Dear Jeremy

Teriflunomide for treating relapsing forms of multiple sclerosis: Appraisal Consultation Document

Biogen Idec thanks NICE for the opportunity to review the Appraisal Consultation Document (ACD) for teriflunomide for treating relapsing forms of multiple sclerosis. Our comments are in relation to the robustness of the health economic model for teriflunomide.

MODEL STRUCTURE

The overall structure appears consistent with previous models used in previous NICE appraisals based on EDSS; however, we note that the structure does not allow for the regression of disability between EDSS states. Excluding regression will result in the patient population progressing rapidly to higher EDSS states and SPMS than it would be expected under real-world conditions. This has an impact on the reliability of the ICER of teriflunomide versus the comparator.

PATIENT POPULATIONS

Disability progression is the main driver of the model. There seems to be a discrepancy with the patient population selection used in the MTC vs. the teriflunomide group. The distribution of SPMS patients in the teriflunomide studies selected appear to have higher baseline EDSS scores compared to those utilized in the MTC. As a consequence patients might move more quickly into high EDSS scores in the teriflunomide group, thus enhancing teriflunomide's ability to demonstrate an impact on disability progression (as per comment above). This would therefore lead to an inaccurate cost-effective analysis.

MTC RESULTS

The hazard ratios and relative rates of relapses are difficult to interpret and threaten the face-validity of the model; for example, the hazard ratio for Betaferon is 1.21, with BSC 1.0. Particular attention should be placed into the results showing interferon1-b having worse clinical outcomes than BSC.

Further, the MTC treatment effects do not appear to be consistent with the head-to-head studies available; e.g. TENERE. This threatens the predictive validity of the MTC.

BLENDED COMPARATOR

As stated in section 3.13 of the NICE ACD report for teriflunomide, there appear to be two deviations in relation to NICE guidance regarding the use of Blended Comparators.

The deviations were that the blended comparator was calculated as the weighted average of the clinical input parameters (e.g. mean relative rates) and secondly that the cost-utility was calculated on the basis of the UK market share data. Further the approach to use a simple weighted mean of each treatment outcome is methodologically flawed and does not reflect the use of individual products in the UK. Teriflunomide should be compared against comparators individually and the base case comparison should be versus the product most likely to be displaced.

Throughout the model, simple assumptions on the weighting have been made without any regard to utilising best available evidence e.g. relative rate leading to hospitalization, annual all-cause withdrawal rate. This goes against the principles of evidence-based decision-making and severely compromises the validity of the model.

ADVERSE EVENTS

The adverse events rates unduly bias in favour of teriflunomide. Teriflunomide is associated with a very short list of adverse events (i.e. nausea, diarrhoea, hair-thinning) compared to the comparators. A comprehensive and transparent list of adverse events for teriflunomide should be provided and included in the MTC analyses by the manufacturer.

In addition, teriflunomide remains in the body for up to 2 years after patients stop treatment. The impact of the long half-life of teriflunomide on adverse event rates and subsequent costs was not explored in the model/submission – the SmPC recommends that women, who have previously taken teriflunomide, should have their levels checked prior to pregnancy to ensure plasma levels are below (above or below?) 0.02mg/l, this requires long-term follow up of patients. It appears that the submission does not explore this scenario in any sensitivity analysis.

Yours sincerely

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