NICE appraisal consultation document for teriflunomide [ID548]

Response from the Multiple Sclerosis Trust

9th October 2013

Please find below comments from the MS Trust in relation to the Appraisal Consultation Document (ACD) for teriflunomide, published in September 2013. The ACD states that the Appraisal Committee is minded not to recommend teriflunomide for the treatment of relapsing-remitting multiple sclerosis (MS).

Our submission will address the following areas, as set out in the ACD, namely:

a) Has all of the relevant evidence been taken into account?
b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
d) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

We do not believe that there are any points relating to item D. All our points relate to the first three items for consideration.

1. The MS Trust wishes to make a general comment pertaining to the composition of the NICE Appraisal Committee. From the list of Appraisal Committee members who were involved in the teriflunomide review, it does not appear that there was anyone with specific neurological expertise. This is regrettable when discussing a complex condition such as multiple sclerosis (MS). We recognise that there were clinical experts present at the Committee meeting in September 2013, but continue to believe that this was insufficient input to ensure that all relevant clinical issues were identified and the clinical context was adequately described and therefore taken into consideration.

2. The MS Trust is very disappointed that the Committee is minded not to recommend teriflunomide for adults with relapsing-remitting multiple sclerosis.

   Our interpretation of the ACD is that the Committee's concerns centre around manipulation of the economic model which generated ICERs of between £6000 to £107,000 per QALY gained compared with glatiramer acetate. The

committee has presented a series of technical questions for the manufacturer but has not been clear about the implications of the results of the additional analyses or what further evidence this is expected to provide.

While we recognise the importance of establishing cost effectiveness for a new treatment, we feel that the appraisal process has been dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the appraisal process being consumed by hypothetical manipulation of the mathematical model and disconnected from the practical reality of clinical practice.

The ACD acknowledges that "teriflunomide was clinically effective in reducing relapse rates compared with placebo, and that it may have a beneficial impact on accumulation of disability". Furthermore, the ACD states that "teriflunomide dominated the blended comparator in the base case…that is, it was less expensive and more effective". On the face of that evidence, that the drug is effective and cost-effective, that is has a positive effect on health outcomes and delivers value for the health service, it seems perverse that NICE would not recommend the drug for use in the NHS.

3. People with relapsing-remitting multiple sclerosis currently have very limited treatment options. The committee heard from both clinical and patient experts about the importance of access to a range of medicines, particularly for those who are unable to tolerate current treatments which are associated with significant side effects as well as injection site reactions.

   Despite the overall efficacy of current treatments for preventing MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy.

   Four of the five current first line treatments (Avonex, Betaferon, Extavia and Rebif) have the same mechanism of action. If a patient fails to respond to one of these drugs or develops side effects, glatiramer acetate is the only alternative treatment with a different mechanism of action.

   All of the current first line treatments are self-injected. Overwhelmingly, an oral route of administration is seen as a real benefit by people with MS. Through supporting people who are taking the current first line treatments, the MS Trust is aware that the requirement for long-term injections places a burden on them and in some cases leads to a decision not to start treatment, delays initiating treatment or results in reduced adherence. Self-injecting is painful, results in anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; and imposes restrictions on a number of aspects of general living.

   Uniquely, teriflunomide is taken as a tablet, it acts in a different way to the current disease modifying drug therapies, and has a different profile of side effects. It will significantly alter the range of treatments available to people with relapsing-remitting MS, providing a genuine alternative to the current therapies.

4. There is no clinical evidence for treatment waning. Treatment waning was introduced by the manufacturer during the fingolimod appraisal (TA254). The manufacturer carried out a sensitivity analysis on their economic model to see what would happen if there was a **hypothetical** treatment waning and, not surprisingly, the ICER increased. The concept of treatment waning is without precedent in previous MS NICE appraisals.

   While we acknowledge that it is difficult to extrapolate two year clinical trial data to long term treatment, we wish to emphasise that there is **no clinical evidence to support loss of efficacy**. Moreover, there is no evidence to justify the arbitrary choice of 25% loss of efficacy at 2 years and 50% loss of efficacy at 5 years. Can the ERG or Committee explain why these levels, and not alternatives, should have been chosen? Treatment waning is **hypothetical,** is being used to test the responsiveness of a mathematical model and is not based on clinical observation.

   The ACD states (4.15, p39) "The Committee heard from the clinical specialists that they could not be confident that the treatment effect would not wane." This is a reasonable, professionally cautious response to the Committee's question. However, this is a leading question; what it does not make clear is the converse is equally true - that clinical specialists could not be confident that treatment effect would wane.

5. The MS Trust agrees with Committee's conclusion that teriflunomide has efficacy equivalent to current first line treatments, and we do not anticipate it being used as an alternative to fingolimod or natalizumab, although these were listed as comparators in the final scope. As stated in the ACD, clinical specialists considered that in clinical practice, teriflunomide would be viewed as a first line treatment option alongside glatiramer acetate and the beta interferons in line with ABN guidelines.

   The ACD states (4.2, p32) "teriflunomide…would be stopped if the person's condition converted to secondary progressive multiple sclerosis, or reached EDSS state 7." We would like to stress that this is not as clear cut as stated; the ABN guideline acknowledges the difficulty of identifying when treatment is no longer of benefit for an individual patient and concludes that it is not feasible to have mandatory stopping criteria that apply in all cases.

6. With respect to treatment sequencing, we wish to stress that there is no treatment pathway in place for disease modifying treatments and it is not within the scope of the current appraisal to be making assumptions on sequence or escalation of treatments.

   The manufacturer explored **hypothetical** treatment sequencing in their submission to test their economic model. Manufacturer provided evidence for:
   - teriflunomide → 2 → 3
   - blended comp → 2 → 3

   where 2 or 3 could be blended comparator, fingolimod, natalizumab or best supportive care.

The Committee has now asked for further combinations "reflecting UK clinical practice" (1.2, p4). We question whether these particular combinations reflect realistic sequences.

- teriflunomide → Rebif → fingolimod - vs - Rebif → fingolimod → nothing
- teriflunomide → Rebif → GA - vs - Rebif → GA → nothing

In UK clinical practice, switching or escalating treatments results from **an individual's** intolerable side effects or sub-optimal response to an initial treatment. An economic model cannot capture the benefit to the individual achieved by switching to an effective treatment.

This reflects an urgent need within the UK for a much broader range of treatment options. As it is impossible to prognosticate for an individual, there is a need for flexibility to allow both clinician and patient to select a treatment that is both tolerable and effective for that person.

7. The innovative nature of oral route of administration is acknowledged in the ACD, in fact the Committee considered that additional QoL benefits were not fully captured in the QALY (4.1, p30 and 4.21, p44). However, this aspect seems to have been overwhelmed by mathematical modelling.

   Those patients who don't tolerate the first line treatments face particularly challenging choices. An oral therapy such as teriflunomide would offer a real alternative for patients who otherwise may face the prospect of treatment withdrawal and consequent return of the pre-treatment rate of relapse and risk of axonal damage with increasing and irreversible disability, with all the associated individual and health service burdens.

8. The MS Trust is confident that the Committee understands the serious nature of a diagnosis of MS and the impact of the condition on an individual's ability to remain in work and maintain independence and quality of life. What is less clear is whether a full account has been taken of the negative impact of a relapse on the person with MS or the real cost of a relapse. There are significant health-care related costs of even a single relapse, but additionally there are broader costs in terms of lost income for the person with MS and also potentially for informal carers who need to provide care and support during the disabling period of relapse. No less significantly there are physical and emotional costs to the person with MS.

Conclusion

Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The EMA has licensed teriflunomide because it is an effective, safe drug for people with MS who have very few available treatment options. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment.

People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that teriflunomide would be an important addition to the small range of available disease modifying therapies for MS.

As with other disease modifying therapies, teriflunomide should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.