romiplostim, 250 microgram vial of powder for solution for subcutaneous injection (Nplate®) No. (553/09) Amgen

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

romiplostim (Nplate®) is accepted for restricted use within NHS Scotland for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Romiplostim is also accepted for restricted use as second line treatment for adult non-splenectomised patients where surgery is contra-indicated. Romiplostim is restricted to use in patients with severe symptomatic ITP or patients with a high risk of bleeding.

Romiplostim was significantly better than placebo in maintaining platelets at (or above) a minimum target level in previously treated patients with ITP.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Romiplostim is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Romiplostim may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.

Dosing information

The initial dose is 1 microgram/kg based on actual body weight administered as a subcutaneous injection once weekly. The dose should be increased by increments of 1 microgram/kg until the patient achieves a platelet count ≥ 50 $x10^9$/L. Platelet counts should be assessed weekly until a stable platelet count has been achieved (≥ 50 $x10^9$/L for at least four weeks without dose adjustment) and should be assessed monthly thereafter. The maximum weekly dose is 10 microgram/kg.

Treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Product availability date

1 October 2009. This product is designated an orphan medicinal product.

Summary of evidence on comparative efficacy

Romiplostim is a novel thrombopoiesis stimulating protein (peptibody) that binds to and activates the human thrombopoietin receptor, the primary growth factor for the regulation for platelet production.

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder predominantly characterised by antibody-mediated platelet destruction and a possible decrease in platelet production, which results in a decrease in the number of circulating platelets and increases the risk of bleeding events.

Efficacy was determined from two parallel, multicentre, double-blind, placebo-controlled studies of identical design. Patients were ≥18 years with a diagnosis of ITP according to the American Society of Haematology guidelines and had completed at least one previous treatment for ITP. One study enrolled ITP patients who had undergone splenectomy a minimum of four weeks prior to study entry and the other enrolled non-splenectomised ITP patients. Patients were required to have no active malignancy or history of stem cell disorder, a mean platelet count less than 30 x 10^9/L (with none greater than 35 x 10^9/L) during screening and adequate renal and liver function and haemoglobin levels. Patients older than 60 years required a documented history of chronic ITP confirmed by bone marrow biopsy. During the study patients could receive concurrent standard of care ITP therapy with corticosteroids, azathioprine or danazol at a constant dose and schedule, which could be reduced once platelet counts were >100 x 10^9/L, but if increased was considered as rescue medication. All other ITP therapies including intravenous immunoglobulin (IVIg), anti-D immunoglobulin (anti-D), alkylating agents and rituximab required an interval of two to 14 weeks prior to the start of the study. Patients were randomised in 2:1 ratio to receive romiplostim 1 microgram/kg or placebo weekly for 24 weeks. Doses were adjusted to achieve the target platelet count of 50 - 200 x 10^9/L up to a maximum weekly dose of 15 microgram/kg. Permitted rescue medications, given at the discretion of the investigator, included corticosteroids (oral and intravenous), IVIg and anti-D to prevent or treat haemorrhage. After 24 weeks, study medication was discontinued and platelet counts were

monitored weekly. Patients completed the study at week 36 or when platelet counts were < 50 x 10^9/L. Patients who completed the study were eligible for entry in an open-label extension study of romiplostim. The primary endpoint was the incidence of durable platelet response, defined as achieving at least six weekly platelet responses (platelets ≥ 50 x 10^9/L) during the last eight weeks of treatment with no rescue medications administered at any time during the 24-week treatment period.

At study entry, the median platelet count in splenectomised patients was 14 x 10^9/L and in non-splenectomised patients was 19 x 10^9/L. In both studies a significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo. Similarly, patients receiving romiplostim had significantly better outcomes for all key secondary endpoints compared with placebo. More patients receiving romiplostim were able to discontinue concurrent ITP therapy or reduce the dose by >25% compared with placebo. In addition rescue medications were required by significantly more patients receiving placebo than patients receiving romiplostim. Health related quality of life (HRQoL) measurements also showed significant improvement with romiplostim compared to placebo in four of the ten ITP-patient assessment questionnaire scales in splenectomised patients and one scale in non-splenectomised patients.

Tabe 1. Efficacy results for primary and key secondary endpoints

	Splenectomised patients study		**Non-splenectomised patients study**	
	Romiplostim N=42	**Placebo N=21**	**Romiplostim N=41**	**Placebo N=21**
Primary endpoint				
Durable platelet response (95% CI)	16 (38%) (24% to 54%)	0 (0%) (0% to 16%)	25 (61%) (44% to 76%)	1 (4.8%) (0.1% to 24%)
Secondary endpoints				
Overall platelet response[1,2] (95% CI)	33 (79%) (63% to 90%)	0 (0%) (0% to 16%)	36 (88%) (74% to 96%)	3 (14%) (3% to 36%)
Mean [SD] number of weeks with platelet response[2] (weeks 2-25)	12.3 [7.9]	0.2 [0.5]	15.2 [7.5]	1.3 [3.5]
Patients requiring rescue medication (95% CI)	11 (26%) (14% to 42%)	12 (57%) (34% to 78%)	7 (17%) (7% to 32%)	13 (62%) (38% to 82%)
Durable platelet response with stable dose[3] (95% CI)	13 (31%) (18% to 47%)	0 (0%) (0% to 16%)	21 (51%) (35% to 67%)	0 (0%) (0% to 16%)

[1]Overall platelet response is defined as achieving durable or transient (platelets ≥ 50 x 10^9/L for 4 or more times during weeks 2-25) platelet responses. [2]Patients may not have a weekly response within 8 weeks after receiving any rescue medicinal product. [3]Stable dose defined as maintained within ± 1microgram/kg during the last 8 weeks of treatment.

In the open-label extension study in which patients were treated for up to 156 weeks (mean 69 weeks), a platelet response was observed at least once in 87% (124/142) of patients and occurred on average 67% of the time in responding patients.

Summary of evidence on comparative safety

The safety data from the two pivotal studies were pooled, as there was no significant difference in safety profile between splenectomised and non-splenectomised patients. The most frequently reported adverse events in the romiplostim arm compared with the placebo arm were headache (35% versus 32%), fatigue (33% versus 29%) and epistaxis (32% versus 24%). There were no marked differences in severe, life-threatening and fatal adverse events in each treatment group. The majority of adverse events were mild to moderate in severity and those which had a >10% incidence in the romiplostim arm compared with placebo included dizziness (17% versus 0%), myalgia (14% versus 2%) and abdominal pain (11% versus 0%). Significant bleeding events (those rated as severe, life threatening, or fatal), were reported in 12% (5/41) of patients in the placebo group and in 7.1% (6/84) of patients in the romiplostim group (invariably at platelet counts $<20 \times 10^9$/L). There were three withdrawals among patients receiving romiplostim including one splenectomised patient due to a bone marrow disorder and two non-splenectomised patients due to B-cell lymphoma and intracranial haemorrhage. One non-splenectomised patient who received placebo withdrew due to metastases to the liver. Three splenectomised patients in the placebo group died (pneumonia, pulmonary embolism and cerebral haemorrhage) and one splenectomised patient in the romiplostim group died (intracranial haemorrhage).

In the open label extension study serious treatment related adverse events occurred in 9.2% of patients (13/142). Bone marrow reticulin was present in samples from eight patients with no evidence of progression to collagen fibrosis or chronic idiopathic myelofibrosis. Bleeding events decreased over time with severe bleeding events reported in 8.5% (12/142) patients. Thrombotic/thromboembolic events were reported in 4.9% (7/142) patients; six of whom had pre-existing risk factors for thrombosis. Neutralising antibodies to romiplostim were reported in one patient at study discontinuation and were absent upon re-testing four months later.

An integrated safety report that included a combined analysis of safety for nine studies including the pivotal and the long-term extension studies reported the incidence and study duration–adjusted event rates (number of events per 100 subject-years for patients on placebo versus romiplostim) for all treatment–emergent adverse events. The maximum exposure was 128 weeks; a total of 19.8 subject-years on study for placebo among 46 patients and 186.5 subject-years on study for romiplostim among 204 patients. For serious adverse events, thrombocytopenia (0 versus 8.6) and platelet count decrease (40.4 versus 2.1) had the highest study duration-adjusted event rates for patients who had received placebo and romiplostim respectively. Clinically significant bleeding event rates were 30.3 versus 18.2 and thrombotic event rates were 10.1 versus 7.0 for patients receiving placebo and romiplostim respectively. Six patients receiving romiplostim and no patients receiving placebo reported a bone marrow abnormality consistent with increased bone marrow reticulin.

Summary of clinical effectiveness issues

There are no comparative studies of romiplostim versus any of the current second-line therapies for ITP. There are also few placebo controlled randomised studies of comparators to romiplostim. Clinical experts in Scotland consulted by SMC indicated that a wide variety of treatment are used, many of which are unlicensed.

Scottish experts indicated that the approach to treatment has become more conservative over time and that initiation of treatment for ITP is based on clinical symptoms and whether an invasive procedure is planned, in addition to the platelet count. Experts suggested that a platelet count of 20 - 30 X 10^9/L alone would not necessarily result in treatment being initiated. Therefore the patient population in the pivotal studies (who were required to have a platelet count ≤ 30 X 10^9/L alone) may not be representative of Scottish patients likely to be considered for treatment with romiplostim in clinical practice.

There are a number of limitations with respect to the pivotal studies. Firstly, although treatment with romiplostim permitted a reduction or discontinuation of other therapies and enabled significantly less use of rescue medication, it was not appropriate to blind researchers to platelet counts and rescue medication may have been given more promptly to those patients suspected to be receiving placebo. Secondly, data on bleeding events were presented as a safety outcome while the EMEA considered this should have been a secondary efficacy endpoint. It was noted, however, that data on reduced bleeding events in romiplostim-treated patients support the efficacy shown in terms of durable platelet response. Although no significant differences in the overall incidence of bleeding events were observed between romiplostim- and placebo-treated patients, clinically significant bleeding events were less frequent in those treated with romiplostim. The EMEA stated that an effect of romiplostim in terms of reduced rate of bleeding events cannot be concluded. Thirdly, there were limitations with respect to the HRQoL data (including small sample size and short study duration) and the authors noted that HRQoL increases may be less than expected in certain scales. In spite of these limitations the EMEA commented that the strength of evidence is uncommon in an orphan condition such as ITP and the effect of romiplostim should be placed in the context of a life-threatening disease where limited therapeutic alternatives are available.

Although long-term safety data are limited, data from the 3 year follow up study indicated that romiplostim was well tolerated. The EMEA notes that specific safety concerns (increased reticulin formation and bone marrow fibrosis, thrombocythemia, thromboembolic events, malignancies, immunogenicity and effects on renal function) need to be further assessed in a larger population and are being addressed through the risk management plan.

Following reconstitution, romiplostim is available as a 500 microgram/mL solution. Calculation of the dose (based on body weight) to be administered will necessitate the use of a dose calculator.

Clinical experts advised that that there is significant unmet need in this condition and that romiplostim would be a valuable addition to the range of available treatment options for ITP. They indicated that in practice it was likely only a very small proportion of patients with ITP would receive this treatment.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis based on a Markov model comparing romiplostim as an additional, early stage option in a treatment pathway to 'usual care' alone. 'Usual care' covered a range of treatments and was defined on the basis on a survey of UK haematologists. Data on the effectiveness of romiplostim and the use of 'rescue medications' (IVIg, anti-D and IV steroids) were taken from the pivotal clinical study, with the open-label follow-up study providing data on which to base the estimate of the duration of response. Data on these variables for other medicines were taken from a search of the clinical research literature. Utility values were taken from a study in UK members of the public, rather than using EQ5D data measured in the clinical study.

For patients who had undergone a splenectomy: over the patient's lifetime the additional cost with romiplostim would be £48,479 and the additional QALYs would be 1.87, giving a cost per QALY of £25,972. For patients who had not undergone a splenectomy, the added costs with romiplostim were £32,113 the added QALYs 1.49 and the cost per QALY was £21,526. Sensitivity analysis identified the use of rescue medication, the costs of prescribing romiplostim and the time horizon as important factors in influencing the result; a probabilistic sensitivity analysis suggested the chance the cost per QALY was over £50k was about 10%.

The main issues with the economic model were as follows:

- The savings from rescue medication avoided were an important element in the cost-effectiveness calculation but clinical experts consulted by the SMC described a trend to being conservative in treating patients where possible. There may be a sub-group of patients who do use rescue medications to this extent and the economic case may be strongest for this group. The manufacturer provided some supplementary analysis looking at cost-effectiveness in a subgroup of patients with bleeding manifestations and this improved the cost per QALY to £15,220 in non-splenectomised patients or £16,673 in splenectomised patients.
- The results were sensitive to the assumption made regarding vial-sharing of romiplostim. Without vial-sharing the costs per QALY were £21,855 and £44,302 in the non-splenectomised and splenectomised patients respectively.

The results suggest a relatively high cost-effectiveness ratio for romiplostim, which has some uncertainty around it. However, the ICER is more acceptable when focusing on a subgroup of patients for whom savings in terms of rescue medications are more probable. Given this, and the potential life-saving nature of this orphan drug, the economic case for use was considered to have been made.

Summary of patient and public involvement

Patient Interest Group Submission: The ITP Support Association

Additional information: guidelines and protocols

Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and pregnancy were developed by the British Committee for Standards in Haematology (BCSH) and published in 2003. The guideline states that for second line therapy in adult patients, additional courses of first line therapies (corticosteroids, IVIg at altered doses or splenectomy) should be considered. In chronic refractory patients, treatment should be tailored to suit the individual and includes high dose steroids, high dose IVIg, vinca alkaloids, danazol, immunosuppressive agents including azathioprine, cyclophosphamide and ciclosporin, combination chemotherapy, dapsone and rituximab.

Additional information: comparators

For splenectomised patients, romiplostim is indicated when patients are refractory to first-line therapies (corticosteroids and IVIg). Azathioprine and vincristine are licensed second-line treatments for chronic refractory ITP.

For non-splenectomised patients (i.e. if splenectomy is contraindicated) romiplostim may be considered as a second-line treatment. Other second-line treatments which are licensed for

ITP include corticosteroids and IVIg (repeating first-line therapy generally at higher doses), and anti-D (suitable for Rh(D) positive patients who are not splenectomised and not recommended for refractory patients following splenectomy).

In addition, agents including rituximab, danazol, ciclosporin, dapsone, cyclophosphamide and mycophenolate mofetil are used outside their licensed indications. A selection of current treatments and typical doses advised by the Scottish experts consulted by SMC are included in the table below.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)	Cost per year (£)
romiplostim	**3 microgram/kg* weekly subcutaneously**		**21,076**
IVIg	2g/kg intravenously daily over 2 days	5,600	
rituximab	375mg/m^2 intravenously weekly for 4 weeks	4,890	
anti-D**	250 IU/kg (50 microgram/kg) intravenously as a single injection	3,762	
ciclosporin	200mg daily*** orally		1,723
danazol	800mg daily orally for at least 6 months (6 months calculated)	410	
dapsone	100mg daily orally		431
vincristine	2mg weekly intravenously for 4 weeks	112	
azathioprine	150mg daily orally		87
methylprednisolone	500mg daily intravenously for 3 days	29	
dexamethasone	40mg daily orally for 4 days	5	

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 05 March 2009. A selection of current treatments and typical doses advised by Scottish experts consulted by SMC are included. *Romiplostim dose of 3 microgram/kg was the median dose used in splenectomised patients. **Only one anti-D product (WinRho®) is licensed for ITP. ***Ciclosporin 200mg daily was an average dose from a range used by SMC experts. Costs per year or per course have been included, as applicable. Doses are based on a 70kg adult and a surface area of 1.8m^2.

Additional information: budget impact

The manufacturer estimated the potential treatment population to be around 200 patients with roughly half having previously had a splenectomy. The manufacturer predicted a market share of 10-20% in year 1, rising to 60-80% in year 5. The gross drug cost of treating 33 patients in year 1 with romiplostim was estimated at £1m, rising to £4.8m in year 5 with 157 patients treated. However the net medicines budget impact was estimated as £201k in year 1 and £870k in year 5 given savings in terms of medicines currently prescribed (including IVIG and anti-D). It should be noted that the manufacturer's estimate of patient numbers and budget impact is likely to overestimate the likely patient population in Scotland given the focus of the SMC recommendation on a subgroup of patients with a high risk of bleeding.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 21 April 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Kuter DJ, Bussel JB, Lyons RM, at al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008; 371(9610):395-403.

British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 2003;120(4):574-596.

The European Medicines Agency (EMEA) European Public Assessment Report. Romiplostim (Nplate®). 16/2/2009, EMEA H-C-942-00-00. www.emea.europa.eu