# Protocol

# Fingolimod (Gilenya®) treatment of relapsing-remitting multiple sclerosis (MS)

## 1 Scope

Treatment of patients with a diagnosis of multiple sclerosis by the MS team at Cambridge University Hospitals NHS Foundation Trust (CUH).

## 2 Purpose

To ensure the safe administration of fingolimod (Gilenya®).

## 3 Introduction

Fingolimod is indicated for treatment of people with highly active relapsing-remitting multiple sclerosis if they have an unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year, despite treatment with beta interferon, glatiramer acetate or dimethyl fumarate.

It is also indicated for patients treated with natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML):

a) anti-JCV IgG antibody status positive
b) have received an immunosuppressant prior to natalizumab
c) have been treated with natalizumab for more than two years

The use of Fingolimod in women of child bearing potential should be carefully considered due the risks of teratogenicity (see section 6.1).

## 4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to carry out the procedure.

## 5 Clinical equipment list

12 lead ECG (pre-treatment screening and pre and post first dose)
Vital signs monitor

# 6 Treatment

## 6.1 Eligibility and screening

Patients will have been assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. NICE technology appraisal guidance TA254 Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (2012) will be followed when assessing eligibility. Risks and benefits will have been discussed. Medications and co-morbidities will have been documented on Epic.

**Pre-treatment screening** will have occurred in the outpatient clinic setting:

- Neurologist asks patient if any concerning **skin lesions**, reviews lesions and refers patient to dermatology if necessary.
- Screening blood tests are sent as outlined in the Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- Vaccine advice given as per Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- 12 lead electrocardiogram (ECG)
- Baseline expanded disability status scale (EDSS)
- Baseline MRI brain scan ordered (should be done within three months of starting treatment)
- Pregnancy, breast feeding and importance of contraception whilst on treatment discussed and documented
- If history of diabetes or uveitis, the patient is referred for baseline ophthalmic assessment to exclude macular oedema
- If history of cardiovascular or cerebrovascular disease patient will have been referred to cardiologist for risk/ benefit assessment

In September 2019, the MHRA issued an alert on the safety of fingolimod (Gilenya) in pregnancy after data from international pregnancy registers demonstrated that exposure in pregnancy leads to an estimated additional two to three major congenital malformations per 100 livebirths compared with the general population (a two-fold increase). Reported malformations include congenital heart disease, such as tetralogy of Fallot, atrial and ventricular septal defects, and renal and musculoskeletal abnormalities. If a woman of childbearing potential is started on fingolimod, she must be informed of the risk of teratogenicity. She must have a negative pregnancy test before receiving the first dose. She should be regularly advised to use effective contraception during treatment and for at least two months after stopping it. Women should be advised that recurrence of disease activity, which can be substantial, may occur after stopping fingolimod to get pregnant. Women of child bearing potential will be counselled of the risks of teratogenicity in the MS clinic and the risks are outlined in the standard consent letter.

**When the patient decides to start fingolimod the MS nurse:**

- Sends a standard letter recording the consent discussions to the patient with copy to GP (using smart text .FINGOLIMODCONSENT). This is sent prior to the admission for the first dose.
- Ensures Blueteq form is completed and patient added to database.
- MS nurse explains the delivery service.
- MS nurse explains to patient plan for Ophthalmology review and pupil dilatation at month 3. MS nurse alerts ophthalmology (via ophthalmology secretary) to expect the patient for screening at month 3

## 6.2 Contraindications and cautions

- Active malignancies including basal cell carcinoma
- Immune deficiency or immune suppression
- Severe active infection or chronic infections (eg hepatitis, tuberculosis)
- Severe liver impairment
- Severe lung disease
- Pregnancy and breastfeeding.
- Hypersensitivity to the active substance or to any of the excipients
- Certain cardiac conditions (advice should be sought from a cardiologist prior to initiation if the patient has a cardiac history) :
    - Second degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, significant QT prolongation, Class III/IV heart failure, and uncontrolled hypertension.
- Patients treated with class Ia or class III antiarrhythmic medicine (risk of torsades de pointes). Fingolimod only to be prescribed on a risk vs benefit basis in patient taking drugs which reduce heart rate (beta-blockers and rate-limiting calcium channel blockers).

## 6.3 Dosage

The dose of fingolimod is 0.5 mg taken orally once daily. This can be taken with or without food. Please see the required monitoring for the first dose.

### 6.3.1 Side effects

Fingolimod is normally well tolerated however the following side effects can occur.

**Very common and common**

- Can increase the risk of infections eg influenza, sinusitis, herpes viral, bronchitis. **During the COVID-19 pandemic the ABN Guidance On The Use Of Disease-Modifying Therapies In Multiple Sclerosis In Response To The COVID19 Pandemic will be followed** (Date: August 2021, published 26/10/21).
- Basal cell carcinoma – see follow up and management
- Lowering in WBC. NB: Lymphopenia (to be expected – see follow up and management)

- Elevated liver function tests
- Depression
- Headache and migraine
- Dizziness
- Bradycardia and AV Block with the first dose – see 'first dose' section
- Hypertension
- Cough and dyspnoea
- Diarrhoea
- Eczema, alopecia and pruritus
- Back pain, myalgia and arthralgia
- Asthenia
- Blood triglycerides increased
- Blurred vision and macular oedema – see follow-up and monitoring

**Uncommon**

- Pneumonia
- Malignant melanoma
- Thrombocytopenia
- Seizure
- Nausea
- Neutrophil count decreased

Progressive multifocal leukoencephalopathy – a small number of cases of PML have been reported in patients who have not previously received natalizumab.

## 6.4 Switching to fingolimod from other therapies

When switching disease modifying treatment the following breaks in treatment are required prior to commencing fingolimod:

- **Beta interferon or glatiramer acetate**: no wash out period is required prior to starting fingolimod.
- **Natalizumab**: there must be no exposure to natalizumab for one to two months prior to fingolimod.

## 6.5 Prescription and booking first dose

- MS nurse arranges date for day admission and informs Outpatient pharmacy of the date supply will be required. Asks for Blueteq form to be completed by MS secretary.
- MS nurse asks consultant neurologist to prescribe outpatient fingolimod on Epic as per following:
- Consultant neurologist prescribes 28 days of treatment on Epic (Outpatient Pharmacy) with 0 refills as follows:
    - Epic button top left of screen -> orders only -> enter patient hospital number -> select patient

- Orders only tab -> 'problem list' section -> ensure relapsing remitting multiple sclerosis entered -> add problem to visit diagnosis by clicking on the icon of a piece of paper with an arrow (next to resolve button)
- In orders only tab go to 'medication and orders' section -> new order box, put cursor in box and press enter -> brings up preference list browser -> DMTs (OP meds) -> tick box for fingolimod capsule 500mcg -> select
- Automatically brings up prescription 'Fingolimod 500 micrograms capsule, take one capsule once daily for 28 days'
- Click on this to open and check details are correct as follows:
  - Fingolimod 500 micrograms capsule
  - Intended use multiple sclerosis as per NHSE policy
  - Dose 500mcg, route oral
  - Frequency daily
  - Duration 28 days
  - **Enter start date**
  - Marked long term
  - Patient instruction 'Take one capsule once daily for 28 days'
  - Dispense 28 capsule, refill 0
    - Class: Outpatient Pharmacy
    - Accept
    - Sign prescription
    - Then sign visit
- MS secretary should be informed of the new starter and prepare the homecare prescription for signing and supply to pharmacy neurology team for screening.

### 6.6 First dose administration

- MS nurse collects fingolimod from Outpatient Pharmacy (preferably on the day before the patient is due for admission).
- Patient attends the infusion unit in the morning, infusion nurse does the following:
  - Asks female patients if there is a possibility of pregnancy and does a pregnancy test in all women of childbearing potential.
  - Records baseline pulse and blood pressure (BP). If pulse rate is below 45 beats per minute consult the neurology doctor prior to administration.
  - Baseline 12 lead ECG

- 12 lead ECG shown to the neurology SpR, if normal the doctor prescribes on the Epic inpatient chart a single dose of fingolimod 500mcg orally
- 1x fingolimod 500mcg capsule administered by nurse
- Hourly pulse and BP recorded for six hours after the first dose
- Follow Trust protocol if an allergic reaction or anaphylaxis occur

- Repeat ECG performed after six hours
- Neurology SpR checks ECG and reviews heart rate to confirm discharge (see criteria for extended cardiac monitoring)
- Supply of fingolimod for 28 days given to patient to take home
- MS nurse sends discharge letter to GP using smartphrase. FINGOLIMODFIRSTDOSE and checks the plan is in place for Ophthalmology review and pupil dilatation at month 3 and MS nurse follow up at month 3. MS nurse alerts ophthalmology (via ophthalmology secretary) to expect the patient for screening at month 3

### 6.7 Criteria for extended cardiac monitoring

Monitor for an extra two hours if:

- Heart rate at six hours is at its lowest since taking fingolimod

Monitor overnight if:

- Pre-existing cardiovascular problems
- New onset of second degree atrioventricular block, Mobitz Type II on ECG
- New onset third degree atrioventricular block on ECG
- Symptomatic bradycardia, particularly if intervention with atropine or isoprenaline has been required
- Heart rate at six hours is less than 45 beats per minute
- QTc interval is greater than 500ms on ECG

## 7 Follow up and monitoring

### 7.1 Outpatient appointments and safety monitoring

Patients are to be monitored after treatment, in a clinic setting, by consultant neurologist and team with special interest in MS. Clinic follow-up should be tailored to the needs of the patient, below is the minimum clinic review schedule:

- MS nurse clinic review at month 3, ensures booked for ophthalmology screening and sends patient to ophthalmology department (clinic 14).
- Ophthalmology department should have entered ophthalmology result onto Epic within two weeks, MS nurse to check. Responsibility for Fingolimod ophthalmology review lies with the nurse doing the month 3 appointment, if despite the MS nurse's best efforts the ophthalmology outcome is not documented on EPIC it should be escalated to the doctor.
- Year 1 MS nurse reviews (asks about skin lesions)
- Year 2 Dr (reviews skin lesions + EDSS)
- Then alternate nurse/Dr annually if stable

To date there have been 151 cases of basal cell carcinoma reported on fingolimod treatment. **The neurologist/MS nurse will ask the patient annually if they have any concerning skin lesion**, review the lesion and refer to dermatology if necessary.

Any pregnancies on fingolimod will be reported to the fingolimod pregnancy register: www.gilenyapregnancyregistry.com and direct to Novartis uk.patientsafety@novartis.com .

To date there have been a small number of cases of PML in patients on fingolimod who have not previously received natalizumab. If PML is suspected, MRI brain should be performed immediately and treatment with fingolimod should be suspended until PML has been excluded.

### 7.2 Blood Monitoring

- Month 1 and 3 (FBC, LFT), then if LFT normal 6 monthly FBC and LFT.
- After month 12 if bloods stable can reduce to annual FBC and LFT during the COVID19 pandemic in line with the ABN Guidelines Oct 2021.
- Suspend fingolimod if the lymphocyte count is $0.1x10^9$/l or less.
- If the lymphocyte count is > $0.1x10^9$/l **but** < $0.2x10^9$/l confirm the result on a repeat of the FBC.
- If confirmed, monitor the FBC and patient closely for signs of infection (including PML) and consider suspending fingolimod.
- Suspend fingolimod if serum hepatic transaminases 5x upper limit of normal. If there is doubt that fingolimod was the cause and LFT recover can restart fingolimod and monitor closely.
- If no symptoms of liver injury and ALT greater than 3x ULN but less than 5xULN, and bilirubin normal, continue fingolimod and monitor more frequently.

### 7.3 Treatment breaks/ missed doses

If a patient has a break in treatment for any reason they may need to be re-admitted for cardiac monitoring as per first dose when re-starting:

- Fingolimod stopped for 1 day or more in the first two weeks of treatment.
- Fingolimod stopped for >7 days in the 3rd and 4th week of treatment.
- Fingolimod stopped for >14 days after the first month on treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

## 8 Stopping criteria

- Development of secondary progression with sustained loss of ambulation for greater than six months
- No reduction in frequency or severity of relapses compared with pre-treatment following at least three months of fingolimod
- Unacceptable adverse effects
- Allergic reaction to fingolimod
- Macular oedema
- Unresolved brady-arrhythmia

- Pregnancy and breast feeding
- Confirmed reduction in lymphocyte count to less than $0.1x10^9$/l (consider stopping if lymphocyte count is greater than $0.1x10^9$/l but less than $0.2x10^9$/l)
- Recurrent infections requiring medical treatment or single serious infection
- Elevation in serum levels of hepatic transaminases. 5x upper limit of normal (can retry when normalised)
- Persistent failure to keep booked appointments
- Patients need to continue to use effective contraception and report signs or symptoms of infection for two months after treatment is stopped

## 9 Monitoring compliance with and the effectiveness of this document

(a) Process for monitoring compliance and effectiveness

- Patients will be assessed as a minimum every 12 months for continued eligibility for treatment by consultant neurologist or MS specialist nurse
- Patients will agree before starting treatment: to comply with treatment protocol, keep appointments and contact relevant healthcare professionals in the event of changes in their underlying MS condition or suspected side effects
- Ongoing maintenance of database of patients offered treatment, undergoing treatment and stopping treatment, including reason for stopping treatment, will be kept by the MS specialist nurse to audit against NICE guidelines
- The MS team will be vigilant for post marketing safety data.

(b) Standards/ key performance indicators

- The audit department will request evidence of compliance with NICE guideline.
- Internal checks on safety, compliance and efficacy will be undertaken by MS team.

## 10 References

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