% versus 0% respectively).[4]
Results (safety)	The most commonly reported treatment-emergent adverse events (TEAEs) in the avatrombopag treatment group were headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding and petechiae, with exposure-adjusted incidence rates that were all comparable with, or lower than placebo. Four patients who received avatrombopag experience Grade 3 TEAEs which included single serious adverse events (SAEs) of epistaxis, petechial, headache and platelet count reduction. There were two Grade 4 TEAEs; one patient with a cerebrovascular accident who discontinued study medication and the other with worsening ITP that was considered not related to study medication. There were no deaths during the study in any treatment group.[4]

ESTIMATED COST

The estimated cost of avatrombopag is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Fostamatinib for treating persistent of chronic immune thrombocytopenia (GID-TA10387). Expected publication date TBC.
- NICE technology appraisal. Romiplostim for treatment of chronic immune (idiopathic) thrombocytopenic purpura (TA221). October 2018
- NICE technology appraisal. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (TA293). October 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (All ages). B09/S/a.
- NHS England. Clinical Commissioning Policy: Rituximab for cytopaenia complicating primary immunodeficiency. 16044/P. July 2016.

OTHER GUIDANCE

- American Society of Hematology (ASH). 2019 Guidelines for Immune Thrombocytopenia. 2019.[20]

ADDITIONAL INFORMATION

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