Response from the MS Trust to the NICE Appraisal consultation document for Fingolimod for the treatment of relapsing remitting multiple sclerosis.

Please find below comments from the MS Trust relating to the recently announced preliminary determination that Fingolimod should not be recommended for the treatment of relapsing – remitting multiple sclerosis (MS).

We are documenting these points having given consideration to the framework for comments set by the National Institute for Health and Clinical Excellence (NICE) namely:

1. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
2. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
3. 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 within the final category relating to discrimination and would wish all our comments to therefore be considered as pertinent to categories 1 & 2.

A. The MS Trust wishes to make one general over arching comment which pertains to the expertise within the NICE committees. It is not apparent from the list of Appraisal Committee members who were involved in the Fingolimod review that there was anybody present with specific neurological expertise. This is regrettable when discussing a complex condition such as multiple sclerosis and as will be explored below some of the points made within the ACD reflect a lack of understanding. We know that two experts were present for the meeting on July 6th but it is unreasonable to expect them to get across all the relevant points within the limitations of one discussion.

B. The NICE assessment has been made against subsets of the Fingolimod trial data to align to the three licence indications granted by the European regulatory authority, and this presents a major issue with the process. Novartis planned the clinical trial programme with the aspiration of a licence for Fingolimod in all people with relapsing remitting MS. For reference in the USA the regulatory authorities have granted a full licence for relapsing remitting MS. The EMA however granted a significantly more limited licence for use in:
    - Adults with relapsing-remitting multiple sclerosis with high disease activity despite treatment with a beta interferon and:
        a. with at least one relapse in the previous year while on therapy and either at least nine T2- hyperintense lesions in cranial MRI (estimated as a T2 volume of greater than 0.5 ml at baseline) or at least one gadolinium-enhancing lesion.
        b. with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.
    - Adults with rapidly evolving, severe, relapsing-remitting multiple sclerosis defined by two or more disabling relapses in 1 year with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.

The MS Trust is supportive of the restricted licence as we are not certain, based on the trial data available to date, how significant a risk there is to people with MS from the potential side effects. However, the difference between the licence indication and the trial protocols adds to the complexity and validity of the NICE process.

The MS Trust would encourage NICE to draw on their experience of assessing Tysabri (Guidance 127) where a similar situation was effectively managed to a good outcome for people with MS and the NHS. At present we do not feel that this approach has been adopted.

C. The ERG cites best supportive care as an appropriate comparator. This is unacceptable from the perspective of people with MS and demonstrates a lack of understating of MS the disease and its management. In no circumstances would best supportive care be appropriate or routine clinical practice for any of the cited treatment groups. Progression of disability in these groups is likely to be twice as fast as in patients with less active disease. The first disease modifying drug therapy was launched in the UK in 1995 and whilst uptake in the UK has remained low in comparison with both the USA and Europe the sub groups of MS for whom a licence has been granted for Fingolimod would not be left without treatment.

D. The ERG considered that natalizumab was an appropriate comparator for the second population type, in line with NICE technology guidance 127. The MS Trust would support this contention but as mentioned above there is the practical issue about the clinical trials which were undertaken for Fingolimod.

E. The ERG has criticised the use of Avonex as the comparator and whilst there is logic to this argument it would have been a fair comparator for the routine treatment of relapsing remitting MS - the original licence intention.

In the context of the points C D & E above we hope that NICE will give more credence to the views of the clinical specialists who according to the NICE documentation provided stated that:

Relapsing-remitting multiple sclerosis is currently treated in UK clinical practice with beta interferons, glatiramer acetate and natalizumab. Beta interferons and glatiramer acetate are administered by subcutaneous injection, and natalizumab is delivered by monthly intravenous infusion. The use of natalizumab is restricted to people whose disease has continued to relapse frequently despite treatment with interferons and /or glatiramer acetate, or whose disease is deemed aggressive on the basis of early, frequent, disabling relapses. People with treatment-refractory or aggressive disease may also be given alemtuzumab or mitoxantrone (both unlicensed for relapsing-remitting multiple sclerosis). However, there are variations in prescribing depending on local funding arrangements. The professional experts indicated that research suggests that it is desirable to treat people with multiple sclerosis early in their disease course, before axonal damage has occurred. The clinical specialists noted that the marketing authorisation for fingolimod covers disparate groups, with different risks of relapse-induced disability. Although beta interferons reduce the elapse rate by about 30% per year, many people will relapse despite being adherent with at least 1 year of treatment.

The clinical and patient experts considered that fingolimod would be a welcome additional treatment option for people with relapsing-remitting multiple sclerosis because it is expected to reduce relapses and disease progression, and in turn reduce disability and improve quality of life. The clinical specialists suggested that fingolimod should be initially considered for:
• people with high disease activity despite treatment with a beta interferon or glatiramer acetate
• people who have previously had high disease activity despite treatment with beta interferons or glatiramer acetate and who have consequently withdrawn from treatment with those drugs while awaiting alternative treatments
• people with rapidly evolving severe relapsing-remitting multiple sclerosis
• people with needle phobia who have been awaiting an oral treatment.

The clinical specialists considered that over time, with enhanced clinical experience, fingolimod use is likely to be broadened but it is unlikely to replace currently available therapies. The clinical specialists noted that population 2 (people with rapidly evolving severe relapsing-remitting multiple sclerosis) in the

manufacturer's submission represents a group of people with poor prognosis, who are currently treated with natalizumab, alemtuzumab or mixantrone. Because of the lack of data for fingolimod in this group, the clinical professionals suggested that they may be reluctant to use fingolimod in these people until the evidence base for this population strengthens.

The MS Trust would support completely the recommendations of the clinical experts and hope that NICE can also agree with their recommendations.

F. The ERG cautioned that the time-horizon for assessing the impact of fingolimod on disease course is much longer than the available follow-up data from the trial populations. This is one of the key discussions that has been ongoing with NICE since the original Guidance 32. MS is a disease for life and clearly the true pay back in terms of costs is related to reducing disability which comes later in the disease course. The MS Trust would ask that NICE takes note of this fact and at the very least adopts a 30 year time horizon, although this is still short for someone being diagnosed in their mid–twenties to mid-thirties. Many people with MS will live with the condition for at least 40 - 50 years.

G. There is no evidence in the NICE judgment that serious consideration has been given to the points made in various submissions about the impact of relapses on the life of a person with MS. There is a tendency for relapses to be dismissed in a numerical fashion and in actual fact there is a complex interplay between number, severity and impact. The NICE documentation included the following statements:

The patient experts stated that relapses have a significant adverse effect on quality of life for people with multiple sclerosis. A relapse lasts, on average, 55 days and some people have two or three relapses per year. This has a significant impact on their ability to work or undertake normal daily activities.
Currently 60% of people with multiple sclerosis become unable to work within 5 years of diagnosis.
The clinical and patient experts considered that fingolimod is likely to improve a person's ability to perform daily activities, and may reduce depression, fatigue, pain and cognitive dysfunction.

Has this data been effectively considered in the calculations of cost efficacy? There is a need to value relapses in the "here and now" for example 55 days off work, needing hospitalisation or care etc. We would also point out that modeling cost efficacy is inherently very complicated. MS does not fit neatly into small boxes; the transition from relapsing remitting to secondary progressive is not a finite happening but rather a slow insidious change and NICE needs to give more consideration to these complexities.

H. Novartis used the same utility data as was used in the Tysabri assessment and published by Orme et al. NICE has criticised the collection methods of the utility data which was undertaken by the MS Trust. We do not think it is appropriate to get into a detailed response to that argument here, but as stated previously there is no reason to suggest that the data was a biased sample and the data correlated well with data from other published sources namely Kobelt et al.

Conclusions:

MS in the UK has for many years felt a second class citizen when compared to all other parts of the world. In the USA circa 60% of people with MS are on the current drug therapies. The figure for Europe is 30% but in the UK only approximately 17% of people are currently prescribed drugs. Fingolimod has been assessed as efficacious and safe by the EMA and granted a licence. If NICE guidance is against its availability on the NHS it will further entrench the view amongst people with MS that their lives are not valued in the UK.
All the research evidence shows that it is desirable to treat people with MS early in their disease course prior to axonal damage. The damage caused by delays cannot be reversed and people with MS will have to live their life with accrued disability.

In particular NICE should consider that people with MS can be a huge drain on UK plc if they are no longer able to work. Currently 60% of people with MS are out of work within five years of diagnosis. A recent report from the Work Foundation showed that on average people with MS lost 18 years from their working life – a very significant cost to the state. All the drug therapies have the potential to improve this statistic and should be available on the NHS. In addition the cost of caring for people with MS in the UK is very significant and whilst this is often done by a family member it cannot be discounted in the assessment.

We recognise that it is difficult to demonstrate cost efficacy within MS, but we hope that NICE will work with all the relevant parties to manage the cost of Fingolimod without destabilising other Schemes currently in place

The clinical professionals involved in the NICE committee meeting stated that fingolimod should be started and monitored only in specialist clinics by neurologists and nurses experienced in multiple sclerosis care. The MS Trust would support this view and encourage NICE to work to achieve this outcome.