Meindert Boysen

Programme Director, Centre for Health Technology Evaluation

5th January 2014

Dear Dr Boysen

Thank you for asking me to comment on the appraisal consultation document for the Single Technology Appraisal of Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis.

In answer to the specific questions asked, all of the relevant evidence has not been taken into account; the summaries of clinical effectiveness are not reasonable interpretations of the evidence; and the provisional recommendations are not a sound and a suitable basis for guidance to the NHS.

I agree that the further analyses requested by NICE of the manufacturer in 1.2 of the ACD are reasonable and helpful.

My concern is with the committee's assessment of the clinical effectiveness of alemtuzumab.

I agree with its conclusion, in 4.8, that alemtuzumab is a more effective treatment for relapsing–remitting multiple sclerosis than subcutaneous interferon beta-1a and that it represents a "step change in the treatment of relapsing–remitting multiple sclerosis" (4.14).

However, the decision (4.9) that alemtuzumab should not be recommended for rapidly evolving severe multiple sclerosis and highly active relapsing–remitting multiple sclerosis despite interferon is not logical, fails to consider the totality of the evidence and contradicts the licence granted by the European Medicines Agency, and contemporary concepts on the treatment of multiple sclerosis which has established that initial severity of disease predicts disability and requires early intervention with the most effective therapies.

The committee bases its view of alemtuzumab's efficacy in these two disease subgroups entirely on the mixed treatment comparisons reported in 3.8 which showed lower relapse rates on alemtuzumab treatment than either fingolimod or natalizumab, albeit without statistically significant differences. I recommend that the committee also take into consideration these three points:

1. In phase 2 or phase 3 trials, neither fingolimod nor natalizumab have shown superior efficacy to interferon in terms of preventing the accumulation of disability in multiple sclerosis, which is a more important outcome for patients than relapse rate. Yet alemtuzumab has achieved this threshold in one phase 2 and one phase 3 trial, for all included patients and for those fulfilling the definition of rapidly evolving multiple sclerosis (see Table B6.5.6 of the manufacturer's submission).
2. Even if alemtuzumab had only equivalent efficacy to fingolimod or natalizumab in the active multiple sclerosis subgroups, it would be an attractive alternative for several groups of patients, for instance women wishing to become pregnant (not possible whilst under on treatment with fingolimod or natalizumab) or those who fear the risk of progressive

multifocal leucoencephalopathy following natalizumab (which may be as high as 1/90 for those with positive JC virus serology after two years of natalizumab therapy).

3. As the committee recognises, alemtuzumab is a more efficacious drug than interferon with a potentially serious safety profile which needs careful management. It is therefore illogical, and defies the available evidence from clinical trials, to endorse its use as first-line therapy but not to more aggressive forms of multiple sclerosis that have either failed to be controlled on interferon, or for whom interferon is considered futile. Please note that conservative decision-makers, such as Health Canada and a few individuals within the Committee for Medicinal Products for Human Use of the European Medicines Agency (as noted in 4.13), have taken the opposite view, proposing that alemtuzumab should be reserved for those with continued disease activity on interferon and other multiple sclerosis therapies. Indeed, I imagine that most neurologists in the UK would –if permitted- first use alemtuzumab in this situation in place of natalizumab or fingolimod; Genzyme estimate >70% alemtuzumab will initially be used for rapidly evolving severe multiple sclerosis and highly active relapsing–remitting multiple sclerosis. However, over time, as physicians become comfortable with handling the drug and monitoring programme, I anticipate that – if permitted – increasing proportions of treatment-naïve patients will receive the drug.

With best wishes

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