

HEALTH TECHNOLOGY BRIEFING JULY 2020

Avatrombopag for chemotherapy induced thrombocytopenia in patients with non-haematological cancers

NIHRIO ID	28847	NICE ID	10376
Developer/Company	Swedish Orphan Biovitrum Ltd	UKPS ID	655203

Licensing and market availability plans	Currently in phase III clinical trial.
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SUMMARY

Avatrombopag is in clinical development for the treatment of chemotherapy-induced thrombocytopenia (CIT) in patients with active non-haematological cancers. CIT refers to abnormally low platelet (type of blood cells) count, with or without bleeding, in cancer patients receiving myelosuppressive chemotherapy (treatment that stops or slows the growth of blood-forming cells in the bone marrow). Most chemotherapy agents can induce thrombocytopenia. CIT can complicate surgical procedures and lead to chemotherapy dose delays, dose reductions, or discontinuation, which may result in suboptimal patient outcomes. CIT also increases the likelihood of serious bleeding events, which may result in hospitalisation.

Avatrombopag is administered orally. It works by attaching to a hormone called thrombopoietin, which stimulates the production of platelets by attaching to receptors (targets) in the bone marrow and helping in increasing the platelet count. Avatrombopag 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. If licensed, avatrombopag will provide a treatment option for CIT in patients with active non-haematological cancers.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of chemotherapy-induced thrombocytopenia (CIT) in adult patients with active non-haematological cancers.^a

TECHNOLOGY

DESCRIPTION

Avatrombopag (Doptelet) is an orally-administered small molecule thrombopoietin (TPO) receptor agonist. TPO is a glycoprotein hormone that acts as one of the main regulators of platelet production and activation.¹ 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.² 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.^{1,3,4} Unlike other TPO agonists which may block TPO binding, avatrombopag works synergistically with TPO to increase platelet count.¹

Avatrombopag is in clinical development for the treatment of patients with CIT with active non-haematological cancers. In the phase III clinical trial (NCT03471078), patients will receive avatrombopag 60 mg orally once daily for 5 days prior to chemotherapy and 5 days following treatment.^{a,5}

INNOVATION AND/OR ADVANTAGES

Avatrombopag is different from other TPO receptor agonists in that it does not have a boxed safety warning for hepatotoxicity; it 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 $\geq 10\%$ of people, include: headache, fatigue, pyrexia, contusion, 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
- Thrombocytopenia in cancer and liver diseases

Avatrombopag is currently in phase III clinical development for:¹⁰

- Chronic thrombocytopenia and immune thrombocytopenia

Avatrombopag was granted FDA orphan designation in December 2019 for the treatment of CIT.¹¹

^a Information provided by Swedish Orphan Biovitrum Ltd

PATIENT GROUP

DISEASE BACKGROUND

Thrombocytopenia is condition in which blood has lower than normal number of blood cell fragments called platelets. Platelets are made in bone marrow and they travel through blood vessels and stick together to stop any bleeding that may happen if a blood vessel is damaged.¹² CIT is defined as a peripheral platelet count less than $100 \times 10^9/L$, with or without bleeding in cancer patients receiving myelosuppressive chemotherapy. Platelets are released by their progenitor cells in the bone marrow, megakaryocytes, into sinusoidal blood vessels. Chemotherapeutic drugs suppress megakaryocyte development and platelet production. CIT carries the risk of sub-optimal overall survival and bleeding, and increases the need for chemotherapy dose reduction, treatment delay and platelet transfusion.¹³

The most common cause of thrombocytopenia in people with cancer is bone marrow suppression related to chemotherapy. Chemotherapy destroys rapidly dividing cells, such as those in the bone marrow which become platelets. Many chemotherapy drugs do not affect platelet levels to a degree which is significant enough to require treatment, but some drugs are much more likely than others to reduce counts.¹⁴

The most common signs and symptoms include easy or excessive bruising (purpura), small red or purple spots on the skin (petechiae), prolonged bleeding from cuts, bleeding from gums or nose, blood in urine or stools, unusually heavy menstrual flows, fatigue and enlarged spleen.¹⁵

CLINICAL NEED AND BURDEN OF DISEASE

In a US study of 215,508 cancer chemotherapy patients, CIT incidence during the chemotherapy course was 9.7%. This ranged from 6.1% for regimens containing cyclophosphamide to 13.5% for regimens containing gemcitabine.¹⁶ Further retrospective cohort studies have reported treatment-related thrombocytopenia rates of 16.5% and 21.8% and more than 30% for platinum or gemcitabine-based regimens.¹⁷ Incidence data for the UK was not identified.

Data from patients in England treated with chemotherapy between 2013 and 2015 for ovarian, lung (small cell and non-small cell) and bladder cancer suggest that 53,340 patients received chemotherapy as part of their treatment.¹⁸

Hospital episode statistics (HES) for England 2018-19 recorded 6,804 finished consultant episode (FCE) and 6,047 admissions for thrombocytopenia, unspecified (ICD-10 code D69.6), resulting in 3,891 day cases and 5,146 FCE bed days.¹⁹ The population likely to be eligible to receive avatrombopag could not be estimated from available published sources.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Thrombocytopenia can last for days or years. People with mild thrombocytopenia might not need treatment. For patients who do need treatment for thrombocytopenia, treatment depends on it is caused and how severe it is. The most common treatments for thrombocytopenia include blood or platelet transfusions, medications, surgery and plasma exchange.²⁰ Most chemotherapy agents can induce thrombocytopenia.²¹ In the event of CIT, the universal practice is to stop the suspected chemotherapy treatment. Platelet counts usually recover within several days to 2 weeks. Platelet transfusions may be required to treat patients

with severe thrombocytopenia and bleeding. Other supportive measures include high dose intravenous immunoglobulin, a brief course of corticosteroids, or even plasmapheresis.²²

CURRENT TREATMENT OPTIONS

There are currently no approved pharmacological options for the treatment of CIT in patients with active non-haematological cancers.

PLACE OF TECHNOLOGY

If licensed, avatrombopag will provide an additional treatment option for chemotherapy-induced thrombocytopenia (CIT) in patients with active non-haematological cancer.^b

CLINICAL TRIAL INFORMATION

Trial	<p>NCT03471078; A randomized, double-blind, placebo-controlled study with an open-label extension to evaluate the efficacy and safety of avatrombopag for the treatment of chemotherapy-induced thrombocytopenia in subjects with active non-haematological cancers</p> <p>Phase III- Ongoing</p> <p>Location(s): EU (excluding UK), USA and other countries</p> <p>Primary completion date: November 2020</p>
Trial design	Randomised, parallel assignment, double blinded
Population	N= 120 (planned); 18 years and older; ovarian, lung (small cell or non-small cell) or bladder cancer requiring systemic chemotherapy; receiving a chemotherapy regimen given in a 21 or 28-day cycle, including 1 or more of the following agents or class of agents: nucleoside analog, including gemcitabine and fluorouracil, carboplatin or cisplatin, anthracycline, or alkylating agent; experienced severe thrombocytopenia.
Intervention(s)	<p>Avatrombopag</p> <ul style="list-style-type: none"> Avatrombopag administered orally once daily for 5 days prior to chemotherapy and 5 days following chemotherapy treatment.
Comparator(s)	<p>Placebo</p> <ul style="list-style-type: none"> Placebo administered orally once daily for 5 days prior to chemotherapy and 5 days following chemotherapy treatment.
Outcome(s)	<ul style="list-style-type: none"> Evaluate the efficacy of avatrombopag in proportion of responders (Time frame: randomization up to 33 days) <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

^b Information provided Swedish Orphan Biovitrum Ltd on UK PharmaScan

ESTIMATED COST

The estimated cost of avatrombopag is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

- NHS: Northern Cancer Alliance. Guidelines for the Management of Chemotherapy and Systemic Anticancer Therapy Induced Toxicities With in Primary Care. June 2018.²¹
- British Society for Haematology. Guidelines for the use of platelet transfusions. February 2016.²³

ADDITIONAL INFORMATION

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