Annex 6 - Details of proposed additional risk minimization activities (if applicable)

This annex contains key messages of the proposed educational program for Gilenya (fingolimod), which includes a Physician's checklist for adult and pediatric patients, a Patient / Parent / Caregiver guide, and a Pregnancy-specific patient reminder card.

Approved Key Messages of the Additional Risk Minimization Measures

Physician's checklist

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
  - Perform blood pressure measurement prior to the first dose of GILENYA
  - Perform liver function test, including transaminases and bilirubin, prior to (within 6 months) treatment initiation
  - Arrange ophthalmological assessment before starting GILENYA treatment in patients with diabetes mellitus or with a history of uveitis
  - A negative pregnancy test result must be confirmed prior to starting treatment

  Until 6 hours after first dose

  - 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

  - 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 re-initiating GILENYA therapy after treatment interruption
  - The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for
  - One day or more during the first 2 weeks of treatment;
  - More than 7 days during weeks 3 and 4 of treatment;
  - More than 2 weeks after at least 1 month of treatment

- Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation)
  - 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/re-initiation. Repeat the first dose monitoring after the second dose of GILENYA.

- Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
  - With third degree AV block occurring at any time.
  - Where at the 6-hour time point:
  a. Heart rate <45 bpm, <55 bpm in pediatric patients aged 12 years old and above, or <60 bpm in pediatric patients 10 to below 12 years of age;
  b. New onset second degree or higher AV block;
  c. QTc interval ≥500 msec.

- GILENYA is contraindicated in patients with:
  - 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;
  - Severe liver impairment (Child-Pugh class C);
  - In the previous 6 months, myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure;
  - Severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products;
  - Second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker;
  - Patients with a baseline QTc interval ≥500 msec;
  - Pregnant women and women of childbearing potential not using effective contraception;
  - Hypersensitivity to the active substance or to any of the excipients.

- GILENYA is not recommended in patients with:
  - Sino-atrial heart block;
  - QTc prolongation >470 msec (adult females), QTc >460 msec (paediatric females) or >450 msec (adult and pediatric males);
  - History of cardiac arrest;
  - Severe sleep apnea;
  - 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 medicines 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. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored during treatment with GILENYA. Treatment should be interrupted if lymphocyte count is confirmed as $<0.2x10^9$/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of $\leq$ 40 kg) when restarting Gilenya should be administered. Other dosing regimens have not been approved.
- GILENYA has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.
    - 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. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.
    - Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Specific recommendations regarding vaccination for patients initiating GILENYA treatment.
    - Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is

recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.
  - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; appropriate treatment, if diagnosed, should be initiated.
  - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on GILENYA treatment.
  - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown
  - Cases of progressive multifocal leukoencephalopathy (PML) have occurred after approximately 2-3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with GILENYA should be suspended until PML has been excluded.
  - Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.
- A full ophthalmological assessment should be considered:
  - 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema.
  - During treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.
- GILENYA is teratogenic. It is contraindicated in women of childbearing potential (including female adolescents) not using effective contraception and in pregnant women,
  - A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
  - Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of GILENYA to the foetus, facilitated by the pregnancy-specific patient reminder card.
  - Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation.
  - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, GILENYA must be discontinued. When stopping GILENYA therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered. Medical advice should be given regarding the risk of

harmful effects to the foetus associated with GILENYA treatment and ultrasonography examinations should be performed.
- GILENYA must be stopped 2 months before planning a pregnancy.
- Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the GILENYA pregnancy registry.

- Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. Therefore, liver function should be monitored carefully.
  - Before initiation of treatment, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available;
  - During treatment, in the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation;
  - During treatment, in the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, Gilenya should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), Gilenya may be restarted based on a careful benefit-risk assessment of the patient;
- The approved dosing of 0.5 mg daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of ≤40 kg) should be administered. Other dosing regimens have not been approved.
- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping GILENYA. The possibility of recurrence of exceptionally high disease activity should be considered.
- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.
- Physicians should reassess on an annual basis the benefit of GILENYA treatment versus risk in each patient, especially pediatric patients.
- Physicians should provide patients/parents/caregivers with the patients/parents/caregiver's guide and with the pregnancy-specific patient reminder card.

The safety profile in pediatric patients is similar to adults and therefore the warnings and precautions in adults also apply for pediatric patients.

Specifically, with pediatric patients, physicians should also:
- Assess Tanner staging and measure height and weight as per standard of care;
- Perform cardiovascular monitoring;
- Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;

- Monitor the patient for sign and symptoms of depression and anxiety;
- Emphasize treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
- Emphasize GILENYA immunosuppressive effects;
- Consider a complete vaccination schedule before starting GILENYA;
- Provide guidance on seizure monitoring.

Patient/Parent/Caregiver's guide

The patient/parents/caregiver guide shall contain the following key messages:

- What GILENYA is and how it works;
- What multiple sclerosis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG and blood pressure measurement prior to receiving the first dose of GILENYA.
- Heart rate should be monitored for 6 or more hours after the first dose of GILENYA, including hourly pulse and blood pressure checks. Patients may be monitored with a continuous ECG during the first 6 hours. An ECG at 6 hours should also be performed and, in some circumstances, monitoring may involve an overnight stay.
- Patients should call their doctor in case of treatment interruption as the 1st dose monitoring may need to be repeated, depending on duration of interruption and time since starting of GILENYA treatment.
- Patients should 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.
- Signs and symptoms of infection, which should be immediately reported to the prescriber physician during and up to two months after GILENYA treatment, including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, either caused by a fungal or viral infection);
    - Symptoms such as weakness, visual changes, or new/worsening MS symptoms (may be symptoms of progressive multifocal leukoencephalopathy [PML]).

- The need to undergo cancer screening, including Pap test, and vaccination for HPV-related cancer, as per standard of care, will be assessed by the prescriber physician.
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.
- GILENYA is teratogenic. Women of child-bearing potential, including adolescent females, should:

  - Be informed before treatment initiation and regularly thereafter by their physician about GILENYA's serious risks to the foetus, and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the pregnancy-specific patient reminder card.
  - Have a negative pregnancy test before starting GILENYA;
  - Be using effective contraception during and for at least two months following discontinuation of GILENYA treatment;
  - Report immediately to the prescribing physician any (intended or unintended) pregnancy during and up to two months following discontinuation of GILENYA treatment;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter, until 2 months after Gilenya discontinuation. Patients should inform their doctor if they notice yellowing of their skin or the whites of their eyes, abnormally dark urine, pain on the right side of the stomach area, tiredness, feeling less hungry than usual or unexplained nausea and vomiting as these can be signs of liver injury;
- Skin cancers have been reported in multiple sclerosis patients treated with GILENYA. Patients should inform their doctor immediately if any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape or size over time;
- Seizure may occur. The doctor should be informed about a pre-existing history or family history of epilepsy;
- Stopping GILENYA therapy may result in return of disease activity. The prescribing physician should decide whether and how the patient should be monitored after stopping GILENYA.

Specifically for Pediatric patients:

The following should be considered:

- Physicians should assess Tanner staging and measure height and weight as per standard of care;
- Precautions should be taken during the first dose of GILENYA and when patients are switched from 0.25 to 0.5 mg daily;
- Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population and have been reported also in pediatric patients treated with GILENYA;
- Cardiac monitoring guidance;
- Patients should ensure medication compliance and avoid misuse, especially treatment interruption, and repeat cardiac monitoring;
- Signs and symptoms of infection;
- Seizure monitoring guidance.

Pregnancy-specific patient reminder card

The pregnancy-specific patient reminder card shall contain the following key messages:

- GILENYA is contraindicated during pregnancy and in women of childbearing potential not using effective contraception;
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the teratogenic risk of GILENYA and required actions to minimise this risk.
- Patients must use effective contraception while taking GILENYA;
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals;
- Patients will be informed by their doctor of the need foreffective contraception while on treatment and for 2 months after discontinuation;
- Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy;
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, GILENYA must be discontinued;
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with GILENYA;
- Women exposed to GILENYA during pregnancy are encouraged to join the pregnancy exposure registry that monitors outcomes of pregnancy.