RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT (2) ON ROMIPLOSTIM
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1. Executive Summary

We welcome the preliminary recommendation from the Appraisal Committee (AC) that romiplostim is both clinically and cost effective for the treatment of chronic idiopathic (immune) thrombocytopenia purpura (ITP) patients whose condition is refractory to standard active treatments and rescue therapies or who have severe disease and a high risk of bleeding that requires frequent courses of rescue therapies. We have carefully reviewed and assessed the Appraisal Committee's consideration of the evidence on romiplostim. We welcome the opportunity to respond to the appraisal consultation document (ACD), and in our response, we have addressed points of clarification and identified factual inaccuracies.

We would first like to address the four questions posed by the Appraisal Committee.

i) Has all of the relevant evidence been taken into account?

We believe that all of the relevant evidence has been taken into account. The Committee noted that romiplostim significantly improved platelet count and reduced the frequency of bleeding – particularly the occurrence of moderate to severe bleeding episodes. The Committee also considered that the available data demonstrated that romiplostim was clinically effective in people with severe ITP at high risk of bleeding. These considerations are in line with the existing evidence for romiplostim and are also in line with the considerations in the EMA assessment report[1]. For example, the EMA considered the strength of evidence for romiplostim uncommon in an orphan condition and commented that the effect of romiplostim should be placed in the context of a life-threatening disease where limited therapeutic alternatives are possible.

ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries of clinical and cost effectiveness of romiplostim in the ACD issued on 29 November 2010 are reasonable interpretations of the evidence. The Committee concluded that the ICERs would be under £20,000 per QALY gained for the treatment of splenectomised patients, and around £30,000 per QALY gained for treatment of non-splenectomised patients. These ICERs are an accurate and clinically appropriate reflection of the cost effectiveness of romiplostim relative to active treatments in the UK.

iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Yes, we believe that the provisional recommendations are sound and a suitable basis for guidance to the NHS.

iv) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

None.

v) Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

None.

We welcome the preliminary recommendations from the Appraisal Committee and believe that all the available evidence for romiplostim in evaluating the clinical and cost-effectiveness and the patient access scheme have been duly taken into account to produce recommendations that form a sound and suitable basis for guidance to the NHS.

2. The technology

In this section, we would like to clarify a statement contained in paragraph 2.2 as stated below.

ACD Section 2.2

"Romiplostim should also be discontinued if a peripheral blood smear indicates increased bone marrow reticulin."

We would like to point out that this statement is not fully aligned with the SPC. An abnormal blood smear may indicate presence of bone marrow reticulin (and a bone marrow biopsy with appropriate staining for reticulin should be considered). Romiplostim should be discontinued if an abnormal peripheral blood smear as well as a loss of efficacy is observed. We have provided the statement contained in the SPC for clarification (section 4.4, page 4)[2]:

"*If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of romiplostim and alternative ITP treatment options should be re-assessed*."

3. Clinical effectiveness

We would like to clarify a few points in this section as outlined below.

ACD Section 3.1

"Outcomes included platelet count, response rate, durable response, need for rescue therapies, use of concurrent treatments, reduction in symptoms, adverse events, mortality and health-related quality of life."

The outcomes stated here reflect those included in the phase III clinical trials for romiplostim. We would like to seek more clarity on the outcome 'reduction in symptoms', specifically if this refers to a reduction in bleeding symptoms. The data on bleeding events was collected prospectively as part of safety data in the phase III trials. The grading of the severity of bleeds (i.e. mild, moderate, severe, life-threatening and fatal) was prospectively graded for severity by the clinical investigators. The statistical analysis on the reduction in bleeding symptoms was conducted as a post-hoc data analysis of prospectively reported and graded safety data in the phase III trials[3].

ACD Section 3.1

"In both RCTs, patients with ITP (defined as the mean of three platelet counts being below or equal to 30 × 10^9 per litre, with none of the three counts being above 35 × 10^9 per litre) whose condition was refractory to at least one previous treatment were randomised to romiplostim plus standard care or to standard care alone (placebo) for 24 weeks."

We would like to add to the statement above that while the requirement for entering the trials was that the mean of three platelet counts be below or equal to 30×10^9 per litre, the actual mean platelet count at baseline in the trials was even lower at 18×10^9 in the non-splenectomised group and 15×10^9 in the splenectomised group[4]. This demonstrates that the patients enrolled into the phase III trials were a particularly severe group of ITP patients.

ACD Section 3.3

"Six non-RCTs investigating safety of romiplostim and one open-label extension study of the phase III RCTs were reported in the manufacturer's submission. In the latter, patients treated with romiplostim or placebo who had completed the phase III studies, and whose platelet counts subsequently fell to below 50 x 10^9 per litre after discontinuation of romiplostim or placebo, were eligible to enrol in the study and to receive open-label romiplostim. Data from patients going into this extension study were used to calculate time to failure for romiplostim, as this could not be calculated from the phase III studies alone because the interventions ended after 24 weeks."

As stated above, we used data from the extension study to calculate time to failure for romiplostim. This could not be calculated from the phase III studies alone because the studies ended after 24 weeks. We would like to clarify that the open-label extension study allowed enrolment of patients who completed the phase III trials and whose platelet counts subsequently fell to ≤ 50×10^9 per litre, as well as patients completing other studies of romiplostim (phase I, II and IIIb studies) again once their platelet counts were less than or equal to 50×10^9. We would like to propose that the description in Section 3.3 be changed to reflect this as follows: "*In the latter, patients treated with romiplostim or placebo who had completed the phase III and other clinical studies of romiplostim, and whose platelet counts subsequently fell to ≤ 50×10^9 per litre after discontinuation of romiplostim or placebo, were eligible to enrol in the study and to receive open-label romiplostim".* We apologise for the lack of clarity on this point in our original evidence submission. The majority of the data used to estimate time to failure in the model came from the phase III studies as they made up 70% of patients in this data set. We would like to point out that the resulting impact on the ICERs (of including only phase III patients enrolled in the open-label extension study to estimate time to failure for romiplostim) is negligible and within an acceptable margin of error at £25,041 for non-splenectomised patients (versus £24,795 in the base case) and £5,309 for splenectomised patients (versus £4,615 in the base case).

ACD Section 3.4

"Other outcomes were: incidence of an overall platelet response (....); time to platelet response (Kaplan–Meier estimated time to first platelet response); duration of platelet response; use of rescue therapies; mortality; adverse events of treatment; and health-related quality of life."

We would like to clarify that the definition of one of the outcomes included in this paragraph, namely 'duration of platelet response' should be defined as 'number of weeks with platelet response' instead, as this was how it was measured and summarised in the phase III trials[5].

4. Cost effectiveness

We would like to clarify one point in this section as outlined below.

ACD Section 3.33

"The ERG conducted one-way sensitivity analyses by varying individual parameters in the revised base-case model to check the impact on the ICERs. These changes included increasing the use of comparator treatments by 25%; increasing the response time for comparators by 50%; increasing response rates for comparators by 25%; reducing the use of rescue therapies to 80% of the base case in both the comparator and romiplostim arms; using alternative utility values; and assuming a 'worst case scenario' where all patients who withdrew from treatment with romiplostim before the end of the follow-up period no longer responded to romiplostim."

"The ERG noted that when it was assumed that patients who withdrew from treatment before the end of the follow-up period no longer responded to romiplostim the ICER rose from £24,795 to £31,601 per QALY gained for non-splenectomised patients and from £4,615 to £18,647 per QALY gained for splenectomised patients."

The description of the 'worst case scenario' here seems incorrect as it refers to all patients who withdrew from treatment with romiplostim when it should be described as all patients who were censored from treatment with romiplostim in the open-label extension study. In addition, the description above does not seem to be in line with the description contained in the ERG report (commenting on the patient access scheme submission) in which the ERG assumed a 'worst case scenario' where all censored patients no longer responded to romiplostim, in effect assuming that all censored patients would be treated as withdrawals. Therefore, we propose that the description in Section 3.3 reflect that in the ERG report and read as:

"…. assuming a 'worst case scenario' where all patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals"

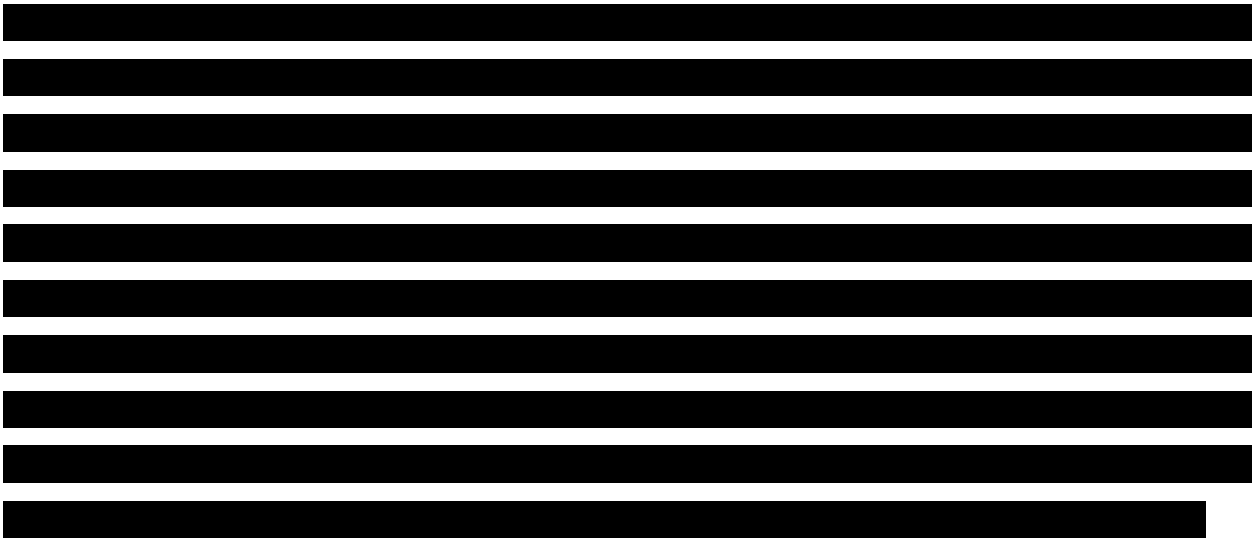
"The ERG noted that when it was assumed that patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals"

We would like to clarify that patients who withdrew from the open-label extension study before the end of the follow-up period were indeed treated as withdrawals (i.e. assumed to have no longer responded to romiplostim and were withdrawn) in the evaluation of time to failure for romiplostim. We would also like to provide further clarity on censored patients. Censored patients

were those who had a last observed visit that was not recorded as a withdrawal in the open-label extension study. However, at the time of the cut-off date for this analysis, there was no further information on whether these patients continued up to the final time point for this analysis or withdrew from the study. Hence, censored patients were treated as 'lost to follow-up' in the evaluation of time to failure for romiplostim.

We agree that there could be uncertainty around patients who were censored in the open-label extension study as they may not have had the same outcomes as patients for whom data were available (i.e. those who continued up to the final time point for this analysis or withdrew from the study) and consequently this could affect the calculation of time to failure for romiplostim. We have performed additional analysis to understand the outcomes of patients who were censored during any time period in the open-label extension study compared to the outcomes of those for whom data were available (see Table 6.4.2 in original submission for data used in this analysis). Censored patients had similar outcomes, measured by mean platelet count, as those for whom data were available. This is illustrated in Fig. 1 below where the mean platelet count of all censored patients, before they were censored and excluded from the sample in subsequent periods, is compared to the mean platelet count of all non-censored patients (i.e. those for whom data were available). It is evident from Fig. 1 that the mean platelet counts for censored patients are comparable to and not systematically different from those for non-censored patients. It is also noteworthy that in both groups, the mean platelet count is consistently above 50×10^{9} (as shown by the mean counts that consistently lie above the dotted line drawn at 50×10^{9} mark) in Fig. 1.

Figure 1: [redacted]



It is reasonable to conclude that censoring, in this instance, can be assumed to be independent of the risk of non-response and that the worst-case scenario explored by the ERG, where all censored patients are treated as non-responders and withdrawn, is unlikely to be plausible.

5. Consideration of the evidence

We are of the view that all relevant evidence has been taken into account in the consideration of evidence and the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We would like to clarify two points in this section as outlined below.

ACD Section 4.2

"The Committee considered the nature of the condition and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with chronic ITP. The Committee heard that the signs and symptoms associated with low platelet counts vary, and that bleeding and bruising can have considerable impact on the daily activities of people with chronic ITP, may attract a social stigma associated with the appearance of bruises, and can limit lifestyle choices. The Committee heard that many people with ITP experience fatigue, but that there is no clear relationship between fatigue and platelet count or haemoglobin concentration. The Committee understood that anxiety about the risk of bleeding can affect a person's quality of life and the ability to work, travel and/or undertake leisure activities. The Committee understood from patient experts that a bleed could result in a person seeking medical care to receive rescue therapies, and if the bleeding was severe the person could require hospitalisation."

We note and welcome the addition to this paragraph, from the ACD issued in October 2009, that severe bleeding could require hospitalisation in this section describing the nature of ITP condition. We would like to highlight the debilitating nature of chronic ITP in this group of patients with severe symptoms and high risk of bleeding. We heard from the patient expert at the last Appraisal Committee meeting about the devastating nature of this condition and the detrimental impact it has on a patient's quality of life in terms of frequent and potentially life-threatening emergency visits to the hospital as well as the potentially life limiting adverse side effects of existing treatments. Indeed, romiplostim was designated as an orphan medicine by the EMA based on the combination of disease severity and rarity. The EMA report considered that "*the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible*"[1]. Published literature provides further evidence that ITP patients who are refractory to currently available treatments and have a persistently low platelet count are the ones who appear to be at the highest risk of severe bleeding and mortality. One study found a 60% increased mortality (with evidence of bleeding or infection as the cause of death) in a substantial number of ITP patients, illustrating that ITP is a serious and potentially life-threatening illness[6].

ACD Section 4.15

"The Committee noted the ERG's concern that if romiplostim were no longer effective in patients lost to follow-up during the trial period, the ICERs increased substantively. However, the Committee heard from the manufacturer that a response to romiplostim had still been observed in 94% of the patients who were subsequently lost to follow-up."

In the open-label extension study that was used to calculate time to failure for romiplostim, patients were categorised as censored if they had a last observed visit that was not recorded as a withdrawal, or as withdrawn, if they withdrew from the study. At the last Appraisal Committee meeting, we clarified that of the 31 patients who withdrew during the open-label extension study (see Table 6.4.2 in original submission), only 2 patients, i.e. 6%, withdrew for reasons of lack of response to romiplostim (implying that 94% of patients withdrew for reasons other than lack of response to romiplostim). This statistic does not relate to the patients who were censored. We apologise for any lack of clarity on this point during the Appraisal Committee meeting.

We have since performed additional analysis to understand how the censored patients behaved immediately before they were censored during any time period in the open-label extension study. We analysed their last observed platelet count before they were censored (74% of patients had their last platelet count within one week of being censored) to evaluate the potential number of patients who were responders at time of censoring; defined as achieving a platelet count of $\geq 50\times10^{9}$. The vast majority of censored patients, 81%, continued to respond immediately before they were censored. The ERG evaluation report notes that the cut-off of 50×10^{9} is likely to be higher than would typically be used in practice in the UK. Using a lower cut-off of 30×10^{9}, an even higher proportion of censored patients, 89%, continued to respond immediately before they were censored.

This provides assurance that the vast majority of patients who were censored during the extension study continued to achieve a response to romiplostim immediately before they were censored and it is therefore unlikely that romiplostim would no longer be effective in these patients.

6. Other issues

We would also like to highlight two typographical errors in the ACD, 4.5 and 4.16, where ITP has been incorrectly written as IPT.

References

[1] The European Medicines Agency (EMEA) European Public Assessment Report. Romiplostim (Nplate®). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000942/WC500039475.pdf

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[3] Gernsheimer TB, George JN, Aledort LM, Tarantino MD et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). J Thromb Haemost 2010; 8:1372–82

[4] Amgen Clinical Summary of Efficacy, Data on file, Amgen. 2007

[5] Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008; 371(9610):395-403

[6] Schoonen MW, Kucera G, Coalson J, Li L, Rutstein M et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British Journal of Haematology, 2009:145, 235–244