## Thrombocytopenic purpura - eltrombopag (rev TA205)

GlaxoSmithKline (GSK) welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for eltrombopag as a treatment for thrombocytopenic purpura (rev TA205).

We have structured our comments in line with the specific questions posed by NICE. A number of factual inaccuracies are noted at the end of this document.

1. **Has all of the relevant evidence been taken into account?**

   GlaxoSmithKline (GSK) considers that all the relevant evidence for eltrombopag has been taken into account and is reflected in the ACD.

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

   GSK agrees with NICE's conclusion that eltrombopag is clinically effective and that eltrombopag can be considered cost-effective compared with romiplostim. However, GSK disagrees with the Committee's interpretation of the indirect treatment comparison between eltrombopag and romiplostim in paragraph 4.11 (ACD, p. 33) where it states that "The Committee agreed that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag rather than equally effective....". The Committee does not appear to have exercised the ERG's advised caution when interpreting the results of the analysis in this way and appears to contradict their conclusion that "the statistical evidence was not robust enough to confirm clinically important differences in eltrombopag compared with romiplostim" (ACD, p. 35). We reiterate GSK's core belief that the indirect treatment comparison does not provide evidence of clinical superiority of one treatment relative to the other, particularly in this case given the following additional factors:

   - Important differences in the design of the romiplostim and eltrombopag studies may have biased the analysis against eltrombopag:
     - Overall response was defined as the sum of 'durable response' and 'transient response'. Durable response was similarly defined in the romiplostim trials and the eltrombopag post hoc analysis: a response in at least six of the last eight visits of the treatment period. However, the definition of 'transient response' was different: a transient response in the romiplostim analysis required a response at *any four, weekly visits* during the study, whereas the eltrombopag analysis required *four consecutive weekly visits*. In a disease where platelet counts fluctuate, it is reasonable to expect that four consecutive responses are more difficult to achieve and this is likely to have biased the ITC against eltrombopag.

     - The romiplostim study did not allow tapering or interruptions of concomitant immune thrombocytopenic purpura (ITP) medications during the last 12 weeks of the study, whilst in RAISE (the eltrombopag pivotal trial) physicians were encouraged to reduce concomitant ITP medications once a stable dose of eltrombopag was achieved. This was more likely to occur towards the end of the

trial, when durable response was assessed in the post hoc analysis. Tapering ITP medications may well result in reductions in platelet count and this is likely to have negatively impacted the estimates of response for eltrombopag.

- Platelet counts >400x$10^9$/L, which represent an excessive response to treatment, are not considered to be responses in the RAISE post hoc analysis of durable and overall response, but were considered to represent responses in the original Kuter 2008 analysis. This would likely bias against eltrombopag in the indirect comparison.

- The number of durable and overall responders in the placebo arm of the romiplostim study was very low. As such, the results of any indirect comparison incorporating these data would be sensitive to small changes in the event rate. For example for durable response, the indirect comparison point estimates favour eltrombopag, rather than romiplostim, when the number of events in the placebo arm of Kuter 2008 is increased by ≥1 (splenectomised group) and ≥2 (non-splenectomised or pooled groups).

There are no head to head data comparing eltrombopag and romiplostim because both interventions were developed in parallel. Additionally, the orphan nature of cITP means that it is a challenge to recruit large numbers of patients into clinical trials, so sample sizes are small. Consequently, any attempt to make a comparison via indirect methods will inevitably be associated with a degree of uncertainty. Given the points detailed above, GSK consider it entirely appropriate to have assumed no difference in efficacy between eltrombopag and romiplostim in the economic modelling. This position is supported by clinicians (as acknowledged by the Committee), is consistent with the identical licensed indications for eltrombopag and romiplostim, and with both the International Consensus Report and ASH Guidelines, which recommend the products for the same patients and at the same points in the cITP treatment pathway. In the resulting economic model scenarios, eltrombopag dominated romiplostim (i.e. was at least as effective and less costly).

Page 12 of the ACD states “The manufacturer did conclude that eltrombopag and romiplostim have ‘equal efficacy’…” GSK would like to highlight the distinction between concluding that two drugs are the same and making an assumption for the purposes of an economic evaluation that two drugs are the same on the basis that there is no evidence of a difference between them. The basis of GSK’s approach in the base case of the model was the belief that there is no evidence of a difference between the two drugs in the TPO-RA class. GSK believe that the above statement is an inaccurate interpretation of our approach and would like to request that this wording is amended accordingly.

With regard to the Committee’s assertion that romiplostim is likely to be more effective than eltrombopag, GSK would argue strongly that it is not credible to suggest that eltrombopag and romiplostim differ meaningfully in terms of clinical efficacy on the basis of the results obtained from the indirect analyses. Indeed, if such analyses were used by a manufacturer to support a claim of superiority for any given product, a conclusion like this would be unlikely to be considered sufficiently robust. GSK propose that the wording within the ACD should reflect that there was insufficient evidence to support any clinically important difference between eltrombopag and romiplostim.

**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

GSK welcomes the provisional recommendation for eltrombopag and considers this a sound and suitable basis for guidance to the NHS. The guidance will provide a well-tolerated and effective oral alternative to romiplostim for patients with cITP.

**Points of factual inaccuracy/clarification**

There are a number of points in the ACD where some clarification might improve the accuracy and/or completeness of the document. These are detailed in the table below.

| Page | Current text | Proposed text or clarification |
|---|---|---|
| 14 | "In a cohort of patients starting a treatment, the model permits the platelet count to reach a level of $50\times10^9$ per litre or more (equal to a response) in the first, second, third or fourth cycle, **when each cycle represents a specific treatment**. When the platelet count reaches a level of $50\times10^9$ per litre, patients have a treatment-specific probability of losing the response in each cycle, and of receiving rescue therapy when bleeding occurs or a patient is at high risk of bleeding. If the platelet count does not reach a level of $50\times10^9$ per litre, patients stop treatment, but may receive rescue therapy (intravenous immunoglobulin, anti-D and corticosteroids), which would result in a temporary platelet response lasting for 1 cycle. During each cycle, a proportion of patients whose platelet count did not respond exit the 'nonresponder' state and move on to other treatments further down the treatment sequence" | Proposed text:<br>In a cohort of patients starting a treatment, the model permits the platelet count to reach a level of 50×10P9 per litre or more (equal to a response) in the first, second, third or fourth cycle, **dependent on the time to response associated with each treatment.** When the platelet count reaches a level of $50\times10^9$ per litre, patients have a treatment-specific probability of losing the response in each cycle, and of receiving rescue therapy when bleeding occurs or a patient is at high risk of bleeding. If the platelet count does not reach a level of $50\times10^9$ per litre **or patients lose their response,** patients stop treatment, but may receive rescue therapy (intravenous immunoglobulin, anti-D and corticosteroids), which **may** result in a temporary platelet response lasting for 1 cycle. During each cycle, a proportion of patients whose platelet count did not respond **to rescue or who experienced a bleed** exit the 'nonresponder' state and move on to other treatments further down the treatment sequence. |
| 17 | "The analysis showed that, among patients who achieved a response to treatment, those who had a splenectomy spend less time on eltrombopag **or romiplostim** than those who did not have a splenectomy" | Proposed text:<br>The analysis showed that, among patients who achieved a response to treatment, those who had a splenectomy spend less time on eltrombopag than those who did not have a splenectomy. |
| 24 | "Because the manufacturer had presented the indirect comparison stratified by splenectomy status, the analyses do not preserve randomisation in RAISE, and the ERG considered them to be observational analyses" | Clarification:<br>The RAISE trial was stratified by splenectomy status. Presenting results by splenectomy status does not break randomisation. |
| 25 | "The ERG noted that, in the Kuter et al. (2008) trials, the average romiplostim dose in patients whose condition had responded was 40–60% lower than that across the trial as a whole" | Proposed text:<br>The ERG noted that, in the Kuter et al. (2008) trials, the average **(median)** romiplostim dose in patients whose condition had responded was 40–60% lower than that across the trial as a whole.<br>Rationale:<br>The mean dose in these patients is likely to be significantly higher. |
| 32 | "The clinical specialists indicated that the manufacturer's indirect comparison may have underestimated the clinical effectiveness of romiplostim given that romiplostim preceded eltrombopag, and so trials for romiplostim enrolled patients whose condition was relatively more severe" | Clarification:<br>Although the romiplostim trials were conducted before RAISE, this does not mean that they recruited more severe patients. RAISE was conducted at sites across 23 different countries. The romiplostim studies were conducted in the United States, the Netherlands, France and the UK. 73% of the subjects in RAISE were not from countries where they could have been enrolled in the romiplostim trials. |