



Regional Drug and
Therapeutics Centre

FINGOLIMOD[▼]

BNF Category: 8.2.4

NICE: Due December 2011

PBR Status: Excluded

Fingolimod is a sphingosine-1-phosphate modulator indicated for use in relapsing-remitting multiple sclerosis (RRMS). It is the first oral option available for treatment of RRMS, and has been shown to be more efficacious than placebo and interferon beta at reducing annualised relapse rates. Although the safety profile appears favourable, there are potentially risks of infection, cardiovascular effects, macular oedema and elevated liver-enzyme levels, which need further long-term assessment.

What is it?

Fingolimod (Gilenya^{®▼}, Novartis) is an orally-active sphingosine-1-phosphate (S1P) modulator which prevents lymphocytes from exiting lymph nodes, thereby preventing T cells from crossing the blood-brain barrier and causing damage to myelin sheaths.¹ It is licensed for use in relapsing-remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with interferon beta and in patients with rapidly evolving severe RRMS, as defined in the summary of product characteristics. Fingolimod is administered orally at a dose of 500 microgram daily.¹ A phase III trial is currently in progress for the additional indication of primary progressive multiple sclerosis.^{2,3}

How effective is it?

Two phase III double-blind trials in patients with RRMS who had ≥ 1 or ≥ 2 relapses in the previous year or two years respectively, have been published.^{4,5} Patients were randomised to receive fingolimod 500 microgram or 1.25mg daily, placebo (in the FREEDOMS study) or interferon beta-1a 30 micrograms weekly (in the TRANSFORMS study). This dose of interferon beta-1a is licensed for treatment of MS in the UK.⁶

After two years treatment, the FREEDOMS study ($n = 1272$) found that fingolimod 500 micrograms daily significantly reduced the annualised MS relapse rate (ARR, primary endpoint) compared with placebo (0.18 vs. 0.40, $p < 0.001$, number needed to treat for one year to prevent one relapse [NNT]=5), as did fingolimod 1.25mg (0.16 vs. 0.40, $p < 0.001$, NNT=5). Both doses also reduced the risk of disability progression during the trial, as measured by the Extended Disability Status Scale (EDSS) (hazard ratios [HR] 0.70 and 0.68 respectively, $p = 0.02$).⁴

After one year of treatment, the TRANSFORMS study ($n = 1292$, half with previous interferon beta therapy) found that fingolimod 500 microgram daily significantly reduced the ARR compared to interferon beta (0.16 vs. 0.33, $p < 0.001$, NNT=6), as did fingolimod 1.25mg (0.20 vs. 0.33, $p < 0.001$, NNT=8). There were no significant differences seen between the treatment groups in terms of disability progression.⁵

A one-year extension to the TRANSFORMS study showed that the benefits of fingolimod were maintained during the second year of treatment.⁷ Those who received interferon beta in the main trial were randomised to either dose of fingolimod in the extension, and a relative reduction in their ARR was seen.

Trial Limitations

Both trials were appropriately designed and powered, and participants had well-balanced baseline characteristics. However both studies enrolled patients with a maximum score of 5.5 on

the 10-point EDSS scale, which may prevent application of the findings to more disabled patients. In addition, the trial populations do not precisely match the marketing authorisation and only a small proportion of trial subjects would be eligible for fingolimod under the licensed indications, thus limiting the applicability of trial results to the population who will receive fingolimod.⁸ In each case data were collected by investigators but analysed by the manufacturer.

During phase III trials patients received fingolimod for a maximum of 24 months, so the long-term safety and efficacy remain uncertain.

How safe is it?

In the FREEDOMS study, adverse events (AEs) were recorded in 94% of patients in both fingolimod groups and 93% of patients in the placebo group. The high background rate of AEs is largely due to upper respiratory tract infections such as nasopharyngitis. Lower respiratory tract infection (primarily bronchitis) and abnormal liver function test (LFT) results were more common with fingolimod. Discontinuation due to treatment-related AEs was more common in those receiving fingolimod 1.25mg (14.2%) than in the other two groups (7.5% & 7.7%).⁴

In the TRANSFORMS study, AEs were reported in fewer patients in the fingolimod 500 microgram group (86%) than in the fingolimod 1.25mg (91%) or interferon beta 1a (92%) groups. The most commonly reported AEs reported in all three groups were nasopharyngitis, headache and fatigue, with no significant differences observed between groups. Discontinuation due to treatment-related AEs was more common in the fingolimod 1.25mg group, as were serious AEs.⁵ The most common serious AEs reported in FREEDOMS were bradycardia, MS relapse and basal-cell carcinoma, while bradycardia was most common in TRANSFORMS.

Initiation of treatment with fingolimod results in transient bradycardia, and may also cause atrioventricular conduction delays. With continued administration, heart rate returns to normal within one month.¹ Fingolimod is contraindicated in patients with immunodeficiency syndrome, those at risk of opportunistic infection, with active infections that are severe or chronic, patients with most active malignancies and those with severe liver impairment. Macular oedema was reported in 0.4% of patients receiving fingolimod 500 microgram, therefore ophthalmologic evaluation is recommended three to four months after treatment initiation.

All suspected adverse reactions to black triangle drugs such as fingolimod should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

What other options are there?

Currently interferon beta, glatiramer acetate and natalizumab are licensed for treatment of RRMS, all of which are administered by injection or infusion. Of these, only natalizumab is recommended for use by the National Institute for Health and Clinical Excellence (NICE), and then only for the treatment of rapidly evolving severe RRMS.^{9,10} Interferon beta and glatiramer acetate are still available through the NHS via a risk-sharing scheme.¹¹

Existing NICE guidelines for MS were published in November 2003, and a potential update is currently under review.¹² A NICE Single Technology Appraisal of fingolimod is currently in progress (Wave 20) and is expected to report in December 2011.¹³

When should it be used?

The licensed indication for fingolimod restricts its use to patients with high disease activity despite interferon beta therapy, or with rapidly evolving RRMS. In each case it will compete directly with natalizumab, which has the same indications.¹⁴ The oral route of administration and higher cost of fingolimod (see chart below) may influence choice, as might its relatively short safety record and the administration costs of natalizumab, which is given as a monthly intravenous infusion. Until its place in therapy and safety

profile are better understood, it may be appropriate to restrict use of fingolimod to patients who have not responded to an adequate therapeutic trial of natalizumab.

A survey by the MS Society found that 95% of patients would prefer to take an oral formulation than receive injections or infusions.¹⁵ There may therefore be considerable pressure on clinicians to prescribe fingolimod, including pressure to prescribe outside the licensed indications.

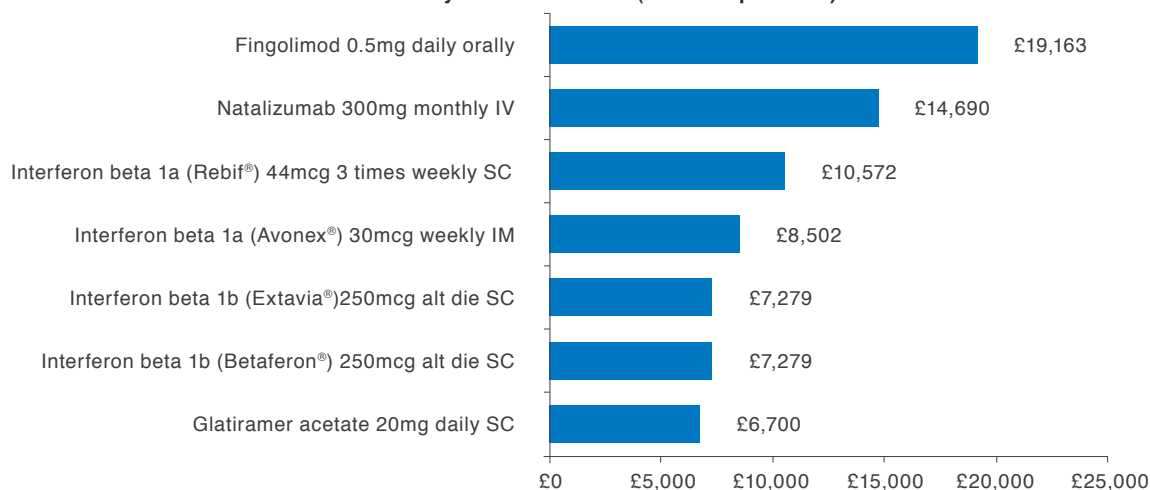
Treatment with fingolimod should be initiated and supervised by a physician experienced in MS, although in future GPs may be asked to prescribe fingolimod, under an appropriate shared care agreement.

Economic Impact

NICE estimate the incidence and prevalence of MS at 3-7 per 100,000 and 100-120 per 100,000, respectively in England and Wales, and roughly 80% of those newly diagnosed have RRMS.¹² It is estimated that 22.2% of RRMS patients who are eligible for disease-modifying treatment have rapidly evolving disease, and may therefore be eligible to receive fingolimod. This equates to 472 patients in the North of England, at a cost of approximately £19,000 per patient.¹⁶

How much does it cost?

Cost for 1 year of treatment (eMIMS April 2011)



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KEY G - guideline, R - review, RCT - randomised controlled trial

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