Thrombocytopenic purpura - eltrombopag (rev TA205)

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

GSK has reviewed the ACD and welcomes the positive recommendation for eltrombopag as an alternative to romiplostim. Eltrombopag offers patients, clinicians and the NHS a less costly, oral alternative treatment in an orphan disease area where there are few evidence based therapies.

We have structured our comments in line with the specific questions posed by NICE.

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

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 has several concerns with respect to the Committee's interpretation of the available evidence. These are outlined below.

i) The Committee's assertion that romiplostim is likely to be more effective than eltrombopag.

GSK welcomes the Committee's acknowledgement of the uncertainty surrounding the indirect comparison, however we would like to reiterate our belief that there is no robust evidence (statistical or otherwise) of a clinically meaningful difference between the two TPO-RAs. The uncertainty associated with any indirect treatment comparison of these two treatments is to be expected given the small patient populations in this orphan disease area and the heterogeneity between the pivotal trials, specifically in terms of trial design and end point definitions. Furthermore, given that in clinical practice, supported by various published guidelines, the two TPO-RAs are deemed interchangeable, GSK believes that there is no robust basis for the Committee's assertion that romiplostim is likely to be superior to eltrombopag and that this statement is in fact misleading. cITP is an orphan disease area and the evidence base will always be limited. There is not sufficient evidence to be able to make robust conclusions regarding comparative efficacy of the two TPO-RAs and in light of the available evidence GSK do not believe that the Committee's conclusion can be reasonably justified.

ii) Misrepresentation of clinical expert opinion

GSK believes that comments from the clinical experts at the first Committee meeting have been misrepresented on page 36 of the ACD. The ACD states "..The committee agreed with the clinical specialists that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag rather than equally effective…" This is not consistent with contemporaneous notes taken at the meeting, which suggest that the clinical experts stated that although there was not enough evidence to make any conclusions regarding comparative efficacy, they viewed the two TPO-RAs as interchangeable and would offer patients a choice of TPO-RA. It should also be noted

that the current wording was not in the first ACD and so presumably was added as a result of discussions that took place at the second appraisal committee meeting, at which there were no clinical experts present.

iii) Assumption that patients in the romiplostim trials were likely to be more severe than those enrolled in the eltrombopag trial because the romiplostim trials preceded the eltrombopag trial

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 whereas the romiplostim studies were conducted in the United States, the Netherlands, France and the UK. 73% of the subjects in RAISE were from countries where the romiplostim trials were not running and are therefore likely to reflect a similar severity of disease.

iv) Inappropriate romiplostim dosing assumptions used in ERG's supplementary analysis

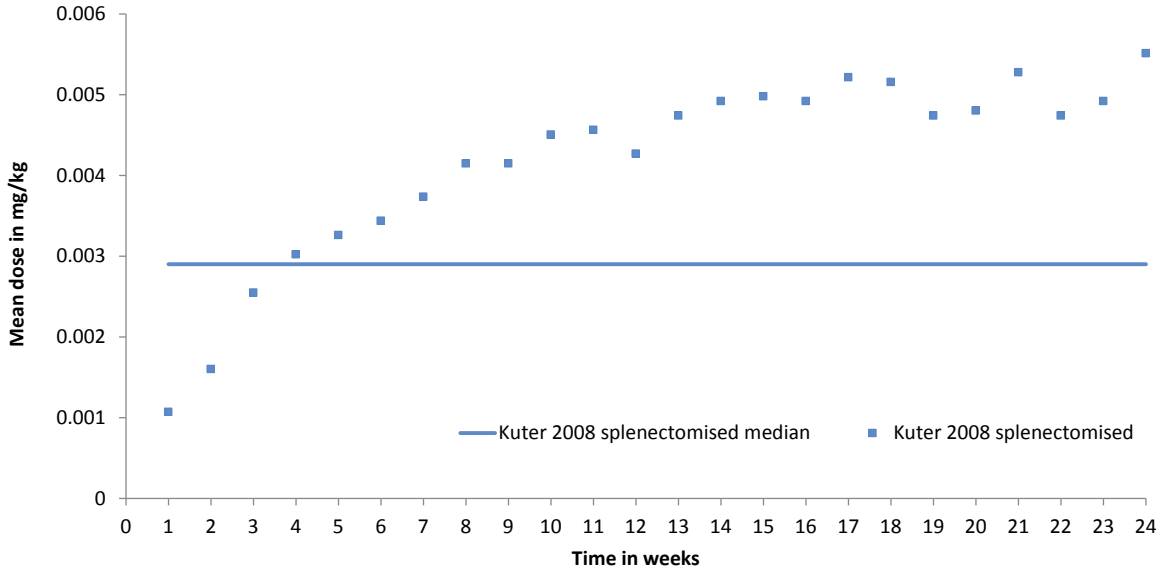
GSK has concerns regarding the lower dosing assumptions used for romiplostim in the ERG's supplementary analysis. Although for the purpose of the economic model it may be appropriate to use the dose corresponding to patients classified as responders, the ERG's analysis only made this adjustment for romiplostim and not for eltrombopag. This introduces bias into the comparison as there may also be a lower dose of eltrombopag in patients classified as responders.

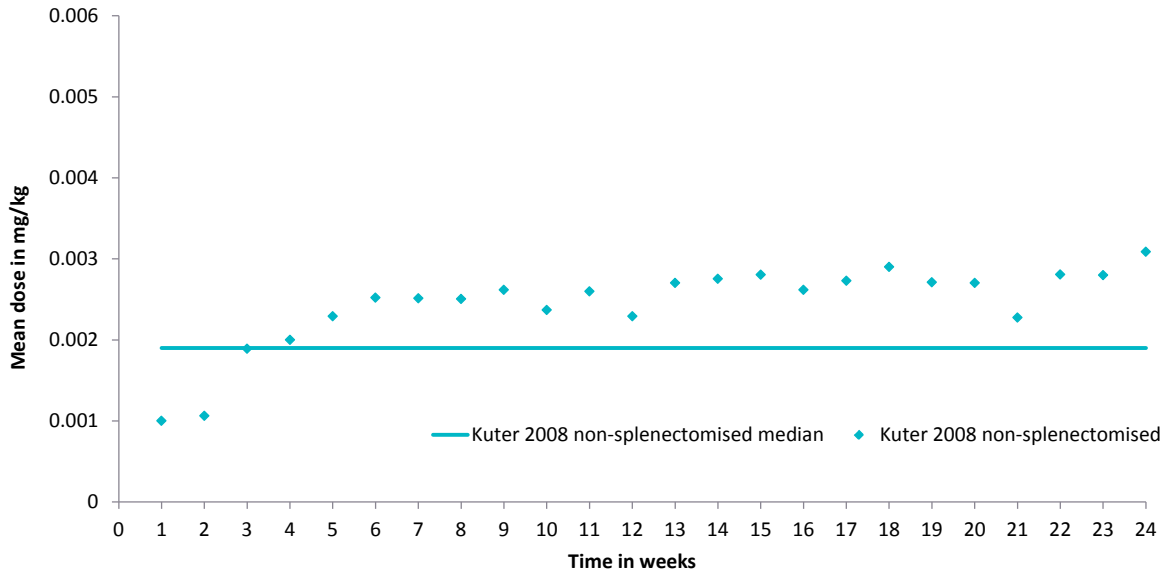
Assuming there is a relationship between response and dosing, use of the durable responder dosing to represent all patients meeting the responder definition in RAISE or the overall response definition in Kuter 2008 is likely to be inappropriate (in the economic model the RAISE definition was used in the base case and the overall response definition used in a sensitivity analysis). Durable responders represent only 48% (splenectomised) and 69% (non-splenectomised) of overall responders in Kuter 2008. It is therefore expected that the romiplostim dose will be higher for patients classified as responders using the RAISE definition of response or the overall response definition.

The use of the median rather than the mean may be driving a large majority of the dose reduction observed in this scenario. The FDA advisory committee reported median "stabilized" doses for the Kuter 2008 splenectomised (2.9µg/kg) and non-splenectomised (1.9µg/kg) trials[1]. Comparing these medians to the means reported in Kuter 2008[2] (Figure 1) suggests that the use of medians rather than means is likely to significantly underestimate the dose and therefore the cost.

Amgen's response to the first ACD refers to an observational study which reports the mean dose of romiplostim as 2.8ug/kg[3]. This is incorrect and misleading, since the abstract states that this is actually a median dose, which as stated above is likely to be lower than the mean dose. The abstract also concludes that the real world dose of romiplostim is similar to that reported in Kuter 2008. GSK believes that using the mean doses reported in Kuter 2008 is therefore entirely justified. In fact, our approach may have been conservative as results from the romiplostim extension study and a French compassionate use program (both of which are likely to see non-responders withdrawn from therapy) suggest that higher average doses of romiplostim are used in clinical practice.[4,5]

Figure 1. Comparison of mean and median romiplostim dose in Kuter 2008





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.

References

1. FDA Advisory Committee Briefing Document. 2008 Mar 12. Report No.: Biological License Application (BLA) 125268
2. Kuter DJ et al. Lancet 2008 Feb 2;371(9610):395-403
3. Selleslag D et al. ASH Annual Meeting Abstracts 2012. Abstract 3316
4. Bussel J.B et al. Blood 2009 113: 2161-2171.
5. Khellaf et al. Blood 2011;118(16):4338-45.