Lay summary

Eltrombopag (Revolade) is a new drug to treat severe aplastic anaemia. Eltrombopag is taken by mouth and makes the body produce more platelet cells by activating a hormone called thrombopoietin.

This briefing is based on information available at the time of research 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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Aplastic anaemia: severe – first line.

TECHNOLOGY

DESCRIPTION

Eltrombopag (Revolade; Promacta; 497115; eltrombopag olamine; SB-497115) is a thrombopoietin receptor agonist. Eltrombopag is administered orally at 50mg daily; the dose is adjusted every 2 weeks according to the platelet count (increased by 25mg per day up to 150mg per day)\(^a\).

Eltrombopag is licensed in the EU as Revolade for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in patients aged ≥1 years old who are refractory to other treatments (e.g. corticosteroids and immunoglobulins); for the treatment of thrombocytopenia associated with chronic hepatitis C infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy; and in adult patients with acquired severe aplastic anaemia who are either refractory to prior immunosuppressive therapy or heavily pretreated, and are unsuitable for haematopoietic stem cell transplantation\(^1,a\).

In the severe aplastic anaemia study population, very common (≥1/10) adverse effects of eltrombopag include: insomnia; headache; dizziness; cough; dyspnoea; oropharyngeal pain; rhinorrhea; abdominal pain; diarrhoea; nausea; increased serum levels of liver transaminases; ecchymosis; arthralgia; muscle spasms; pain in extremity; fatigue; febrile neutropenia; and pyrexia\(^1\).

Common (≥1/100 to <1/10) adverse effects of eltrombopag in this study population include: neutropenia; splenic infarction; iron overload; decreased appetite; hypoglycaemia; increased appetite; anxiety; depression; syncope; dry eye; eye pruritus; ocular icterus; blurred vision; visual impairment; vitreous floaters; epistaxis; gingival bleeding; oral mucosal blistering; oral pain; vomiting; abdominal discomfort; abdominal pain; constipation; abdominal distension; dysphagia; discoloured faeces; swollen tongue; gastrointestinal motility disorder; flatulence; hyperbilirubinaemia; jaundice; petechiae; rash; pruritus; urticaria; skin lesion; macular rash; back pain, myalgia; bone pain; chromaturia; asthenia; peripheral oedema; chills; malaise; and increased blood creatinine phosphokinase\(^7\). Expert opinion notes that a number of these adverse effects are likely to be due to the aplastic anaemia not treatment with eltrombopag\(^b\).

Eltrombopag is also in phase III clinical trials for myelodysplastic syndrome, and in phase II clinical trials for thrombocytopenia in patients who have suffered a radio/chemotherapy-induced injury.

INNOVATION and/or ADVANTAGES

If licensed, eltrombopag will offer an additional oral first line treatment option for patients with severe aplastic anaemia.

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\(^a\) Company provided information.

\(^b\) Expert personal communication.
Aplastic anaemia is defined as pancytopenia with a hypo-cellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin\textsuperscript{2,3}. It is a rare and heterogeneous condition that is potentially life-threatening\textsuperscript{2}. The majority of acquired cases are categorised as idiopathic (with unknown primary aetiology); in only a minority of cases is it possible to identify a cause likely to have precipitated the condition\textsuperscript{2}. In such cases, recognised causes include drugs, such as chloramphenicol, sulphonamides, gold and penicillamine, or infections, such as seronegative hepatitis (5-10\% of severe acquired aplastic anaemia), Ebstein-Barr Virus, HIV, and parvovirus\textsuperscript{3}. Toxic exposure to radiation or chemicals, such as benzene, is also known to precipitate the condition\textsuperscript{4}. For around 15-20\% of patients, the condition is inherited\textsuperscript{2}.

The most common symptoms of aplastic anaemia arise directly from the effects of anaemia, including pallor, headache, palpitations, dyspnoea, fatigue or ankle oedema. The effects of thrombocytopenia, such as skin or mucosal haemorrhage, visual disturbance due to retinal haemorrhage and petechial rashes, are also common symptoms\textsuperscript{3}. Acquired aplastic anaemia is classified as non-severe, severe, or very severe on the basis of the degree of peripheral-blood pancytopenia. Aplastic anaemia is classified as severe where bone marrow cellularity <25\%, or is 25-50\% with <30\% residual haemopoietic cells, and there is also two of the following: neutrophils <0.5 x 10\(^9\)/L, platelets <20 x 10\(^9\)/L, and/or reticulocytes <60 x 10\(^9\)/L\textsuperscript{3}. Very severe disease is defined in the same way as severe disease, but with neutrophils <0.2 x 10\(^9\)/L.

The precise incidence of aplastic anaemia is difficult to determine due to the imprecision in establishing a diagnosis. Idiopathic aplastic anaemia is estimated to have a prevalence of 0.4 per 100,000 population in Europe\textsuperscript{4}, representing an estimated 212 people in England. The annual incidence of aplastic anaemia has been estimated at around two cases per million population based on data collected from Europe and Israel\textsuperscript{5}. Additionally, the incidence of aplastic anaemia is subject to wide variation throughout the world\textsuperscript{6}.

In England, there were 13,462 hospital admissions due to all forms of aplastic anaemia (ICD-10 D61) in 2014-15, resulting in 14,944 finished consultant episodes and 20,046 bed days\textsuperscript{7}. In 2014, all forms of aplastic anaemia (ICD-10 D60-D61.9) accounted for 256 deaths in England and Wales, the majority of which were classed as ‘other aplastic anaemias’ (n=128) or ‘aplastic anaemia, unspecified’ (n=125)\textsuperscript{8}. These statistics do not distinguish

\[^{c}\text{Expert personal communication.}\]
between the types of aplastic anaemia or the severity of the disease and expert opinion therefore suggests that these data are inaccurate⁴.

The population likely to be eligible to receive eltrombopag could not easily be estimated from available routine published sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**


**NHS England Policies and Guidance**


**Other Guidance**

- British Society for Haematology. Diagnosis and Management of Aplastic Anaemia. 2015³.

### CURRENT TREATMENT OPTIONS

Treatment for aplastic anaemia aims to correct the hypo-cellular bone marrow while providing supportive care where appropriate. The main two effective treatments for those with acquired severe aplastic anaemia are²,³:

- **Allogeneic bone marrow (haematopoietic) stem cell transplantation (HSCT)** is potentially curative and restores haematopoiesis in patients with severe aplastic anaemia. Most patients are not suitable candidates for optimal initial HSCT because of a lack of a matched sibling donor, lead time to identify a suitable unrelated donor, age, comorbidities, or access to transplantation. HSCT aims to replace the damaged bone marrow. It is the initial treatment choice for newly diagnosed severe or very severe aplastic anaemia patients where a human leukocyte antigen (HLA)-compatible identical sibling donor is available and the patient is young (35-50 years)³.

- **Immunosuppressive therapy** – aims to prevent the immune system from mistakenly attacking normal haematopoietic cells. The British Committee for Standards in Haematology (BCSH) recommends a combination of antithymocyte globulin (ATG) and ciclosporin A for patients with severe or very severe aplastic anaemia aged 35-50 years, or for younger patients with severe or very severe disease where an HLA-identical sibling donor is not available³.

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³ Expert personal communication.
Other potential treatments include:

- **Matched unrelated donor bone marrow transplantation** – may be considered to treat severe aplastic anaemia when a suitably matched donor is available, the patient is <50 years and when a patient has failed at least one course of ATG and ciclosporin².
- **Oxymetholone** – may be used as an alternative to immunosuppressive therapy, however the BCSH guidelines advise caution in women (risk of masculinisation) and the elderly (risk of cardiac failure, high risk of liver toxicity, high serum cholesterol, impaired glucose tolerance and prostatism)²,³. However, the response rate is low at only 25%.

**Supportive care.**
A number of steps can be taken to support patients with aplastic anaemia before primary treatment, where primary treatment has failed, or where a patient is not suitable for primary treatment.

- **Transfusions** - platelet and red blood cell (RBC) transfusions where required to maintain a safe blood count²,³.
  - Platelet transfusions should be considered when the platelet count is <10 x 10⁹/L.
  - Irradiated blood components should be given in those whom marrow transplantation may be attempted or who are immunosuppressed¹.
  - Transfusion of irradiated granulocytes may be considered in patients with life-threatening neutropenic sepsis.
  - In heavily transfused patients, iron overload can cause significant problems, therefore iron chelation therapy should be considered if serum ferritin is >1,000μg/L.
- **Growth factors** – a short course of granulocyte colony-stimulating factor (G-CSF) may be considered in patients with overwhelming infection who have not responded to the appropriate intravenous antibacterial or antifungal treatment²,³. However, expert opinion suggests that the drug is usually ineffective in severe aplastic anaemia.
- **Antibiotics** – should be considered in a number of situations, including²,³:
  - Patients with a high risk of infection.
  - Patients with absolute neutrophil counts consistently lower than 0.5 x 10⁹/L.
  - Patients with febrile neutropenia.
  - Prophylaxis for *Pneumocystis jirovecii* pneumonia should also be given to all patients for at least six months after bone marrow transplantation.
- **Psychological support** is extremely important, and the chronic nature and slow response to treatment should be discussed early. They should be offered information about relevant support groups.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02148133, 200926; eltrombopag; phase II.</th>
<th>NCT01623167, 120150, 12-H-0150; eltrombopag with horse ATG and cyclosporine A (ciclosporin A, CSA); phase I/II.</th>
<th>EBMT-RACE, NCT02099747, 2014-000363-40; eltrombopag with h-ATG and CSA vs h-ATG and CSA alone; phase III.</th>
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<tbody>
<tr>
<td>Location</td>
<td>Japan.</td>
<td>USA.</td>
<td>EU (incl UK).</td>
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* Expert personal communication.
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<tr>
<td>Participants</td>
<td>n=21 (planned); aged 18-79 yrs; aplastic anaemia with platelet count &lt;30,000/μl; refractory to ATG-based immunosuppressive therapy (IST), relapsed after ATG-based IST, or ineligible for ATG-based IST.</td>
<td>n=150 (planned); aplastic anaemia; severe; aged ≥2 yrs; weight ≥12kg.</td>
<td>n=200 (planned); aplastic anaemia; severe or very severe; aged ≥15 yrs.</td>
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<tr>
<td>Schedule</td>
<td>Participants receive eltrombopag at 25 mg oral once daily under fasting conditions. The dose is adjusted every 2 wks according to the platelet count (increased by 25mg/day up to a maximum 100mg/day).</td>
<td>Participants receive h-ATG for 4 days in combination with CSA plus eltrombopag 150mg oral once daily for up to 6 mnths. Cohort 1 given eltrombopag from day 14 up to 6 mnths; cohort 2 from day 14 to 3 mnths; cohort 3 from day 1 to 3 mnths.</td>
<td>Randomised to h-ATG for 4 days in combination with CSA for 6 mnths; or h-ATG for 4 days in combination with CSA with eltrombopag 150mg oral once daily for 6 mnths.</td>
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<td>Follow-up</td>
<td>Active treatment period not reported, follow-up 2.5 yrs.</td>
<td>Active treatment for up to 6 mnths, follow up 5 yrs.</td>
<td>Active treatment 6 mnths, follow up 2 yrs.</td>
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<tr>
<td>Primary outcomes</td>
<td>Platelet count; haemoglobin level; neutrophil count.</td>
<td>Complete haematological response at 6 mnths.</td>
<td>Complete haematological response at 3 mnths.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Time to haematological response and duration of response; frequency and volume of transfusions (platelet and red blood cell); transfusion independence; adverse events; bleeding and severity of bleeding; pharmacokinetics. No quality of life measures included in trial outcomes.</td>
<td>Relapse; robust haematological blood count recovery at 3, 6, and 12 mnths; survival; clonal evolution to myelodysplasia and leukaemia; marrow stem cell content. No quality of life measures included in trial outcomes.</td>
<td>Time to best haematological response; haematological response at 6, 12, 18 and 24 mnths; any response; overall survival; event-free survival; relapse; clonal evolution; paroxysmal nocturnal haemoglobinuria (PNH); discontinuation of immunosuppressive therapy; CSA-independent haematological response at 24 mnths; need for transfusions; need for supportive care; serious AEs (SAEs); safety and tolerability. No quality of life measures included in trial outcomes.</td>
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<tr>
<td>Key results</td>
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<td>Overall response (OR) at 6 mnths was 80%, 87% and 92%, respectively for the three cohorts; Complete response (CR) at 6 mnths was 33%, 26%, and 54%, respectively. For all patients evaluable to date, OR at 3 and 6 mnths was 80% and 85%,</td>
<td>-</td>
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respectively, and CR at 3 and 6 mnths was 28% and 34%, respectively; these results are higher than historical control rates (p<0.001 for both 3 and 6 mnths).

| Adverse effects (AEs) | Eltrombopag was well tolerated when combined with CsA and hATG. At median follow up 15 mnths (range 1–42), cytogenetic abnormalities occurred in 7 patients and clonal evolution to myelodysplastic syndrome occurred at a similar frequency compared to historic experience with standard IST |

| Expected reporting date | Study completion date reported as October 2017. | Study completion date reported as January 2018. | Study completion date reported as January 2018. |

**Trial SOAR, NCT02998645, CETB115E2403; aged ≥6 yrs; eltrombopag and cyclosporine A (ciclosporin A); phase II.**

**Sponsor** Novartis Pharmaceuticals.

**Status** Ongoing.

**Source of information** Trial registry 14, manufacturer.

**Location** Brazil, France and Spain.

**Design** Non-randomised, uncontrolled.

**Participants** n=50 (planned); aplastic anaemia; severe; no prior immunosuppressive therapy.

**Schedule** Participants receive eltrombopag orally once daily at a dose based on age and ethnicity, in combination with cyclosporine A every 12 hrs at a dose based on body weight.

**Follow-up** Active treatment for 6 mnths with eltrombopag and 30 mnths with cyclosporine A; follow-up 60 mnths.

**Primary outcomes** Overall haematological response (complete and partial response).

**Secondary outcomes** Duration of haematological response; treatment with immunosuppressive therapy; clonal evolution to myelodysplasia, PNH or acute leukaemia; receipt of blood or platelet transfusions; duration of platelet and blood transfusion independence; overall survival; FACIT-Fatigue Patient Reported Outcome score; pharmacokinetics.

**Expected reporting date** Estimated primary completion date May 2023.

**ESTIMATED COST and IMPACT**

**COST**

Eltrombopag is already marketed in the UK as Revolade; a pack of 28 x 25mg tablets costs £770, and treatment with 25mg per day for 28 days would cost £7701.
## IMPACT - SPECULATIVE

### Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: potential for reduced dependence on transfusion.
- No impact identified

### Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services: oral treatment option.
- Re-organisation of existing services
- Need for new services: experts highlight the importance of training for haematologists to ensure full knowledge of the drug and the exclusion criteria, as well as required patient monitoring when prescribing.
- Other
- None identified

### Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain cost compared to existing alternative therapeutic approaches.
- None identified

### Other Issues
- Clinical uncertainty or other research question identified: there is currently no published data on use of eltrombopag as a single agent for first line treatment of severe aplastic anaemia. Response rate of 40-45% is reported in the key published data on use for refractory severe disease. More research is needed to determine the response rate in first line treatment.
- There are concerns about using eltrombopag monotherapy due to the increased risk of clonal transformation with abnormal cytogenetic clones, especially monosomy 7 with myelodysplastic syndrome, which carries very high risk of malignant transformation to acute myeloid leukaemia. The increased risk when used as a monotherapy compared to when used in combination with ATG and CSA is postulated by experts to be a result of more proliferative stress on remaining stem cells. The concern over increased risk of myelodysplastic syndrome and acute myeloid leukaemia is increased in older patients who may have increased risk for these diseases due to the risk of acquired somatic mutations increasing with age.

1 Expert personal communication.
REFERENCES


