Sir Andrew Dillon
Chief Executive
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15th August 2011

Dear Sir Andrew

NICE Appraisal Consultation Document: fingolimod for the treatment of multiple sclerosis.

The preliminary recommendation from the NICE Appraisal Committee that ***"fingolimod is not recommended for the treatment of relapsing–remitting multiple sclerosis"*** has raised specific issues that we as neurologists treating patients with multiple sclerosis in the United Kingdom feel need to be addressed.

The Committee's use of best supportive care (rather than one of the currently available disease-modifying therapies) as the most appropriate comparator demonstrates a lack of understanding of this specialist disease area. "Best supportive care" essentially means no disease-modifying therapy. It is inconceivable that patients, who fulfill the EMA's marketing authorisation for fingolimod, with ***"high disease activity despite treatment with beta-interferon"*** or ***"rapidly evolving severe relapsing remitting multiple sclerosis"*** should receive no disease-modifying therapy at all[1]. Progression of disability in these patients is approximately twice as fast as in patients with less active multiple sclerosis.

Although patients with ***"high disease activity despite treatment with beta-interferon"*** continue to experience clinically apparent disease activity, such as relapses, whilst on beta-interferon, this does not mean that beta-interferon is having no clinical benefit at all. These patients will either remain on interferon-beta, be switched to glatiramer acetate or be considered for treatment with the more effective biological natalizumab if they have ***"rapidly evolving severe relapsing remitting multiple sclerosis"***. It is important to note that Natalizumab has been assessed by NICE and found to be a cost-effective therapy for ***"rapidly evolving severe relapsing remitting multiple sclerosis"*** on the NHS. The appraisal of natalizumab by NICE was based on a comparison against the therapies that are currently available under the Department of Health's Risk Sharing Scheme. Our understanding is therefore that fingolimod has been rejected on the basis of an economic evaluation that used an inadequate comparator, i.e. "best supportive care". The clinically correct comparison is with the licensed disease-modifying therapies, which are currently being used for treating people with MS in the UK. This comparison may lead to a different conclusion regarding the cost-effectiveness of fingolimod.

Another important reason for making fingolimod available for NHS patients with ***"rapidly evolving severe relapsing remitting multiple sclerosis"*** is the recent data regarding the risk stratification for developing progressive multifocal leukoencephalopathy (PML) as a serious side effect of natalizumab with a high mortality and morbidity[2]. The major risk of PML resides in patients who are seropositive for JC-virus and who have been on natalizumab for over 24 months. The risk of developing PML increases further (to ~1%), if these patients on natalizumab have previously been treated with cytotoxic or immunosuppressive drugs. Some of these patients find the risk of developing PML unacceptably high. As most of these patients would have previously failed treatment with 1st line disease modifying therapies (beta interferon, glatiramer acetate), fingolimod would be an important alternative for this patient population for which there would otherwise be no alternative treatment with proven efficacy. There are also some patients with rapidly evolving severe relapsing-remitting MS who are unable to take natalizumab because of

adverse effects (e.g. hypersensitivity reaction which occurs in 4%) or in whom that treatment is not effective (this is likely to happen in ~6% who develop anti-natalizumab antibodies): it would fall well short of best clinical care to not be able to prescribe fingolimod as an effective and licensed alternative treatment for such patients.

The EMA's marketing authorization, although restricted, should not detract from the data that demonstrates that fingolimod is an effective disease-modifying therapy. Although there is no long-term data on the duration of benefit of fingolimod there is emerging evidence on the long-term benefits of conventional disease-modifying therapies; over a 10 to 20 year horizon. We have no reason to believe that fingolimod won't have similar long-term benefits.

If the recommendation in the Appraisal Consultation Document (ACD) concerning fingolimod was to be confirmed by NICE, treatment of MS in the UK would fall below international standards of care. Further knock-on effects include the following:

1. Fingolimod is the first orally available disease modifying treatment for MS, which will be clearly attractive for some patients.
2. Fingolimod has a novel mechanism of action and allowing such a treatment in the NHS would shows support of innovation; failure to support innovation could lead pharmaceutical companies to reconsider their development programs of other novel therapeutic agents for multiple sclerosis within the United Kingdom.
3. It would become increasingly difficult for British researchers to take part in clinical trials for patients with MS, and thus further erode the UK's position as a country with a track record in innovative pharmaceutical research.
4. Access to fingolimod for British patients who participated in the pivotal clinical trials of this drug would be denied continuation of this treatment once the fingolimod extension studies have been completed; this would leave these patients in limbo and raises several ethical issues for the principal investigators involved in the clinical trials.

We therefore urge NICE to revise its current ACD on the use of fingolimod in patients with relapsing multiple sclerosis to make this drug available for our patients through the NHS. We further suggest NICE advises Novartis such that it would be feasible for the Department of Health to negotiate a price at which fingolimod becomes cost effective for use in the NHS.

We would appreciate it if you could intervene in this matter on behalf of UK neurologists treating patients with multiple sclerosis, and on behalf of our patients and their families.

Thank you.

Yours sincerely

(This letter has been agreed by the following consultant neurologists specialising in the treatment of multiple sclerosis in the United Kingdom):

Name (email address)	**NHS Hospital or Trust**	**Conflicts of interest**

[1] European medicines agency; summary of opinion 20 January 2011.

"Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

Patients with high disease activity despite treatment with a beta-interferon.

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI".

[2] Kappos et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol. 2011 Aug;10(8):745-58.