ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

Conditions or restrictions with regard to the safe and effective use of medicinal product to be implemented by the member states

The Member States shall agree the final educational material with the Marketing Authorisation Holder (MAH) prior to launch in their territory.

The Member States shall ensure that, at launch and after launch, the MAH provides all physicians who intend to prescribe GILENYA with an updated physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder card

The physician's checklist shall contain the following key messages:

- Monitoring requirements at treatment initiation
  Before first dose
  - Perform baseline ECG prior to the first dose of GILENYA (or when the last dose of GILENYA was more than two weeks previously).
  - Perform blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA was more than two weeks previously).
  - Perform a liver function test prior to treatment initiation.
  - Arrange ophthalmological assessment prior to initiation with GILENYA in patients with diabetes mellitus or with a history of uveitis.

  Until 6 hours after first dose (or if the last dose of GILENYA was more than two weeks previously)
  - Monitor the patient for 6 hours after the first dose of GILENYA has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time) ECG monitoring is recommended.
  - Perform an ECG at the end of the 6-hour monitoring period.

  >6 to 8 hours after first dose (or if the last dose of GILENYA was more than two weeks previously)
  - If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- Recommendation for overnight monitoring after the first dose (or if the last dose of GILENYA was more than two weeks previously).

  Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
  - Requiring pharmacological intervention during monitoring at treatment initiation.
  - With third degree AV block occurring at any time.
  - Where at the 6-hour time point:
    - Heart rate <45 bpm.
    - New onset second degree or higher AV block.
    - QTc interval ≥500 msec.

- That GILENYA is not recommended in patients with:
  - Second degree Mobitz Type II or higher AV block
  - Sick-sinus syndrome
  - Sino-atrial heart block
  - QTc prolongation >470 msec (females) or >450 msec (males)
  - Ischaemic cardiac disease including angina pectoris
  - Cerebrovascular disease
  - History of myocardial infarction
  - Congestive heart failure
  - History of cardiac arrest
  - Severe sleep apnoea
  - History of symptomatic bradycardia
  - History of recurrent syncope
  - Uncontrolled hypertension

  If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.

- GILENYA is not recommended in patients concomitantly taking Class Ia or Class III anti-arrhythmic medicines.

- GILENYA is not recommended in patients concomitantly taking medicines which are known to decrease the heart rate. If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non heart-rate-lowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended.

- GILENYA reduces peripheral blood lymphocyte counts. There is a need to check the patient's peripheral lymphocyte count (CBC) prior to initiation and to monitor during treatment with GILENYA.

- GILENYA may increase the risk of infections. Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Concomitant treatment with immunosuppressant or immune-modulating medicines should be avoided.

- The need to instruct patients to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.

- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.

- The need for a full ophthalmological assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular oedema.

- The need for ophthalmological assessment during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need for a negative pregnancy test result prior to treatment initiation. This should be repeated at suitable intervals.

- The need to advise women of child-bearing potential on the serious risk to the foetus and the need to practice effective contraception during treatment and for at least two months following discontinuation of treatment with GILENYA.

- The need for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- That they will have a baseline ECG and blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago).

- That their heart rate will need to be monitored for 6 or more hours after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago), including hourly pulse and blood pressure checks. Patients may be monitored with a continuous ECG during the first 6 hours. They will need an ECG at 6 hours and in some circumstances monitoring may involve an overnight stay.

- The need to report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of GILENYA.

- GILENYA is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate and they should tell any doctor they see that they are being treated with GILENYA.

- The signs and symptoms of infection and the need to report these immediately to the prescriber during and up to two months after treatment with GILENYA.

- The need to report any symptoms of visual impairment immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.

- That GILENYA is teratogenic so women with childbearing potential must:
  - Have a negative pregnancy test.
  - Be using effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
  - Report any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA immediately to the prescriber.

- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.