

Fingolimod

Fact Sheet

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Fingolimod (Gilenya)

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1. Introduction

Fingolimod (also known as FTY720, brand name Gilenya) is an oral treatment licensed for people with rapidly evolving severe relapsing remitting MS (two or more relapses a year), and as a second line treatment for people whose MS remains active despite treatment with one of the beta interferon drugs or glatiramer acetate.

Fingolimod is also being investigated in phase III clinical trials for primary progressive multiple sclerosis.

In March 2011, the European Medicines Agency (EMA) approved fingolimod 0.5 mg daily as a second line disease modifying treatment to be used if people continue to have relapses or if their relapse rate has increased despite a year's treatment with one of the first line drugs (Avonex, Betaferon, Copaxone, Extavia, Rebif). It can also be used with people with rapidly evolving severe relapsing remitting MS - two or more relapses a year. Novartis launched fingolimod in the UK in April 2011.

The National Institute for Health and Clinical Excellence (NICE) began its appraisal of fingolimod in 2011¹. In August they issued a draft recommendation² that fingolimod was not a cost effective treatment for the NHS in England and Wales to provide. Following a period of consultation, this recommendation was confirmed in December 2011³. NICE has invited

comments on this second draft guidance⁴; the closing date for comments is 5 January 2012. NICE expects to publish its final guidance to the NHS in April 2012.

2. How fingolimod works?

The autoimmune attack that is seen in MS results in the destruction of myelin, the substance covering and protecting nerves in the central nervous system.

Fingolimod acts on certain types of white blood cells (lymphocytes) which are involved in this immune attack. It attaches to special locations (or receptors) on the surface of lymphocytes, called sphingosine-1-phosphate receptors (S1P-R). This causes a large proportion of the lymphocytes to be retained in the lymph nodes which are part of the body's immune system. This reduces the number of lymphocytes circulating in the blood. The number of lymphocytes reaching the central nervous system is decreased, resulting in reduced immune attack on nerve cells in the brain and spinal cord⁵.

In addition, there is evidence that fingolimod may have a direct effect on nerve cell damage and enhance remyelination by acting on sphingosine receptors in the central nervous system^{6,7}.

3. Trials of fingolimod

Phase II

The first study reporting the results of fingolimod in relapsing remitting MS was published in 2007⁸. In this clinical trial 255 people took one of two daily doses of fingolimod (1.25mg or 5.0mg) or placebo for six months.

Inflammation measured on MRI scans was significantly reduced in the two treatment groups when compared to placebo. The relapse rate for people in the two treatment groups was also significantly lower.

In an extension of this study, those receiving fingolimod continued with their treatment, while those on placebo switched to one of the two doses of fingolimod. 227 people completed the six month extension; the number of MRI lesions and relapse rates remained low in the groups receiving continuous treatment with fingolimod and decreased in those switching from placebo.

Results of a further extension of this study have also been published. At two years, 79-91% of participants were free from inflammation measured on MRI scans and up to 77% remained relapse free. During the course of this extension those on the higher dose of fingolimod were switched to 1.25mg because analysis of the data indicated that the higher dose offered no advantage in effectiveness and was associated with a higher incidence of side effects⁹. 155 people have subsequently been followed for up to 48 months. Relapse rates and inflammatory activity on MRI scans have remained low¹⁰.

Phase III

Following the promising results from the phase II studies, several phase III studies were set up.

TRANSFORMS

TRANSFORMS (Trial assessing injectable interferon vs FTY720 oral in RRMS) was a one year phase III study, which has now completed. It compared two doses of fingolimod (0.5mg and 1.25mg) against interferon beta-1a (Avonex) in 1,292 people with relapsing remitting MS.

Analysis of the data reported the relapse rates at one year were 0.33 for interferon beta-1a, 0.16 on the lower dose of fingolimod (a reduction of 52% compared to interferon beta-1a) and 0.2 on the higher dose (a 38% reduction). 80-83% of the fingolimod groups remained relapse-free over the year compared with 69% of those on interferon beta-1a¹¹.

Patients who completed the TRANSFORMS study were given the option to continue in an extension study; 1027 of the initial 1153 participants (89%) chose to continue. Those already taking either dose of fingolimod stayed on the same dose. Those taking interferon beta-1a were reassigned to 0.5 or 1.25mg fingolimod. One year into this extension study, relapse rates and inflammatory activity on MRI scans were significantly lower for those taking fingolimod for the entire two year period, compared to those switching to fingolimod at the beginning of the second year¹².

FREEDOMS

FREEDOMS (FTY720 research evaluating effects of daily oral therapy in multiple sclerosis) was a double-blind, placebo-controlled study involving 1,272 people with relapsing remitting MS in 22 countries. Participants received one of two doses of fingolimod or placebo over two years.

Fingolimod reduced the relapse rate by 54% for the lower dose (0.5mg) and by 60% for the higher dose (1.25mg) compared to placebo. The reduction of progression of disability was 30% and 32% respectively compared to placebo¹³.

Participants in the FREEDOMS trial will be invited to take part in an extension of this study, to measure long-term safety and effectiveness¹⁴.

FREEDOMS II

This study is essentially the same as FREEDOMS, recruiting over 1,000 participants mostly in North America¹⁵.

INFORMS

Initial findings suggest that fingolimod may have a direct effect on nerve repair^{6,7}. The purpose of the INFORMS (FTY720 in patients with primary progressive multiple sclerosis) study is to evaluate whether fingolimod (0.5mg or 1.25mg capsules taken daily for 3 years) is effective in delaying disability progression compared to placebo in 654 people with primary progressive MS¹⁶. This study is not due to finish until December 2013.

4. Side effects and contraindications

Although the trials so far have shown fingolimod to be well tolerated, the side effects that have occurred include headache, upper respiratory tract infection, shortness of breath, diarrhoea and nausea. In addition, increased levels of liver enzymes and blood pressure have been observed although these are generally mild.

In the TRANSFORMS clinical trial, two deaths resulting from herpes virus infections occurred in patients taking the higher dose of fingolimod. Other aspects of the treatments these two patients received may have contributed, but a role for fingolimod cannot be excluded given its immunomodulatory action, which could lead to an increased risk of infections.

In addition, in the TRANSFORMS trial, eight cases of localised skin cancer occurred in the fingolimod groups and were successfully removed. Macular oedema (swelling in the back of the eye) also occurred more frequently in the fingolimod-treated participants. In the extension to the TRANSFORMS study, side effects were similar to those reported in the initial trial year, and included further new cases of skin cancer, herpes virus infections, cardiac disorders and macular oedema, all of which were more common in those on the higher dose¹². No instances of macular oedema or skin cancer occurred during the FREEDOM trial¹³.

Note. Drug trials

Phase I studies primarily assess the safety of a drug or procedure. They usually involve a small number of healthy volunteers (10-100) all of whom are given the same treatment.

Once a medical intervention has been proven safe, phase II trials test its effectiveness and whether it has the potential to be of benefit. These trials are larger, typically involving 100-300 people with the condition for which the intervention has been developed - in this case MS.

If the phase II study shows the treatment to be beneficial, phase III studies are conducted to gain a definitive understanding of the effectiveness, benefits and potential side effects in a large group of people (300-3,000) with the condition to be treated. Interventions have to successfully complete a phase III trial before they can be considered for a licence by regulatory authorities.

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