Eltrombopag (Revolade) for severe aplastic anaemia – second line

SUMMARY

Eltrombopag is intended to be used for the treatment of cytopenias in patients with severe aplastic anaemia who have had an insufficient response to immunosuppressive therapy. If licensed, eltrombopag will offer a treatment option for this patient group. Eltrombopag is a non-peptidyl thrombopoietin (TPO) receptor agonist. TPO is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production and acts through the activation of the TPO receptor. Eltrombopag mimics the effect of TPO thereby stimulating platelet production. Eltrombopag is licensed in the EU for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adult splenectomised patients who are refractory to other treatments, second line treatment of thrombocytopenia in adult non-splenectomised patients where surgery is contraindicated, and for the treatment of thrombocytopenia in adult patients with chronic hepatitis C virus infection.

Aplastic anaemia is a rare condition and its precise incidence is difficult to determine due to the imprecision in establishing a diagnosis. However, estimates indicate that annual incidence is around two cases per million population. The incidence of aplastic anaemia varies throughout the world and is 2-3 times more common in Southeast Asia. In England, there were 12,987 admissions due to forms of aplastic anaemia in 2012-13, resulting in 14,390 finished consultant episodes and 19,658 bed days. In 2012, forms of aplastic anaemia accounted for 216 deaths in England and Wales.

Treatment for aplastic anaemia aims to correct the hypo-cellular bone marrow of the patient while providing supportive care where appropriate. The main two effective treatments for those with acquired severe aplastic anaemia are allogeneic bone marrow stem cell transplantation and immunosuppressive therapy. Supportive care can include platelet and red blood cell transfusions, growth factors and antibiotics. Eltrombopag is currently in uncontrolled phase II clinical trials to determine its effect on haematological response in patients with severe aplastic anaemia. These trials are expected to complete in December 2016.
TARGET GROUP

- Aplastic anaemia: severe; insufficient response to immunosuppressive therapy - second line.

TECHNOLOGY

DESCRIPTION

Eltrombopag (Revolade; Promacta; eltrombopag olamine; SB-497115) is a non-peptidyl thrombopoietin (TPO) receptor agonist. TPO is the principal cytokine involved in the regulation of megakaryopoiesis, the production of bone marrow precursor cells that give rise to blood platelets, and acts through activation of the TPO receptor. Eltrombopag mimics the effect of TPO thereby stimulating platelet production. Eltrombopag is intended to be used for the treatment of cytopenias in patients with severe aplastic anaemia who have had an insufficient response to immunosuppressive therapy. In the phase II clinical trial, eltrombopag was administered orally at 25mg daily under fasting conditions with dose increases of 25mg (up to a maximum of 100mg) every 2 weeks according to platelet count.

Eltrombopag is licensed in the EU for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) in adult splenectomised patients who are refractory to other treatments, and for the second line treatment of thrombocytopenia in adult non-splenectomised patients where surgery is contraindicated. It is also licensed for adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

Eltrombopag in combination with azacitidine is in phase III clinical trials for thrombocytopenia in intermediate or high-risk patients with myelodysplastic syndromes. Eltrombopag is also in phase II clinical trials for adult patients with acute myeloid leukaemia receiving induction chemotherapy with daunorubicin and cytarabine. Eltrombopag in combination with decitabine is in phase II clinical trials for patients with advanced myelodysplastic syndrome.

Recognised very common (≥10%) adverse effects (AEs) of eltrombopag when used for its current licensed indications include: anaemia, decreased appetite, insomnia, headache, cough, nausea/diarrhoea, pruritus, alopecia, myalgia, pyrexia, fatigue, influenza like illness, asthenia, chills and peripheral oedema.

INNOVATION and/or ADVANTAGES

If licensed, eltrombopag will offer a treatment option, other than transfusion therapy and supportive care, for those with severe aplastic anaemia who have had an insufficient response to immunosuppressive therapy or who lack a matched related stem cell donor.

DEVELOPER

GlaxoSmithKline.

AVAILABILITY, LAUNCH OR MARKETING

In phase II clinical trials. Eltrombopag is a designated orphan drug in the USA.
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. It is a rare and heterogeneous condition that is potentially life-threatening. The majority of acquired cases are categorised as idiopathic (with unknown primary aetiology); in only a minority of cases is a cause identified which is likely to have precipitated the condition. In such cases, recognised causes include drugs, such as chloramphenicol, sulphonamides, gold and penicillamine, amongst others, or infections, such as seronegative hepatitis (5-10% of severe acquired aplastic anaemia), Epstein-Barr Virus, HIV, parvovirus and mycobacteria. Toxic exposure to radiation or chemicals, such as benzene, is also known to precipitate the condition. For around 15-20% of patients, the condition is inherited.

The most common symptoms of aplastic anaemia include the effects of anaemia, such as pallor, headache, palpitations, dyspnoea, fatigue or ankle oedema. Thrombocytopenia including skin or mucosal haemorrhage, visual disturbance due to retinal haemorrhage and petechial rashes are also common symptoms. Acquired aplastic anaemia is classified as non-severe, severe, or very severe on the basis of the degree of peripheral-blood pancytopenia. Severe disease is defined as: bone marrow cellularity <25%, or 25-50% with <30% residual haematopoietic cells, with two of the following: neutrophils <0.5 x 10⁹/L, platelets <20 x 10⁹/L, and/or reticulocytes <20 x 10⁹/L. Very severe disease is defined as neutrophils <0.2 x 10⁹/L.

The precise incidence of aplastic anaemia is difficult to determine due to the imprecision in establishing a diagnosis. However, the annual incidence has been estimated at around two cases per million population based on data collected from Europe and Israel. Additionally, the incidence of aplastic anaemia is subject to wide variation throughout the world, for instance aplastic anaemia is 2-3 times more common in Southeast Asia than European countries. It is thought that environment rather than genetic factors play the most significant role in this geographical variation, as those who migrate between global regions appear to acquire the same incidence of aplastic anaemia as the local population. Acquired aplastic anaemia most commonly presents between the ages of 15 years and 25 years but there is a second smaller peak in incidence after age 60 years.

In England, there were 12,987 admissions due to forms of aplastic anaemia (ICD-10 D60-D61) in 2012-13, resulting in 14,390 finished consultant episodes and 19,658 bed days. The majority of these admissions, episodes and bed days were for ‘aplastic anaemia unspecified’ (ICD-10 D61.9, which accounted for 11,912 admissions, 10,715 finished
consultant episodes and 16,798 bed days\(^6\). In 2012, forms of aplastic anaemia (ICD-10 D60-D61) accounted for 216 deaths in England and Wales, the majority of which were classed as ‘other aplastic anaemias’ (n=106) or ‘aplastic anaemia, unspecified’ (n=105)\(^7\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142) (ID541). Expected date of issue August 2014.

**Other Guidance**

- British Committee for Standards in Haematology. Guidelines for the diagnosis and management of aplastic anaemia. 2009\(^2\).

**CURRENT TREATMENT OPTIONS**

Treatment for aplastic anaemia aims to correct the hypo-cellular bone marrow of the patient while providing supportive care where appropriate. The main two effective treatments for those with acquired severe aplastic anaemia are\(^2,3\):

- Allogeneic bone marrow stem cell transplantation – which 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 (<40 years)\(^2,3\).
- Immunosuppressive therapy – which aims to prevent the immune system from mistakenly attacking healthy cells as seen in aplastic anemia. The British Committee for Standards in Haematology (BCSH) recommends a combination of antithymocyte globulin (ATG) and ciclosporin for patients with severe or very severe aplastic anaemia aged >40 years, or for younger patients with severe or very severe disease where an HLA-identical sibling donor is not available\(^2,3\).

Other potential treatments include:

- Matched unrelated donor bone marrow transplantation – may be considered to treat severe aplastic anaemia when a fully matched donor is available, the patient is <50 years and when a patient has failed at least one course of ATG and ciclosporin\(^2\).
- Oxymetholone tablets – 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, liver toxicity, high serum cholesterol, impaired glucose tolerance and prostatism)\(^2,3\).
Supportive care.
A number of steps can be taken to support the care of aplastic anaemia patients 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 count.2
  - Platelet transfusions should be considered when the platelet count is <10 x 10^9/L.2,3
  - Irradiated blood components should be given in those whom marrow transplantation may be attempted or who are immunosuppressed.2,3
  - Transfusion of irradiated granulocytes should be considered in patients with life-threatening neutropenic sepsis.2,3
  - In heavily transfused patients, iron overload can cause significant problems, therefore iron chelation therapy should be considered if serum ferritin is >1,000 μg/L.2,3
- Growth factors - granulocyte colony-stimulating factor (G-CSF) should be considered in patients with overwhelming infection who have not responded to the appropriate intravenous antibacterial or antifungal treatment.2,3
- Antibiotics – should be considered in a number of situations, including:
  - Patients with a high risk of infection.2,3
  - Patients with absolute neutrophil counts consistently lower than 0.5 x 10^9/L.2,3
  - Patients with febrile neutropenia.2,3
  - Prophylaxis for Pneumocystis jirovecii pneumonia should also be given to all patients for at least six months after bone marrow transplantation.2,3

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02148133, 200926; eltrombopag; phase II.</th>
<th>NCT01703169, ELT115895; eltrombopag; phase II.</th>
<th>NCT01891994, 130133, 13-H-0133; eltrombopag; phase II.</th>
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<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
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<tr>
<td>Location</td>
<td>Japan.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, single arm.</td>
<td>Non-randomised, single arm.</td>
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<tr>
<td>Participants</td>
<td>n=20 (planned); aged 18-79 years; diagnosis of moderate (stage II) or more severe aplastic anaemia with platelet count &lt;30,000/µL; patients who have become refractory to ATG-based immunosuppressive therapy (IST) or who have relapsed after ATG-based IST or who are ineligible for ATG-based IST; adequate liver and renal function; Eastern Cooperative Oncology Group (ECOG)</td>
<td>n=20 (planned); aged ≥18 years; severe or very severe aplastic anaemia, or moderate aplastic anaemia with platelet counts below 20,000/µL, moderate bleeding during/after a surgical procedure or minimal mucocutaneous bleeding otherwise noted. Patients excluded if: Fanconi anaemia; infection not responding to appropriate therapy; PNH clone size in neutrophil</td>
<td>n=60 (planned); aged ≥2 years; diagnosis of refractory severe aplastic anaemia; received at least one treatment course of immunosuppression with a regimen containing ATG, alemtuzumab or cyclophosphamide; ≥1 of the following – platelet count ≤30,000/µL, platelet-transfusion-dependence (requiring ≥4 or more transfusions in previous 8 weeks), neutrophil count &lt;5000/µL, haemoglobin</td>
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<td><strong>performance status of 0 or 1; QT interval corrected for heart rate by Fridericia's formula (QTcF) &lt;450 milliseconds (msec) or QTcF&lt;480msec with branch block.</strong></td>
<td><strong>≥50%; HIV; abnormal renal or liver function; chemotherapy received ≤14 days previously; arterial or venous thrombosis within 1 year; ECOG performance status of ≥3; alemtuzumab treatment within 6 mths; significant cardio-vascular disease or arrhythmia; QTc&gt;450msec; other TPO-R medication in previous 4 weeks.</strong></td>
<td><strong>&lt;9.0g/dL or RBC transfusion–dependence (requiring ≥4 units of RBCs in previous 8 weeks); weight &gt;12kg.</strong></td>
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<td><strong>Patients excluded if:</strong> treatment with ATG in the past 12 mths; congenital aplastic anaemia; paroxysmal nocturnal haemoglobinuria (PNH) granulocyte clone size determined by flow cytometry ≥50%; chromosomal aberration; history of thromboembolism; current use of anticoagulants; history of malignancy; hepatitis B or C or HIV; cirrhosis; significant cardiac disorder or arrhythmia with a risk of thrombosis; prior treatment with eltrombopag, romiplostim or any other TPO receptor agonist.</td>
<td><strong>Eltrombopag 25mg orally once a day under fasting conditions with dose adjustment every 2 weeks according to platelet count (25mg increase up to 100mg).</strong></td>
<td><strong>Eltrombopag 150mg orally once a day escalated to a maximum dose of 300mg/day over 12 weeks determined by platelet count.</strong></td>
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<td><strong>Eltrombopag 150mg (75mg for patients from East Asian ethnic groups) orally once daily for 6 mths.</strong></td>
<td><strong>Schedule</strong></td>
<td><strong>Eltrombopag 150mg (75mg for patients from East Asian ethnic groups) orally once daily for 6 mths.</strong></td>
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<td><strong>Follow-up</strong></td>
<td><strong>Active treatment for 10 weeks, follow-up 2.5 yrs.</strong></td>
<td><strong>Active treatment and follow-up for 12 weeks.</strong></td>
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<td><strong>Primary outcome/s</strong></td>
<td><strong>Platelet count response defined as a stable count of ≥50,000/µL during any 4 week period within treatment period, and maximal platelet counts achieved in patients with moderate to very severe aplastic anaemia.</strong></td>
<td><strong>Change in platelet count and/or platelet transfusion requirements, haemoglobin levels, RBC transfusions, and neutrophil counts.</strong></td>
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<td><strong>Secondary outcome/s</strong></td>
<td><strong>Proportion of subjects who achieve platelet counts at least twice their baseline value; haemoglobin; hematocrit; total white blood cell count and absolute neutrophil count; AEs; pharmacokinetics.</strong></td>
<td><strong>Haematological response including relapse or clonal evolution; pre-treatment characteristics predicting response; impact of treatment and treatment response on quality of life.</strong></td>
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<td>RBC); proportion of subjects who become transfusion independent; adverse events (AEs); number and proportion of subjects with bleeding and severity of bleeding; pharmacokinetics.</td>
<td>Study completion date reported as December 2016.</td>
<td>Study completion date reported as November 2015.</td>
<td>Study completion date reported as March 2017.</td>
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<td>Expected reporting date</td>
<td>Study completion date</td>
<td>Study completion date</td>
<td>Study completion date</td>
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| Trial | NCT00922883, ELT112523, NIH study number: 09-H-0154, 090154; eltrombopag; phase II. |
| Sponsor | National Heart, Lung and Blood Institute (NHLBI). |
| Status | Study published in 2012 for 2009-2011 period\(^1\); study summary available from GSK for June 2009-June 2013 period\(^12,\)\(^a\). |
| Source of information | GSK Clinical Study Registry\(^1\); trial registry\(^13\). |
| Location | USA. |
| Design | Non-randomised, single arm. |
| Participants | n=43; aged ≥12 years; diagnosis of severe aplastic anaemia with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/ciclosporin; platelet count ≤30,000/µL. Patient excluded if: diagnosis of Fanconi anaemia; infection not adequately responding to therapy; PNH clone size in neutrophils of ≥50%; HIV positivity; creatinine >2.5; bilirubin >2.0; AST or ALT >5 times the upper limit of normal; hypersensitivity to eltrombopag or its components; history of malignancy other than localised tumours diagnosed >1 year previously and treated surgically with curative intent; congestive heart failure, arrhythmia, arterial or venous thrombosis within previous year, or myocardial infarction within 3 mths; ECOG performance status ≥3; treatment with horse or rabbit ATG or alemtuzumab within 6 mths (concurrent stable treatment with ciclosporin or G-CSF permitted). |
| Schedule | Eltrombopag 50mg (25mg for East Asian patients) administered orally once a day. Eltrombopag dose increased by 25mg every 2 weeks dependent upon platelet response up to a maximum dose of 150mg (75mg maximum dose in East Asian patients). |
| Follow-up | Active treatment for 12 weeks, follow-up 16 weeks. |
| Primary outcome/s | Haematologic response defined as meeting ≥1 of following: platelet count increases to 20,000/µL or stable platelet counts with transfusion independence for ≥8 weeks; haemoglobin increase by ≥1.5g/dL (for subjects with pre-treatment haemoglobin <9g/dL) or a reduction in RBC transfusions by at least 4 units for 8 consecutive weeks; absolute neutrophil count (ANC) increase of 100% (for pre-treatment levels <0.5Gi/L), or an ANC increase >0.5Gi/L. |
| Secondary outcome/s | Incidence of bleeding; changes in serum thrombopoietin level; health-related quality of life (Medical outcomes study 36-item short form general health questionnaire). |
| Key results | Treatment with eltrombopag produced a haematologic response in 40% (n=17) of patients. |
| Adverse effects (AEs) | 93% (n=40) of patients experienced an AE, the most frequently reported AEs were: nausea 33% (n=14), fatigue 28% (n=12), cough 23% (n=10), diarrhoea 21% (n=9), headache 21% (n=9), pain in extremity 19% (n=8), dyspnoea 14% (n=6), pyrexia 14% (n=6), dizziness 14% (n=6), oropharyngeal pain 14% (n=6), febrile neutropenia 14% (n=6), 33% (n=14) of patients reported serious AEs, the most common included: febrile neutropenia 14% (n=6), sepsis 5% (n=2), viral infection 5% (n=2). |

\(^a\) Information and data reported here is from this company source.
ESTIMATED COST and IMPACT

COST

The cost of eltrombopag for severe aplastic anaemia is not yet known. Eltrombopag is currently marketed in the UK for a number of indications at a cost of £770 for a 28-tab pack of 25mg tablets, and £1,540 for a 28-tab pack of 50mg tablets14.

IMPACT - SPECULATIVE

Impact on Patients and Carers
☐ Reduced mortality/increased length of survival  ☑ Reduced symptoms or disability
☐ Other:

Impact on Health and Social Care Services
☐ Increased use of existing services  ☑ Decreased use of existing services
☐ Re-organisation of existing services  ☑ Need for new services
☐ Other:

Impact on Costs and Other Resource Use
☑ Increased drug treatment costs  ☑ Reduced drug treatment costs
☐ Other increase in costs:
☐ Other:

Other Issues
☐ Clinical uncertainty or other research question identified:  ☑ None identified

REFERENCES

8 ClinicalTrials.gov. A study to assess the safety and efficacy of eltrombopag in japanese subjects with refractory, moderate or more severe aplastic anemia. clinicaltrials.gov/ct2/show/NCT02148133 Accessed 4 August 2014.