

# Fingolimod (Gilenya)

# Fact Sheet



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**Freephone** 0800 032 3839 (Lines are open Monday – Friday 9am-5pm)

**email** [infoteam@mstrust.org.uk](mailto:infoteam@mstrust.org.uk)

**write** MS Trust  
Spirella Building  
Letchworth Garden City  
SG6 4ET



# Fingolimod (Gilenya)

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## Contents

<b>1. Introduction</b>	<b>1</b>
<b>2. How does fingolimod work?</b>	<b>2</b>
<b>3. Trials of fingolimod</b>	<b>2</b>
<b>4. How is fingolimod given?</b>	<b>3</b>
<b>5. Side effects and contraindications</b>	<b>4</b>
<b>6. References</b>	<b>6</b>

## 1. Introduction

Fingolimod (brand name Gilenya) is licensed as a second line disease modifying treatment for people with relapsing remitting multiple sclerosis who continue to have relapses or if their relapse rate has increased despite a year's treatment with one of the first line beta interferons (Avonex, Betaferon, Extavia, Rebif). It is also licensed for treating people with rapidly evolving severe relapsing remitting MS - two or more relapses a year.

The National Institute for Health and Clinical Excellence (NICE) began its appraisal of fingolimod in 2011<sup>1</sup>. In March 2012 they issued a final appraisal determination<sup>2</sup> recommending that fingolimod be available on the NHS in England and Wales for people whose relapse rate remains unchanged or worsens despite a year's treatment with one of the beta interferon drugs. This is a subgroup of the population for which fingolimod is licensed. NICE expects to publish its final guidance to the NHS in April 2012.

The Scottish Medicines Consortium announced in March 2012 that fingolimod is not recommended for use in Scotland, stating that the submitting company (Novartis) did not present a sufficiently robust economic analysis<sup>3</sup>.

Fingolimod is also being investigated in phase III clinical trials for primary progressive multiple sclerosis (see section 3).

## **2. How does fingolimod work?**

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, reducing 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 cord<sup>4</sup>.

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<sup>5,6</sup>.

## **3. Trials of fingolimod**

### **Relapsing remitting MS**

Two main studies have provided the evidence to support licensing of fingolimod for relapsing remitting MS:

- The FREEDOMS trial compared two doses of fingolimod with placebo
- The TRANSFORMS trial compared two doses of fingolimod with interferon beta-1a

### **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 placebo<sup>7</sup>.

Participants in the FREEDOMS trial were invited to take part in an extension of this study, to assess long-term safety and effectiveness<sup>8</sup>.

## **TRANSFORMS**

TRANSFORMS (Trial assessing injectable interferon vs FTY720 oral in RRMS) was a one year phase III study. 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-1a<sup>9</sup>.

Patients who completed the TRANSFORMS study were given the option to continue in an extension study; 1,027 of the initial 1,153 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 year<sup>10</sup>.

## **Primary progressive MS**

### **INFORMS**

Laboratory investigations provided evidence that, in addition to its effect on the immune system, fingolimod may have neuroprotective and remyelinating properties in the brain and spinal cord<sup>5,6</sup>. This potential is being evaluated by the INFORMS phase III trial (FTY720 in patients with primary progressive multiple sclerosis). This double blind study is testing whether fingolimod (0.5mg capsules, taken daily for three years) is effective in delaying disability progression compared to placebo in 951 people with primary progressive MS<sup>11</sup>. The study is due to finish in September 2014.

## **4. How is fingolimod given?**

Fingolimod is taken orally as capsules. The standard dose is one 0.5mg capsule daily.

## **5. Side effects and contraindications**

### **Heart side effects**

Fingolimod causes a temporary bradycardia (decrease in the heart rate) and may be associated with atrioventricular block (a type of heart rhythm disorder)<sup>7,9</sup>. For this reason, people should take their first dose of fingolimod under medical supervision and be monitored for signs and symptoms of bradycardia for at least six hours.

The European Medicines Agency (EMA) carried out a formal safety review of fingolimod after reports of people experiencing heart problems, cases of sudden or unexplained deaths, and the death of one person in the USA within 24 hours of receiving their first dose. The EMA concluded that the benefits of fingolimod outweigh the risks and gave more detailed recommendations for monitoring heart rate and blood pressure after the first dose<sup>12</sup>.

### **Herpes virus infections**

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.

### **Other potential side effects**

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 dose<sup>10</sup>. No instances of macular oedema or skin cancer occurred during the FREEDOMS trial<sup>7</sup>.

Commonly reported side effects of fingolimod include headache, chest infection, shortness of breath, diarrhoea and nausea. In addition increased

levels of liver enzymes have been observed although these are generally mild.

Blood tests will generally be carried out before starting and during the first year to check for any effect of fingolimod on the liver. Eye examinations for macular oedema may also be carried out 3-4 months after starting treatment.

### **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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