AWMSG Secretariat Assessment Report – Limited submission

Romiplostim (Nplate®) 125 micrograms powder for solution for injection

Company: Amgen Limited

Licensed indication under consideration: Treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year to < 18 years who are refractory to other treatments (for example, corticosteroids, immunoglobulins).

Date of licence extension: 30 January 2018

Comparator(s)

- Eltrombopag (Revolade®)

Limited submission details

- A minor licence extension for use in patients aged one year up to < 18 years.

Clinical effectiveness

- The key evidence supporting the clinical effectiveness of romiplostim comes from two multicentre, randomised, double-blind, placebo-controlled studies (20080279 and 20060195) comparing romiplostim against placebo in children with chronic immune thrombocytopenic purpura (ITP). Supplementary evidence has also been provided from three uncontrolled, multicentre, long-term, open-label, extension phase III studies (20030213, 20090340, and 20101221). There are no studies directly comparing romiplostim with eltrombopag.
- The pivotal study (20080279) enrolled 62 patients aged ≥ 1 year to < 18 years with previously treated ITP, who had mean platelet counts of 30 x 10^9/l or less. Patients were given a once-weekly subcutaneous injection for 24 weeks with either placebo (n = 20) or romiplostim (n = 42). The primary endpoint was durable platelet response, defined as achieving a weekly platelet response (count of ≥ 50 x 10^9/l without rescue medication use in the preceding four weeks) in six or more of the final eight weeks. A statistically greater proportion of patients treated with romiplostim (52%) achieved a durable platelet response than patients treated with placebo (10%; p = 0.002).
- The Committee for Medicinal Products for Human Use (CHMP) stated that overall, the data provided from these studies showed a clinical benefit in terms of platelet count increase both temporarily and in the long term. In addition, the risk of bleeding events and use of rescue medication were both shown to be reduced in longer-term treatment.
- The CHMP concluded that the safety profile of romiplostim in children appeared similar to that observed in adults. No new safety signals were identified in eight years of post-marketing experience.

Budget impact

- Based on information from a clinical expert in Wales, the company has estimated that each year [commercial in confidence figure removed] paediatric patients with ITP would be eligible to be prescribed second-line therapy with a thrombopoietin mimetic, such as romiplostim or eltrombopag. Based on displacement of eltrombopag the company expects that uptake of romiplostim in paediatric patients in Wales would be 35% in Year 1 ([commercial in confidence figure removed] patients), rising to 55% in Year 5 ([commercial in confidence figure removed] patients).
- Romiplostim and eltrombopag are associated with confidential patient access schemes therefore the net budget impact is commercial in confidence.
- Romiplostim is administered subcutaneously once-weekly whereas eltrombopag is an oral tablet taken daily. The company used NHS reference costs to estimate that romiplostim treatment would have an administration cost of £5,687 per patient per year, which gives a net resource cost of [commercial in confidence figure removed] in Year 1, rising to [commercial in confidence figure removed] in Year 5.

Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- The company estimates the prevalence of adults with chronic ITP to be 52–1,248 in Wales. However, the vast majority of patients do not need any treatment, or will require first line of therapy only; hence the figure for adults eligible for treatment with romiplostim is estimated to be between 13 and 312. In addition, clinical experts have stated that there are approximately 15 paediatric patients eligible in Wales; giving a total of 28–327 overall.
- The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider romiplostim is an orphan medicine.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	ITP is a bleeding disorder in which the immune system destroys platelets, which are needed for blood clotting. Children with platelet counts < 50 x 10^9/l are susceptible to bleeding complications. Children with platelet counts < 10 x 10^9/l can have major bleeds regularly, and those with counts of 20–30 x 10^9/l have a high risk of severe bleeding. Significant bleeds increase risk of intracranial haemorrhage, gastrointestinal and genitourinary bleeds, as well as debilitating menorrhagia; these can be potentially fatal. ITP imposes social limitations on patients: they have to make changes to their lifestyle to accommodate doctor visits, hospitalisations and administration of intravenous therapies. Psychological effects on patients include fear of bleeding, fear of infection after a splenectomy or while taking immunosuppressants, and negative body image due to bruising and weight gain associated with corticosteroid treatment.

NMG/AWMSG considerations	AWTTC comments
Whether the medicine addresses an unmet need (for example, no other licensed medicines).	Children whose ITP is not fully controlled by corticosteroids may go through various other immunomodulating treatments, some of which are used off-label, such as ciclosporin A, rituximab and mycophenolate. Some of these treatments may also have associated safety problems that might restrict their long-term use and are not suitable for all children. Some children may be suitable to have a splenectomy, which can be a potential solution although some may relapse after surgery and need further ITP treatment. The risks associated with surgery, such as infections and thrombotic complications, may make this an unacceptable choice of treatment, particularly because chronic ITP can resolve spontaneously.
Whether the medicine can reverse or cure, rather than stabilise the condition.	The company reported that some adult patients may maintain platelet counts after stopping romiplostim treatment, without needing additional therapy. There is no robust evidence that romiplostim can reverse or cure ITP in children or adults.
Whether the medicine may bridge a gap to a "definitive" therapy (for example, gene therapy) and that this "definitive" therapy is currently in development.	There is no definitive therapy for ITP.
The innovative nature of the medicine.	Romiplostim is administered as a once-weekly subcutaneous injection and has no food or medicine interactions. An initial weight-based dose of romiplostim is given and subsequent doses can be adjusted based on platelet counts. Romiplostim treatment does not involve any dietary restrictions and may be a more convenient option for some children. Romiplostim also has no amino acid sequence homology to endogenous thrombopoietin, which might mitigate the risk of a person producing antibodies to romiplostim that may react with endogenous thrombopoietin. However, the company acknowledges in their SmPC that as with all therapeutic proteins, there is a potential for immunogenicity.
Added value to the patient which may not adequately be captured in the QALY (for example, impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	In the pivotal phase III study in children, romiplostim treatment showed no differences in the quality of life scores (Kid's ITP Tool) for children treated with romiplostim and those treated with placebo. However, mixed-effects analysis showed statistically significantly greater reduction in parental burden from baseline in the romiplostim group compared with the placebo group. A post-hoc analysis of data from two phase III studies in adults with ITP showed improvements in quality of life for romiplostim-treated patients in seven out of ten scales: symptoms; bother; activity; fear; psychological; social activity and female reproductive health (menstruation).
Added value to the patient's family (for example, impact on a carer or family life).	Fewer bleeding episodes in children could improve their parents and carer's quality of life by reducing anxiety about bleeding and the numbers of hospital visits. Reducing the social limitations on children with ITP may also have a beneficial effect on the lives of their family and carers.
AWMSG: All Wales Medicines Strategy Group; ITP: immune thrombocytopenic purpura; NMG: New Medicines Group; QALY: quality-adjusted life-year; SmPC: Summary of Product Characteristics	

Additional information

- The National Institute for Health and Care Excellence (NICE) recommended romiplostim (Nplate®) for treating ITP in adults in England and Wales in 2011 (TA221; updated October 2018).
- AWTTC is of the opinion that, if recommended, romiplostim (Nplate®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 13 September 2018.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Romiplostim (Nplate®) 125 micrograms powder for solution for injection. Reference number: 3103. January 2019.