Cost-effectiveness of eltrombopag (Revolade®) for the treatment of chronic immune thrombocytopenic purpura (ITP).

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Summary

1. On 4th June 2010, Glaxo SmithKline Ireland Ltd. submitted a cost-effectiveness evaluation of eltrombopag versus the comparator romiplostim (NPlate®), and on July 30th a cost-effectiveness analysis versus the comparator rituximab (Mabthera®) was submitted following a request by the NCPE. The purpose of the submission was to support an application for the reimbursement of eltrombopag under the High Tech Drug Scheme. The analysis was undertaken from the Health Service Executive perspective.

2. Eltrombopag, is an orally administered, small molecule, non-peptide, thrombopoietin receptor (TPO-R) agonist that elevates platelet counts by targeting platelet production. In March 2010, eltrombopag was approved under the brand name Revolade® with a licensed indication *'for adult chronic immune thrombocytopenic* purpura *(ITP) in splenectomised patients refractory to other treatments and may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.'*

3. The cost-effectiveness of eltrombopag (50mg daily) was modelled using a Markov model with a 4 week cycle length and a 2 year time horizon. Transition probabilities applied to response determined whether patients entered a controlled (in terms of platelet count) or uncontrolled health state. For the rituximab comparison, patients were not stratified according to splenectomy status as for the romiplostim comparison. Both controlled and uncontrolled patients could transition to 'bleed' heath states depending on their platelet control. Efficacy data inputs for the economic model were based on transient (TR) and durable response (DR) rates.

4. There are no head-to-head trials comparing eltrombopag with either rituximab or romiplostim. The clinical efficacy outcome marker in the eltrombopag and romiplostim randomised controlled trials differed as did the outcome marker in the rituximab observational data (rituximab is unlicensed for the treatment of ITP). Efficacy data inputs (TR and DR) for eltrombopag were derived from a patient-level analysis of the RAISE

study population as the trial end-point was the odds of responding to therapy versus not responding to therapy, (a responder was defined as a patient whose platelet count increased to between 50-400 $x10^9$/L). This allowed an indirect comparison with romiplostim for a non-splenectomised and splenectomised cohort of patients. In RAISE, the odds of bleeding were less among patients treated with eltrombopag compared with placebo (OR 0.24, 95%CI 0.16-0.38; p<0.001). TR and DR data were not available for rituximab – a weighted average response of 50.8% was applied to both cycles 1 and 2 of the model.

5. The NCPE review group considered that the clinical efficacy input parameters for eltrombopag were a source of uncertainty in the romiplostim comparison, as TR and DR estimates had direct implications on transition to controlled or uncontrolled health states. The assumption that platelet counts were sustained for 6 out of the last 8 weeks of the RAISE trial to allow durable response determination was a cause for concern. The review group had reservations concerning maintenance of the platelet count above $50x10^9$/L (using the last-observation carried forward methodology) in this period in the absence of actual monitoring of platelet counts. In addition, the heterogeneity in the inclusion criteria for the eltrombopag and romiplostim trials in terms of baseline platelet counts was noted. Bleed risk was assumed to be the same for rituximab, romiplostim and for eltrombopag but was adjusted for response rate – thus conferring differences in transition probabilities to bleed health states.

6. Eltrombopag is not cost-effective when compared to rituximab. In the base-case analysis, eltrombopag resulted in an incremental cost of €27,913 and a QALY gain of 0.0175 (incremental LYG of 0.0011) per patient. The ICER was estimated at €1,598,577/QALY. The main driver in the model was the significant cost difference between eltrombopag and rituximab. Eltrombopag is given daily for 2 years whereas rituximab is given for a month and response is maintained for the 2 year life cycle of the model.

7. In the base-case comparing eltrombopag to romiplostim for the non-splenectomised cohort, an incremental LYG of 0.0004 and a QALY gain of 0.0039 was obtained for eltrombopag for a cost saving of €15,021 – thus eltrombopag is dominant over romiplostim. In the splenectomised group, there was no difference in life years gained although eltrombopag resulted in a QALY gain of 0.0098, at a cost saving of €5,001. Eltrombopag was also dominant over romiplostim in this patient cohort i.e. less costly and more beneficial.

8. There was little uncertainty over the outcome of the cost-effectiveness assessment of eltrombopag compared to rituximab. In the probabilistic sensitivity analysis, the cost-effectiveness plane demonstrated that 90% and 10% of the cost and QALY pairs were in Quadrants 1 and 4. The corresponding cost-effectiveness acceptability curve (CEAC) showed that eltrombopag had 0% probability of cost-effectiveness under the €20,000 and €45,000 cost-effectiveness thresholds.

9. In the romiplostim comparison, the model was sensitive to eltrombopag response rates, the weekly dose of romiplostim, the inclusion of wastage for romiplostim and the cost of eltrombopag. The corresponding cost-effectiveness acceptability curves for the contra-indicated and refractory populations show that the probability that eltrombopag being cost-effective at the €20,000 threshold was 59% for the former and 60% for the latter.

10. The evaluation has demonstrated that eltrombopag may be considered cost-effective compared with romiplostim but the NCPE review group had concerns over the derivation of the response data for eltrombopag, and the subsequent methodology to estimate the bleed risk and utility data for both agents. To date attenuation of response has not been noted but long-term data is lacking. Discontinuation of therapy results in platelet counts returning to baseline.

11. In the budget impact assessment, should eltrombopag replace romiplostim, the introduction would be cost-saving as romiplostim (€42,308.75 per patient per annum) is more expensive than eltrombopag (€26,308.68 per patient per annum). Depending on the population of patients treated, the savings could range from €443,165 - €946,973 in Year 1. Replacing rituximab with eltrombopag would have cost-implications to the healthcare payer resulting in expenditure of between €561,214 - €1,199,227 per annum in year 1. Due to the small patient cohort, the year 5 projections rise by approximately 10%.

12. Eltrombopag is not cost-effective as compared with rituximab. The cost/QALY obtained for the comparison with romiplostim suggests cost-effectiveness but the review group had concerns over the evidence supporting the efficacy of eltrombopag. Therefore, we do not believe that this product should be reimbursed under the High Tech Drug Scheme at this point in time. Eltrombopag may prove a valuable treatment option for some patients with ITP and in view of the significant additional cost and the requirement for on-going monitoring, this therapy could be restricted to hospital units with expertise in this therapeutic area.