Kent and Medway Policy Recommendation and Guidance Committee Policy Recommendation,
PR 2016-07: Eltrombopag for severe aplastic anaemia in adults.

Recommendation

The EKPG approved the PRGC Recommendation on Eltrombopag for the treatment of severe aplastic anaemia in adults.

Approved by: East Kent Prescribing Group *(Representing Ashford CCG, Canterbury and Coastal CCG, South Kent Coast CCG and Thanet CCG)*
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Kent and Medway Policy Recommendation and Guidance Committee
Policy Recommendation

Policy:	**PR 2016-07: Eltrombopag for severe aplastic anaemia in adults**
Issue Date:	**March 2016**
Review Date:	**March 2019**

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) considered national guidance, the baseline position and evidence of safety, clinical- and cost-effectiveness. All decisions were made with reference to the Ethical Framework. Taking these into account, the PRGC recommends that:

- Eltrombopag[1] is routinely funded for the treatment of adults with acquired severe aplastic anaemia (SAA) according to its licensed indication (i.e. adults with acquired SAA who were either refractory to prior immunosuppressive therapy [IST] or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation [HSCT]), however:
  - Where indicated, a second course of anti-thymocyte globulin (ATG) following failure to respond to a first course (if the patient is ineligible for a matched unrelated donor HSCT) or following relapse after a first course, should be administered before eltrombopag is considered[2,3]
- If no haematological response has occurred (as defined in pivotal study; see SPC for details[4]) after 16 weeks of therapy, treatment should be discontinued
- Eltrombopag should be used with meticulous long-term monitoring for clonal evolution, or following a clinical research protocol[2]

See overleaf for background information and supporting rationale.

This policy recommendation will be reviewed in light of new evidence or guidance from NICE.

Clinical Commissioning Groups (CCGs) in Kent and Medway will always consider appropriate individual funding requests (IFRs) through their IFR process.

[1] Eltrombopag is listed as a High Cost Drug Exclusion (Payment by Results Exclusion).
[2] As specified in guidelines (Killick 2016) on aplastic anaemia by the British Committee for Standards in Haematology (BCSH), a sub-committee of the British Society for Haematology.
[3] According to the 'Indications for NHS England drugs list' (accessed 10 March 2016), the policy, and starting and stopping criteria for ATG – the recommended first-line IST for SAA – are 'BCSH guidelines'.
[4] Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/μl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by >1.5g/dL, or a reduction in ≥4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase >0.5 x 10^9/L.

Supporting Documents
Health Care Intervention Appraisal and Guidance (HCiAG) team (2016) *Eltrombopag for severe aplastic anaemia – Briefing note*

Equality Analysis Screening Tool – Eltrombopag for severe aplastic anaemia (2016)

Key points and rationale

What is aplastic anaemia (AA)?
AA is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis. The majority (70–80%) of cases are idiopathic. Acquired AA is classified as non-severe, severe, or very severe based on the degree of peripheral-blood pancytopenia.

What is the incidence of AA?
The incidence of AA is estimated to be 2.34 cases per million population per year in Europe; mostly (~84%) severe aplastic anaemia (SAA) or very severe aplastic anaemia (VSAA). This translates to an estimated 3–4 people in Kent and Medway diagnosed with SAA each year.

How is SAA managed?
According to guidelines (Killick 2016) on AA by the British Society for Haematology (BSH), first-line treatments for SAA are matched sibling donor haematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy (IST) with anti-thymocyte globulin and ciclosporin (ATG/CSA), depending on patient age, co-morbidities and availability of a suitable donor. A second course of ATG may be indicated following failure to respond to a first course (if the patient is ineligible for a matched unrelated donor HSCT) or following relapse after a first course. First-line treatments for SAA are commissioned by NHS England. No established standard of care exists for SAA patients with an insufficient response to IST who lack a matched related donor for HSCT, other than supportive care. Overall 5-year survival for patients with SAA unresponsive to IST is ~57%.

What is eltrombopag?
Eltrombopag is an oral thrombopoietin receptor (TPO-R) agonist. It induces the proliferation and differentiation of bone marrow stem cells to increase production of blood cells. In September 2015, eltrombopag was granted a license extension for the treatment of adults with acquired SAA who were either refractory to prior IST or heavily pretreated and unsuitable for HSCT. In the UK, eltrombopag is also licensed for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) and thrombocytopenia in adults with chronic hepatitis C virus infection under certain circumstances. In SAA, the dose of eltrombopag may be tapered and treatment discontinued in patients who meet specific response criteria; see SPC for more information.

What does national guidance say?
NICE has terminated development of Technology Appraisal guidance (TA382) on eltrombopag for SAA (Jan. 2016) because no evidence submission was received from Novartis.

According to BSH guidelines (2015), eltrombopag is recommended for elderly patients with SAA (according to the licensed indication). It should be used with meticulous long-term monitoring for clonal evolution, or following a clinical research protocol.

What does current local guidance say?
Currently eltrombopag is not routinely funded in Kent and Medway for acquired AA in adults; this guidance predates the extension of the license for eltrombopag to SAA.

What is the evidence base?
The pivotal study for the license extension was a non-randomised, single-arm, open-label, phase 2 trial of eltrombopag (titrated to 150mg daily) in people with SAA and an insufficient response to IST (N=43). The haematological response rate was 40% (17/43 participants) at 3 to 4 months, including multilineage responses; normalised haematopoiesis was maintained off treatment in robust responders. Considering the rarity of the condition, the poor prognosis and the recognised unmet medical need, results provide evidence of a clinically relevant effect in the treatment of a subset of adults with acquired SAA who were either refractory to prior IST or heavily pre-treated and unsuitable for HSCT. The safety profile of eltrombopag in the treatment of SAA is consistent with the known safety profile of eltrombopag in other licensed indications. However, assessment is hampered by the severity of the underlying condition, the lack of control arm and the small study population. Consequently, there remain some uncertainties on the potential risk of progression to MDS/ cytogenetic abnormalities associated with eltrombopag treatment. The impact on quality of life and survival has not been established. In addition, the cost-effectiveness of eltrombopag for AA has not been determined.

Why is eltrombopag recommended for adults with acquired SAA on the local NHS?
Eltrombopag is the only licensed option for the treatment of adults with acquired SAA with insufficient response to IST – a patient group with a poor prognosis for whom no established standard of care exists. Results from the pivotal study provide evidence of a clinically relevant effect in the treatment of this patient group.

What is the cost impact of this policy recommendation?
The cost impact of treating SAA patients eligible for eltrombopag (according to the licensed indication) is estimated to be an average of £23,608 per year across Kent and Medway CCGs (equates to 0.72 patients per year). This estimate is based on a number of assumptions regarding duration of treatment, and responder and relapse rates. Consequently, it should be treated with caution, especially as the small numbers of patients involved are very vulnerable to outliers. In years where a patient presents with SAA suitable for treatment with eltrombopag, the estimated cost to the responsible CCG would be £57,956 per year in a responder and £16,170 in a non-responder. There may be some offset costs associated with a decreased need for red blood cell/ platelet transfusions associated with eltrombopag treatment, however it has not been possible to confidently quantify these.

Change sheet

Reason for review:

- NHS England has recently clarified that eltrombopag for aplastic anaemia (AA) is the commissioning responsibility of CCGs
- In September 2015, eltrombopag was granted a license extension for the treatment of adults with acquired SAA with insufficient response to immunosuppressive therapy (IST) – a patient group with a poor prognosis for whom no established standard of care exists.
- Four individual funding requests (IFRs) for eltrombopag for AA have been received over the last 12 months

Does the policy recommendation represent a change from the baseline position?:
Yes. Currently eltrombopag is not routinely funded on the local NHS for acquired AA in adults; this guidance predates the extension of the license for eltrombopag to SAA.

Estimated cost impact of implementation of policy:
The cost impact of treating SAA patients eligible for eltrombopag (according to the licensed indication) is estimated to be an average of £23,608 per year across Kent and Medway CCGs (equates to 0.72 patients per year) (Table 1). In years where a patient presents with SAA suitable for treatment with eltrombopag, the cost to the responsible CCG would be £57,956 per year in a responder and £16,170 in a non-responder. There may be some offset costs associated with a decreased need for red blood cell/ platelet transfusions associated with eltrombopag treatment, however it has not been possible to confidently quantify these.

Table 1 – Estimated average annual cost impact to Kent and Medway CCGs of commissioning eltrombopag for SAA patients

CCG	Eltrombopag recommended for AA according to licensed indication
Ashford	£1,628
CC	£2,708
DGS	£3,370
Medway	£3,627
South Kent Coast	£2,724
Swale	£1,467
Thanet	£1,830
West Kent	£6,254
Total (Kent and Medway)	**£23,608**