Department of Health

Rheynn Slaynt

Clinical Recommendations Committee

Recommendation 06/13

The Isle of Man Department of Health recommend Gilenya® (fingolimod) – as a HIGH PRIORITY - as an option for the treatment of highly active relapsing-remitting multiple sclerosis in adults subject to meeting criteria described in current NICE Guidance – TA254.

Approved by the Minister on 27 January 2014

Clinical Background Information

Burden of disease\textsuperscript{3,4} It is estimated that there are 100,000 people with multiple sclerosis in the UK\textsuperscript{3}. Of these, most people are diagnosed between the ages of 20-40, but it can affect younger and older people too. It can take up to 2 years for a diagnosis to be made. Almost twice as many women have MS than men. Relapsing remitting MS is the most common type of MS, affecting around 85 per cent of everyone diagnosed. There is no cure for MS, but there are different ways to manage it. This might include drug treatments for individual symptoms or relapses, diet, exercise and complementary and alternative therapies. Not all patients receive treatment.

The treated RRMS population in the UK was estimated at around 15,000 in 2011\textsuperscript{4}. 44\% of DMT treated patients fit the relapse criteria for NICE, giving a total of around 6,600 patients suitable for Gilenya treatment\textsuperscript{4}.

Pharmacology\textsuperscript{1,5,6,7} Multiple Sclerosis (MS) is a chronic, autoimmune, inflammatory and neurodegenerative disease of the Central Nervous System (CNS). In people with MS, circulating autoreactive lymphocytes infiltrate the CNS, leading to inflammation, tissue damage and ultimately brain atrophy.

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system. By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the
infiltration of pathogenic lymphocyte cells into the central nervous system, where they would be involved in nerve inflammation and nervous tissue damage.

**Staffing Implications**
The patients need to be monitored by nursing staff with regular ECGs during the first 6 hours after the initial dose. Thereafter, patients have blood tests at 1, 3, 6, 9 and 12 months and periodically thereafter. All patients will also require an eye examination for macular oedema as a one-off at 3-4 months from initiation.

When compared with the current treatment for these patients which is Natalizumab (requiring monthly infusions in hospital plus monthly blood tests for the duration of treatment), Fingolimod will be less labour intensive for hospital staff and require less capacity.

**Local Priorities**
The use of this medication will benefit patients with aggressive disease by reducing relapses and therefore minimizing hospital admissions, radiology tests and emergency treatment.

**Equity**
Fingolimod is now routinely prescribed by almost all the MS prescribing Centre’s in the UK. If fingolimod is not available for prescription here then this will be inequitable.

**Patient views**
The PANGAEA study is a real world observational study of fingolimod in Germany. 12 month interim results in 428 patients were presented and showed that 42.5% and 51.4% of patients rated the tolerability of fingolimod very good or good respectively at their last study visit (poster presented by Ziemssen T et al at AAN 2012. Also at 12 months, 83.7% of 168 patients in the pharmacoeconomic subset of the PANGAEA study reported that fingolimod was extremely easy and comfortable to use (Ziemssen T et al. Poster P302 presented at ECTRIMS 2012).

The MS Society and MS Trust both agree that people with MS should have access to any NICE approved medication which may be of benefit to them (http://www.mssociety.org.uk/ms-resources/how-to-access-medicines-england accessed 5th July 2013)

**Implications of not introducing this policy**
Fingolimod provides an effective option for a group of patients who had previously only been able to cycle through injectable medications which are not as effective or to be prescribed tysabri which is more costly, has significant side effects associated with it and is delivered by 4 weekly infusions requiring a hospital stay of not less than 3 hours

**Criteria/Pathway**

**Licensed Indication**

Fingolimod 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.

- 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.

Evidence (NICE/SIGN)

(see note 1)
NICE TA254, published 25 April 2012

Results of HTA\textsuperscript{14}

NICE TA254, published 25 April 2012

NICE guidance:

1.1 Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if: they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.

1.2 People currently receiving fingolimod whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

Guidelines for treatment\textsuperscript{12,13}

- Clinical guidelines were published in 2003 by NICE; these are currently under review
- The Association of British Neurologists published ABN guidelines for treatment of multiple sclerosis with Beta Interferon and Glatiramer acetate in November 2009

NB These guidelines were published prior to the grant of Marketing Authorisation for fingolimod.

Current practice

The population on the Isle of Man is approximately 80,000. NICE estimate that 6.4 patients per 100,000 will be eligible for treatment with Fingolimod. This means that there would be up to 5 patients on the island requiring treatment with this drug.

Currently, those patients have failed on the currently available medications and therefore are at risk of increased relapses and disability.
Evidence of effectiveness

CLINICAL EVIDENCE

Please note:

The following efficacy data is derived from the pivotal trials, FREEDOMS and TRANSFORMS. These studies contained patients that fall outside of the licence indication. The SmPC states: ‘Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients’.

**Efficacy Data**

The efficacy of fingolimod has been demonstrated in two studies which evaluated once-daily doses of fingolimod 0.5 mg and 1.25 mg in patients with relapsing-remitting multiple sclerosis (RRMS). Both studies included patients who had experienced ≥2 relapses in the prior 2 years or ≥1 relapse during the prior year. Expanded Disability Status Score (EDSS) was between 0 and 5.5.

**Efficacy data versus placebo**

FREEDOMS was a 2-year randomised, double-blind, placebo-controlled Phase III study of 1,272 patients (n=425 on 0.5 mg, 429 on 1.25 mg, 418 on placebo). Median values for baseline characteristics were: age 37 years, disease duration 6.7 years, and EDSS score 2.0.

**Relapse rates**

Over the two years, patients receiving 0.5mg fingolimod had a significantly lower annualised relapse rate than patients receiving placebo, with a relative risk reduction of 54% (absolute relapse rate reduction of 0.22, p<0.001). In addition, 70% of those taking fingolimod remained relapse-free compared with 46% of those taking placebo at 24 months (p<0.01).

**Disability progression**

Fingolimod significantly reduced the risk of disability progression over the 24-month period (defined as 1-point increase in EDSS confirmed 3 months later). The cumulative probability of progression, confirmed after 3 months, was 17% for 0.5mg fingolimod and 24% for placebo. Over the 24-month study period EDSS scores and MSFC z scores remained stable or improved slightly in the fingolimod group and worsened in the placebo group.

**MRI related measures**

Fingolimod was significantly superior to placebo with regard to MRI-related measures:

- Median (mean) new or enlarging T2-weighted lesions: 0.0 (2.5) for fingolimod and 5.0 (9.8) for placebo (p<0.001).
- Median (mean) gadolinium-enhancing lesions: 0.0 (0.2) for fingolimod and 0.0 (1.1) for placebo (p<0.001).
- Median (mean) % change in brain volume at 24 months: -0.7 (-0.8) for fingolimod and -1.0 (-1.3) for placebo (p<0.001)
There was no significant difference in the magnitude of treatment effect between patients who had previously undergone disease modifying treatment and those who had not.

**Please note:** As stated in the SmPC¹, further analyses of clinical trial data⁸ demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients.

**Efficacy data versus an active comparator¹,⁶,⁹**

TRANSFORMS was a 1-year randomised, double-blind, double-dummy, active (interferon beta-1a)-controlled Phase III study of 1,280 patients (n=429 on 0.5 mg, 420 on 1.25 mg, 431 on interferon beta-1a, 30 µg by intramuscular injection once weekly). Median values for baseline characteristics were: age 36 years, disease duration 5.9 years, and EDSS score 2.0.

**Relapse rates**

Over 12 months, patients receiving 0.5mg fingolimod had a significantly lower annualised relapse rate than patients receiving interferon beta 1a, with a relative risk reduction of 52% (absolute relapse rate reduction of 0.17, p<0.001). In addition, 83% of those taking fingolimod remained relapse-free compared with 71% of those on interferon beta-1a (p<0.001).

In an extension study for TRANSFORMS over 24 months, patients receiving continuous 0.5mg fingolimod showed persistent benefits in ARR [n=356], 0·12 [95% CI 0·08–0·17] in months 0–12 vs. 0·11 [0·08–0·16] in months 13–24. In patients who initially received interferon beta-1a, ARR was lower after switching to fingolimod compared with the previous 12 months (interferon beta-1a to 0·5 mg fingolimod [n=167], 0·31 [95% CI 0·22–0·43] in months 0–12 vs. 0·22 [0·15–0·31], in months 13–24 p=0·049.

**Disability progression**

There was no significant difference in the proportion of patients with 3-month confirmed disability progression (defined as 1-point increase in EDSS confirmed 3 months later) treated with fingolimod or interferon beta 1a. There was a significant improvement in MSFC z scores from baseline for both fingolimod groups compared to the interferon group.

**MRI related measures**

At 12 months, fingolimod was significantly superior to interferon beta 1a with regard to MRI-related measures:

- Median (mean) new or enlarging T₂-weighted lesions: 0.0 (1.7) for fingolimod and 1.0 (2.6) for interferon beta 1a (p<0.01).
- Median (mean) gadolinium-enhancing lesions: 0.0 (0.2) for fingolimod and 0.0 (0.5) for interferon beta 1a (p<0.001)
- Median (mean) % change in brain volume over 12 months: -0.2 (-0.3) for fingolimod and -0.4 (-0.5) for interferon beta 1a (p<0.001).

After switching to fingolimod, numbers of new or newly enlarging T₂ and gadolinium (Gd)-enhancing T₁ lesions were significantly reduced for 0.5mg
Fingolimod compared with the previous 12 months of interferon beta-1a therapy (p<0.0001 for T2 lesions, p=0.002 for T1), and the pattern of adverse events shifted towards that typical for fingolimod.

There was no significant difference in the magnitude of treatment effect between patients who had previously undergone disease modifying treatment and those who had not.

Please note: As stated in the SmPC, further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients.

In randomized, double blind clinical trials, Copaxone (glatiramer acetate) has shown reductions of annualized relapse rate of 29% vs placebo and 35% reduction in MRI active lesions (Gd-enhanced T1 lesions) vs placebo. Avonex (interferon beta 1a) showed reductions in relapse rates of 32% vs placebo and 33% of MRI active lesions vs placebo (ref: Goodin DS et al. Neurology 2002; 58: 169-178).

Safety Profile

Fingolimod is generally well tolerated. More than 41,000 patients worldwide have been treated with fingolimod. There are up to 7 years monitoring of some patients in fingolimod clinical trials and monitoring is still ongoing.

In the phase III studies, the most commonly reported adverse events, seen in more than 10% of patients, were headache, influenza, diarrhoea, back pain, liver enzyme elevations, cough, fatigue, urinary tract infection and nasopharyngitis.

Specific identified AEs that were more frequently reported in patients treated with fingolimod and those that have specific observational requirements associated with them include:

**Bradyarrhythmias**

Initiation of fingolimod results in a transient decrease (within 4-5 hours) in heart rate, on average 12-13 bpm, which returns to baseline within 1 month of chronic treatment. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. All patients should be observed for a period of 6 hours for signs and symptoms of bradycardia.

**Macular Oedema**

Macular oedema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod, occurring predominantly in the first 3-4 months of therapy. An ophthalmological evaluation is recommended at 3-4 months after treatment initiation. In patients with diabetes mellitus or a history of uveitis an ophthalmological exam is recommended prior to initiating fingolimod therapy and periodically thereafter.
**Infections**
Peripheral lymphocyte count decreases to approximately 30% of baseline within 2 weeks. Upon fingolimod discontinuation, typically normal counts are reached within one to two months.

In clinical trials, the overall rate of infections (72%) and serious infections (2%) was similar to placebo. However, lower respiratory tract infections, primarily bronchitis and, to a lesser extent, pneumonia was more common in fingolimod-treated patients. Before initiating fingolimod, a recent complete blood count (CBC) (i.e. within 6 months) should be available. Initiation of treatment with fingolimod should be delayed in patients with severe active infection until resolution and VZV vaccination of antibody negative patients should be considered prior to commencing treatment with fingolimod.

**Reproductive toxicity**
Before initiation of treatment in women of childbearing potential a negative pregnancy test result needs to be available. While on treatment, women should not become pregnant and active contraception is recommended.

**Liver Transaminase Elevations**
During clinical trials, 8% of fingolimod patients had elevations ≥ 3X upper limit of normal (ULN) in liver transaminases versus 2% of placebo patients. Elevations 5X ULN occurred in 2% of patients on fingolimod and 1% of patients on placebo. Levels generally returned to normal within approximately 2 months after discontinuation of fingolimod. Recent (i.e. within the last six months) transaminase and bilirubin levels should be available before initiation of fingolimod and monitored at months 1, 3 and 6 on therapy and periodically thereafter.

**Hypertension**
In MS clinical trials, there was an average increase of approximately 3 mmHg in systolic pressure, and 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. Blood pressure should be regularly monitored during treatment with fingolimod.

**Bronchoconstriction**
In trials, at month 24, the reduction from baseline values in percentage of predicted FEV$_1$ was 3.1% for fingolimod and 2.0% for placebo and DLCO the reductions at month 24 were 3.8% for fingolimod and 2.7% for placebo. This generally started at month 1 and remained stable thereafter.

**Contraindications**
- Known immunodeficiency syndrome.
- Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
- Severe active infections, active chronic infections (hepatitis, tuberculosis).
- Known active malignancies, except for patients with cutaneous basal cell carcinoma.

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- Severe liver impairment (Child-Pugh class C).
- Hypersensitivity to the active substance or to any of the excipients.

**Cost-effectiveness**

**Numbers needed to treat**

FREEDOMS Study: NNT with fingolimod for 1 additional patient to remain relapse free after 2 years compared with placebo = 4

Clause 3.33 of NICE Technology Appraisal for fingolimod TA254 states that the ERG ran the manufacturer’s updated model including the patient access scheme and produced a probabilistic base-case ICER for fingolimod compared with Avonex of £14,997 per QALY gained. However, please be aware that the current NICE model may underestimate the numbers of patients suitable for treatment with Gilenya.

*NNT - Based on the following calculation:

**FREEDOMS:**

- Fingolimod 0.5mg (425 total patients)  
  - Placebo (418 total patients)

  Endpoint: Zero relapses at 24 months  
  - 299 patients  
  - 190 patients

  Proportion of patients benefiting from treatment  
  - 0.704  
  - 0.455

  NNT = 1 / (proportion benefiting from Fingolimod – proportion benefiting from placebo)

  NNT = 1 / (0.704 - 0.455)

  **NNT = 4 patients** (NNT with fingolimod for 1 additional patient to remain relapse free after 2 years compared with placebo)

- In order to calculate NNT, a dichotomous clinical end-point that measures the number of patients that meet a particular threshold is used (the number of patients relapse free at the end of the study). This allows the calculation of the absolute difference in the proportion of patients benefiting from an intervention versus those that benefit from the control.

- The closest approximation to a clinically relevant NNT calculation, given the constraints of IFN treatment failure data, can be derived from the available phase III studies:

  a. NNT of fingolimod vs. placebo (FREEDOMS) = 4 [please note, patients who fail on IFN therapy are typically not taken off active treatment].

  b. NNT of fingolimod vs. IFN (TRANSFORMS) = 8 [please note, this contains data from a mixed population of IFN naive and treatment experienced patients and assumes equivalent first line positioning of fingolimod to IFNs].

- With fingolimod licensed for use in IFN treatment failure patients, the most appropriate NNT calculation would be a NNT of fingolimod versus IFN treatment failures. There is no data to show how effective IFN is in treating IFN treatment failures and the pivotal clinical trials lack this data. As a result of these factors, NNT for fingolimod versus IFN treatment failures cannot be calculated.
Audit process for NICE guidance
Prescribing will be carefully audited and monitored in accordance with NICE guidelines.

Financial Impact

**Cost**
Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470.

**Dosage**
0.5mg orally once daily

The manufacturer should provide fingolimod with the discount agreed as part of the patient access scheme. – NICE Guidance - NICE TA254, published 25 April 2012.

Financial Resources
This recommendation was approved by the Minister to be funded from within the current Department of Health budget allocation.

Acknowledgements
Dr Christine Burness Consultant Neurologist, Noble’s Hospital, Isle of Man

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