נובמבר 2020

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Gilenya 0.5 mg
גילניה 0.5 מ״ג

התכשיר שבנדון רשום בישראל להתוויה הבאה:

Gilenya is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

המרכיב הפעיל: Fingolimod 0.5 mg

אנו מודיעים על עדכונים בעלון לרופא ובעלון לצרכן.

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בברכה,

רוני דוידוביץ׳
רוקחת ממונה

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

נוברטיס ישראל בע״מ
רח׳ תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

Gilenya 0.5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GILENYA is provided as 0.5 mg hard gelatin capsules for oral use.

Each 0.5 mg capsule contains 0.56 mg of fingolimod hydrochloride, equivalent to 0.5 mg of fingolimod.

For the full list of excipients, see section 12.

3 PHARMACEUTICAL FORM

Hard capsule.

Hard capsules with a white opaque body and bright yellow opaque cap; radial imprint in black ink "FTY 0.5 mg" on the cap and 2 radial bands imprinted on the capsule body with yellow ink.

Fingolimod hydrochloride is a white to almost white crystalline powder.

4 THERAPEUTIC INDICATIONS

Gilenya is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

5 DOSAGE AND ADMINISTRATION

General target population

The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily, which can be taken with or without food.

If a dose is missed, treatment should be continued with the next dose as planned.

Before initiating treatment with Gilenya, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count <0.2x109/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0.2x109/l.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya. In the absence of clinical symptoms, liver transaminases should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminase values have normalised.

For recommendations related to switching patients from other disease modifying therapies to Gilenya, see section 7 Warnings and precautions: Prior treatment with immunosuppressive or immune-modulating therapies.

First Dose Monitoring

Initiation of Gilenya treatment results in a decrease in heart rate (see 7 Warnings and Precautions and 13 Clinical Pharmacology). After the first dose of Gilenya, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients.

The first dose of Gilenya should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement.

Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.

Additional observation should be instituted until the finding has resolved in the following situations:

- If the heart rate 6 hours post-dose is <45 bpm
- Or if the heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart may not have occurred)
- Or if the ECG 6-hours post-dose shows new onset second degree or higher AV block

Should post-dose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of Gilenya.

Patients with some pre-existing conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of symptomatic bradycardia, history of recurrent syncope, uncontrolled hypertension, severe untreated sleep apnea, AV block, sino-atrial heart block) may poorly tolerate the Gilenya-induced bradycardia, or experience serious rhythm disturbances after the first dose of Gilenya. Prior to treatment with Gilenya, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with Gilenya, should be monitored overnight with continuous ECG in a medical facility after the first dose.

Gilenya is contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure) (see 6 Contraindications).

Since initiation of Gilenya treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QT interval (>450 msec males, >470 msec females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of Torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin): advice from a cardiologist should be sought and the patients should be monitored overnight with continuous ECG in a medical facility (see 9 Drug Interactions).

Experience with Gilenya is limited in patients receiving concurrent therapy with drugs that slow heart rate (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of Gilenya treatment is also associated with slowing of the heart rate, concomitant use of these drugs during Gilenya initiation may be associated with severe bradycardia or heart block. The possibility to switch to non-heart-rate lowering drugs should be evaluated by the physician prescribing the heart-rate lowering drug before initiating Gilenya. In patients who cannot switch, overnight continuous ECG monitoring after the first dose is recommended (see 9 Drug Interactions).

Clinical data indicate effects of Gilenya on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2-4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

Re-initiation of Therapy Following Discontinuation

If Gilenya therapy is discontinued for more than 14 days, after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of Gilenya treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days.

Dosing in special populations

Renal impairment

No Gilenya dose adjustments are needed in patients with renal impairment (see section 13 Clinical pharmacology).

Hepatic impairment

No Gilenya dose adjustments are needed in patients with mild or moderate hepatic impairment. Gilenya should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see section 13 Clinical pharmacology).

Pediatrics patients

Gilenya is not indicated for use in pediatric patients (see section 13 Clinical pharmacology).

Geriatrics patients

Gilenya should be used with caution in patients aged 65 years and over (see section 13 Clinical pharmacology).

Ethnicity

No Gilenya dose adjustments are needed based on ethnic origin (see section 13 Clinical pharmacology).

Gender

No Gilenya dose adjustments are needed based on gender (see section 13 Clinical pharmacology).

Diabetic patients

Gilenya should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema (see section 7 Warnings and precautions).

6 CONTRAINDICATIONS

GILENYA is contraindicated in patients who have:

- in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure
- a history or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker *[see Warnings and Precautions (7.1)]*
- a baseline QTc interval $\geq$ 500 msec
- cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs
- had a hypersensitivity reaction to fingolimod or any of the excipients in GILENYA listed in section 12. Observed reactions include rash, urticaria and angioedema upon treatment initiation *[see Warnings and Precautions (7.14)]*.

7 WARNINGS AND PRECAUTIONS

7.1 Bradyarrhythmia and Atrioventricular Blocks

Because of a risk for bradyarrhythmia and AV blocks, patients should be monitored during GILENYA treatment initiation *[see Dosage and Administration (5)]*.

Reduction in Heart Rate

After the first dose of GILENYA, the heart rate decrease starts within an hour. On Day 1, the maximum decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours post-dose. Because of physiological diurnal variation, there is a second period of heart rate decrease within 24 hours after the first dose. In some patients, heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Heart rates below 40 beats per minute (bpm) in adults occurred rarely. In controlled clinical trials in adult patients, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving GILENYA 0.5 mg and in 0.1% of patients on placebo. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue,

palpitations, and/or chest pain that usually resolved within the first 24 hours on treatment.

Patients with some preexisting conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block) may poorly tolerate the GILENYA-induced bradycardia, or experience serious rhythm disturbances after the first dose of GILENYA. Prior to treatment with GILENYA, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and if treated with GILENYA, should be monitored overnight with continuous ECG in a medical facility after the first dose.

Since initiation of GILENYA treatment, results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (> 450 msec adult males, > 470 msec adult females) before dosing or during 6-hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility.

Following the second dose, a further decrease in heart rate may occur when compared to the heart rate prior to the second dose, but this change is of a smaller magnitude than that observed following the first dose. With continued dosing, the heart rate returns to baseline within 1 month of chronic treatment. Clinical data indicate effects of GILENYA on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2 to 4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

Atrioventricular Blocks

Initiation of GILENYA treatment has resulted in transient AV conduction delays. In controlled clinical trials in adult patients, first-degree AV block after the first dose occurred in 4.7% of patients receiving GILENYA and 1.6% of patients on placebo. In a study of 697 patients with available 24-hour Holter monitoring data after their first dose (N = 351 receiving GILENYA and N = 346 on placebo), second-degree AV blocks (Mobitz Types I [Wenckebach] or 2:1 AV blocks) occurred in 4% (N = 14) of patients receiving GILENYA and 2% (N = 7) of patients on placebo. Of the 14 patients receiving GILENYA, 7 patients had 2:1 AV block (5 patients within the first 6 hours post-dose and 2 patients after 6 hours post-dose). All second degree AV blocks on placebo were Mobitz Type I and occurred after the first 12 hours post-dose. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol.

Postmarketing Experience

In the post-marketing setting, third-degree AV block and AV block with junctional escape have been observed during the first-dose 6-hour observation period with GILENYA. Isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These events were confounded by concomitant medications and/or preexisting disease, and the relationship to GILENYA is uncertain. Cases of syncope were also reported after the first dose of GILENYA.

7.2 Infections

Risk of Infections

GILENYA causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. GILENYA may therefore increase the risk of infections, some serious in nature *[see Clinical Pharmacology (13.2)]*. Life-threatening and fatal infections have occurred in association with GILENYA.

Before initiating treatment with GILENYA, a recent complete blood count (CBC) (i.e., within 6 months or after discontinuation of prior therapy) should be available. Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy. Because the elimination of fingolimod after discontinuation may take up to 2 months, continue monitoring for infections throughout this period. Instruct patients receiving GILENYA to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved.

In MS placebo-controlled trials in adult patients, the overall rate of infections (72%) with GILENYA was similar to

placebo. However, bronchitis, herpes zoster, influenza, sinusitis, and pneumonia were more common in GILENYA-treated patients. Serious infections occurred at a rate of 2.3% in the GILENYA group versus 1.6% in the placebo group.

In the postmarketing setting, serious infections with opportunistic pathogens including viruses (e.g., John Cunningham virus (JCV), herpes simplex viruses 1 and 2, varicella zoster virus), fungi (e.g., cryptococci), and bacteria (e.g., atypical mycobacteria) have been reported with GILENYA. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and appropriate treatment.

Herpes Viral Infections

In placebo-controlled trials in adult patients, the rate of herpetic infections was 9% in patients receiving GILENYA 0.5 mg and 7% on placebo.

Two patients died of herpetic infections during controlled trials. One death was due to disseminated primary herpes zoster and the other was to herpes simplex encephalitis. In both cases, the patients were taking a 1.25 mg dose of fingolimod (higher than the recommended 0.5 mg dose) and had received high-dose corticosteroid therapy to treat suspected MS relapses.

Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with GILENYA in the postmarketing setting. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving GILENYA and present with an atypical MS relapse or multiorgan failure.

Cases of Kaposi's sarcoma have been reported in the postmarketing setting. Kaposi's sarcoma is an angioproliferative disorder that is associated with infection with human herpes virus 8 (HHV-8). Patients with symptoms or signs consistent with Kaposi's sarcoma should be referred for prompt diagnostic evaluation and management.

Cryptococcal Infections

Cryptococcal infections, including cases of fatal cryptococcal meningitis and disseminated cryptococcal infections, have been reported with GILENYA in the postmarketing setting. Cryptococcal infections have generally occurred after approximately 2 years of GILENYA treatment, but may occur earlier. The relationship between the risk of cryptococcal infection and the duration of treatment is unknown. Patients with symptoms and signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment.

Prior and Concomitant Treatment with Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies

In clinical studies, patients who received GILENYA did not receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of GILENYA with any of these therapies, and also with corticosteroids, would be expected to increase the risk of immunosuppression *[see Drug Interactions (9.4)]*.

When switching to GILENYA from immune-modulating or immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Varicella Zoster Virus Antibody Testing/Vaccination

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating GILENYA. VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for 1 month to allow the full effect of vaccination to occur *[see Drug Interactions (9.3)]*.

Human Papilloma Virus (HPV) Infection

Human papilloma virus (HPV) infections, including papilloma, dysplasia, warts, and HPV-related cancer, have been reported in patients treated with GILENYA in the postmarketing setting. Vaccination against HPV should be considered prior to treatment initiation with GILENYA, taking into account vaccination recommendations. Cancer screening, including Papanicolaou (Pap) test, is recommended as per standard of care for patients using an immunosuppressive therapy.

7.3 Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with MS who received GILENYA in the post-marketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, were not taking any other immunosuppressive or immunomodulatory medications concomitantly, and did not have any ongoing systemic medical conditions resulting in compromised immune system function. The majority of cases have occurred in patients treated with GILENYA for at least 2 years. The relationship between the risk of PML and the duration of treatment is unknown.

At the first sign or symptom suggestive of PML, withhold GILENYA and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. MRI findings may be apparent before clinical signs or symptoms. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. Cases of asymptomatic PML based on MRI findings and positive JCV DNA in the cerebrospinal fluid have been reported in patients treated with fingolimod. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Lower PML-related mortality and morbidity have been reported following discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

7.4 Macular Edema

Fingolimod increases the risk of macular edema. Perform an examination of the fundus, including the macula in all patients before starting treatment, again 3 to 4 months after starting treatment, and again at any time after a patient reports visual disturbances while on GILENYA therapy.

A dose-dependent increase in the risk of macular edema occurred in the GILENYA clinical development program.

In 2-year double-blind, placebo-controlled studies in adult patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 1.5% of patients (11/799) treated with fingolimod 1.25 mg, 0.5% of patients (4/783) treated with GILENYA 0.5 mg, and 0.4% of patients (3/773) treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. These clinical trials excluded patients with diabetes mellitus, a known risk factor for macular edema (see below *Macular Edema in Patients with History of Uveitis or Diabetes Mellitus).* Symptoms of macular edema included blurred vision and decreased visual acuity. Routine ophthalmological examination detected macular edema in some patients with no visual symptoms. Macular edema generally partially or completely resolved with or without treatment after drug discontinuation. Some patients had residual visual acuity loss even after resolution of macular edema. Macular edema has also been reported in patients taking GILENYA in the post-marketing setting, usually within the first 6 months of treatment.

Continuation of GILENYA in patients who develop macular edema has not been evaluated. A decision on whether or not to discontinue GILENYA therapy should include an assessment of the potential benefits and risks for the individual patient. The risk of recurrence after rechallenge has not been evaluated.

Macular Edema in Patients with History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the combined clinical trial experience in adult patients with all doses of fingolimod, the rate of macular edema was approximately 20% in MS patients with a history of uveitis versus 0.6% in those without a history of uveitis. GILENYA has not been tested in MS patients with diabetes mellitus. In addition to the examination of the fundus, including the macula prior to treatment and at 3 to 4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

7.5 Liver Injury

Clinically significant liver injury has occurred in patients treated with GILENYA in the post-marketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose and have also been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

In 2-year placebo-controlled clinical trials in adult patients, elevation of liver enzymes (ALT, AST, and GGT) to 3-fold the upper limit of normal (ULN) or greater occurred in 14% of patients treated with GILENYA 0.5 mg and 3% of patients on placebo. Elevations 5-fold the ULN or greater occurred in 4.5% of patients on GILENYA and 1% of patients on placebo. The majority of elevations occurred within 6 to 9 months. In clinical trials, GILENYA was discontinued if the elevation exceeded 5 times the ULN. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA. Recurrence of liver transaminase elevations occurred with rechallenge in some patients.

Prior to starting treatment with GILENYA (within 6 months), obtain serum transaminases (ALT and AST) and total bilirubin levels. Obtain transaminase levels and total bilirubin levels periodically until two months after GILENYA discontinuation.

Patients should be monitored for signs and symptoms of any hepatic injury. Measure liver transaminase and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In this clinical context, if liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminase values have normalised. Treatment should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury.

Because GILENYA exposure is doubled in patients with severe hepatic impairment, these patients should be closely monitored, as the risk of adverse reactions is greater *[see Use in Specific Populations (10.6), Clinical Pharmacology (13.3)]*.

7.6 Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in adult patients receiving GILENYA. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances, and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, GILENYA should be discontinued.

7.7 Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with GILENYA as early as 1 month after treatment initiation. In 2-year placebo-controlled trials in adult patients, the reduction from baseline in the percent of predicted values for FEV1 at the time of last assessment on drug was 2.8% for GILENYA 0.5 mg and 1.0% for placebo. For DLCO, the reduction from baseline in percent of predicted values at the time of last assessment on drug was 3.3% for GILENYA 0.5 mg and 0.5% for placebo. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation. In MS placebo-controlled trials in adult patients, dyspnea was reported in 9% of patients receiving GILENYA 0.5 mg and 7% of patients receiving placebo. Several patients discontinued GILENYA because of unexplained dyspnea during the extension (uncontrolled) studies. GILENYA has not been tested in MS patients with compromised respiratory function.

Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with GILENYA if clinically indicated.

7.8 Fetal Risk

Based on findings from animal studies, GILENYA may cause fetal harm when administered to a pregnant woman.

In animal reproduction studies conducted in rats and rabbits, developmental toxicity was observed with administration of fingolimod at doses less than the recommended human dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Because it takes approximately 2 months to eliminate GILENYA from the body, advise females of reproductive potential to use effective contraception to avoid pregnancy during and for 2 months after stopping GILENYA treatment *[see Use in Specific Populations (10.1, 10.3)]*.

7.9 Severe Increase in Disability After Stopping GILENYA

Severe increase in disability accompanied by multiple new lesions on MRI has been reported after discontinuation of GILENYA in the post-marketing setting. Patients in most of these reported cases did not return to the functional status they had before stopping GILENYA. The increase in disability generally occurred within 12 weeks after stopping GILENYA, but was reported up to 24 weeks after GILENYA discontinuation.

Monitor patients for development of severe increase in disability following discontinuation of GILENYA and begin appropriate treatment as needed.

7.10 Tumefactive Multiple Sclerosis

MS relapses with tumefactive demyelinating lesions on imaging have been observed during GILENYA therapy and after GILENYA discontinuation in the post-marketing setting. Most reported cases of tumefactive MS in patients receiving Gilenya have occurred within the first 9 months after GILENYA initiation, but tumefactive MS may occur at any point during treatment. Cases of tumefactive MS have also been reported within the first 4 months after Gilenya discontinuation. Tumefactive MS should be considered when a severe MS relapse occurs during GILENYA treatment, especially during initiation, or after discontinuation of GILENYA, prompting imaging evaluation and initiation of appropriate treatment.

7.11 Increased Blood Pressure

In adult MS controlled clinical trials, patients treated with GILENYA 0.5 mg had an average increase over placebo of approximately 3 mmHg in systolic pressure, and approximately 2 mmHg in diastolic pressure, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. Hypertension was reported as an adverse reaction in 8% of patients on GILENYA 0.5 mg and in 4% of patients on placebo. Blood pressure should be monitored during treatment with GILENYA.

7.12 Malignancies

Cutaneous Malignancies

The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with GILENYA. In two-year placebo-controlled trials in adult patients, the incidence of BCC was 2% in patients on GILENYA 0.5 mg and 1% in patients on placebo *[see Adverse Reactions (6.1)]*. Melanoma, squamous cell carcinoma and Merkel cell carcinoma have been reported with GILENYA in the post-marketing setting. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoma

Cases of lymphoma, including both T-cell and B-cell types and CNS lymphoma, have occurred in patients receiving GILENYA. The reporting rate of non-Hodgkin lymphoma with GILENYA is greater than that expected in the general population adjusted by age, gender, and region. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported with GILENYA in the post-marketing setting.

7.13 Immune System Effects Following GILENYA Discontinuation

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose of GILENYA. Lymphocyte counts generally return to the normal range within 1-2 months of stopping therapy *[see Clinical Pharmacology (12.2)]*. Because of the continuing pharmacodynamic effects of fingolimod, initiating other drugs during this period warrants the same considerations needed for concomitant administration (e.g., risk of additive immunosuppressant effects) *[see Drug Interactions (9.4)]*.

7.14 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, urticaria, and angioedema have been reported with GILENYA in the post-marketing setting. GILENYA is contraindicated in patients with history of hypersensitivity to fingolimod or any of its excipients *[see Contraindications (6)]*.

8 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Bradyarrhythmia and Atrioventricular Blocks *[see Warnings and Precautions (7.1)]*
- Infections *[see Warnings and Precautions (7.2)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (7.3)]*
- Macular Edema *[see Warnings and Precautions (7.4)]*
- Liver Injury *[see Warnings and Precautions (7.5)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (7.6)]*
- Respiratory Effects *[see Warnings and Precautions (7.7)]*
- Fetal Risk *[see Warnings and Precautions (7.8)]*
- Severe Increase in Disability After Stopping GILENYA *[see Warnings and Precautions (7.9)]*
- Tumefactive Multiple Sclerosis *[see Warnings and Precautions (7.10)]*
- Increased Blood Pressure *[see Warnings and Precautions (7.11)]*
- Malignancies *[see Warnings and Precautions (7.12)]*
- Immune System Effects Following GILENYA Discontinuation *[see Warnings and Precautions (7.13)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (7.14)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

In clinical trials (Studies 1, 2, and 3), a total of 1212 patients with relapsing forms of multiple sclerosis received GILENYA 0.5 mg. This included 783 patients who received GILENYA 0.5 mg in the 2-year placebo-controlled trials (Studies 1 and 3) and 429 patients who received GILENYA 0.5 mg in the 1-year active-controlled trial (Study 2). The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients received at least 2 years of treatment with GILENYA 0.5 mg. In all clinical studies, including uncontrolled extension studies, the exposure to GILENYA 0.5 mg was approximately 4119 person-years.

In placebo-controlled trials, the most frequent adverse reactions (incidence ≥ 10% and greater than placebo) for GILENYA 0.5 mg were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. Adverse events that led to treatment discontinuation and occurred in more than 1% of patients taking GILENYA 0.5 mg, were serum transaminase elevations (4.7% compared to 1% on placebo) and basal cell carcinoma (1% compared to 0.5% on placebo).

Table 1 lists adverse reactions in clinical studies in adults that occurred in ≥ 1% of GILENYA-treated patients and ≥ 1% higher rate than for placebo.

Table 1: Adverse Reactions Reported in Adult Studies 1 and 3 (Occurring in ≥ 1% of Patients and Reported for GILENYA 0.5 mg at ≥ 1% Higher Rate Than for Placebo)

Adverse Drug Reactions	GILENYA 0.5 mg N = 783 %	Placebo N = 773 %
Infections		
Influenza	11	8
Sinusitis	11	8
Bronchitis	8	5
Herpes zoster	2	1

Tinea versicolor	2	< 1
Cardiac disorders		
Bradycardia	3	1
Nervous system disorders		
Headache	25	24
Migraine	6	4
Gastrointestinal disorders		
Nausea	13	12
Diarrhea	13	10
Abdominal pain	11	10
General disorders and administration-site conditions		
Asthenia	2	1
Musculoskeletal and connective tissue disorders		
Back pain	10	9
Pain in extremity	10	7
Skin and subcutaneous tissue disorders		
Alopecia	3	2
Actinic keratosis	2	1
Investigations		
Liver transaminase elevations (ALT/GGT/AST)	15	4

Blood triglycerides increased	3	1
Respiratory, thoracic, and mediastinal disorders		
Cough	12	11
Dyspnea	9	7
Eye disorders		
Vision blurred	4	2
Vascular disorders		
Hypertension	8	4
Blood and lymphatic system disorders		
Lymphopenia	7	< 1
Leukopenia	2	< 1
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		
Skin papilloma	3	2
Basal cell carcinoma	2	1

Adverse reactions of seizure, dizziness, pneumonia, eczema, and pruritus were also reported in Studies 1 and 3, but did not meet the reporting rate criteria for inclusion in Table 1 (difference was less than 1%).

Adverse reactions with GILENYA 0.5 mg in Study 2, the 1-year active-controlled (versus interferon beta-1a) study were generally similar to those in Studies 1 and 3.

Vascular Events

Vascular events, including ischemic and hemorrhagic strokes, and peripheral arterial occlusive disease were reported in premarketing clinical trials in patients who received GILENYA doses (1.25-5 mg) higher than recommended for use in MS. Similar events have been reported with GILENYA in the post-marketing setting although a causal relationship has not been established.

Seizure

Cases of seizures, including status epilepticus, have been reported with the use of GILENYA in clinical trials and in the post-marketing setting in adults *[see Adverse Reactions (8.2)]*. In adult clinical trials, the rate of seizures was 0.9% in GILENYA-treated patients and 0.3% in placebo-treated patients. It is unknown whether these events were related to the effects of multiple sclerosis alone, to GILENYA, or to a combination of both.

8.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of GILENYA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Hemolytic anemia and thrombocytopenia

Hepatobiliary Disorders: Liver injury *[see Warnings and Precautions (7.5)]*

Infections: infections, including cryptococcal infections *[see Warnings and Precautions (7.2)]*, human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer *[see Warnings and Precautions (7.2)]*, progressive multifocal leukoencephalopathy *[see Warnings and Precautions (7.3)]*

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

Nervous system disorders: posterior reversible encephalopathy syndrome *[see Warnings and Precautions (7.6)]*, seizures, including status epilepticus *[see Adverse Reactions (8.1)]*

Neoplasms, benign, malignant, and unspecified (including cysts and polyps): melanoma, Merkel cell carcinoma, and cutaneous T-cell lymphoma (including mycosis fungoides) *[see Warnings and Precautions (7.12)]*

Skin and subcutaneous tissue disorders: hypersensitivity *[see Warnings and Precautions (7.14)]*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

9.1 QT Prolonging Drugs

GILENYA has not been studied in patients treated with drugs that prolong the QT interval. Drugs that prolong the QT interval have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of GILENYA treatment results in decreased heart rate and may prolong the QT interval, patients on QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility *[see Dosage and Administration (5.4), Warnings and Precautions (7.1)]*.

9.2 Ketoconazole

The blood levels of fingolimod and fingolimod-phosphate are increased by 1.7-fold when used concomitantly with ketoconazole. Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater.

9.3 Vaccines

GILENYA reduces the immune response to vaccination. Vaccination may be less effective during and for up to 2 months after discontinuation of treatment with GILENYA *[see Clinical Pharmacology (13.2)]*. Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.

9.4 Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies

Antineoplastic, immune-modulating, or immunosuppressive therapies, (including corticosteroids) are expected to increase the risk of immunosuppression, and the risk of additive immune system effects must be considered if these therapies are coadministered with GILENYA. When switching from drugs with prolonged immune effects, such as natalizumab, teriflunomide or mitoxantrone, the duration and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects when initiating GILENYA *[see Warnings and Precautions (7.2)]*.

9.5 Drugs That Slow Heart Rate or Atrioventricular Conduction (e.g., beta blockers or diltiazem)

Experience with GILENYA in patients receiving concurrent therapy with drugs that slow the heart rate or AV conduction (e.g., beta blockers, digoxin, or heart rate-slowing calcium channel blockers, such as diltiazem or verapamil) is limited. Because initiation of GILENYA treatment may result in an additional decrease in heart rate, concomitant use of these drugs during GILENYA initiation may be associated with severe bradycardia or heart block. Seek advice from the physician prescribing these drugs regarding the possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction before initiating GILENYA. Patients who cannot switch should have overnight continuous ECG monitoring after the first dose *[see Dosage and Administration (5.4), Warnings and Precautions (7.1)]*.

9.6 Laboratory Test Interaction

Because GILENYA reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with GILENYA. A recent CBC should be available before initiating treatment with GILENYA.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on findings from animal studies, GILENYA may cause fetal harm when administered to a pregnant woman. Data from prospective reports to the GILENYA Pregnancy Registry (GPR) are currently not sufficient to allow for an adequate assessment of the drug-associated risk for birth defects and miscarriage in humans.

In oral studies conducted in rats and rabbits, fingolimod demonstrated developmental toxicity, including an increase in malformations (rats) and embryolethality, when given to pregnant animals. In rats, the highest no-effect dose was less than the recommended human dose of 0.5 mg/day on a body surface area (mg/m^2) basis. The most common fetal visceral malformations in rats were persistent truncus arteriosus and ventricular septal defect. The receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis *(see Data).* Advise pregnant women of the potential risk to a fetus.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

In females planning to become pregnant, GILENYA should be stopped 2 months before planned conception.

The possibility of severe increase in disability should be considered in women who discontinue or are considering discontinuation of GILENYA because of pregnancy or planned pregnancy. In many of the cases in which increase in disability was reported after stopping GILENYA, patients had stopped GILENYA because of pregnancy or planned pregnancy *[see Warnings and Precautions (7.9)]*.

Data

Animal Data

When fingolimod was orally administered to pregnant rats during the period of organogenesis (0, 0.03, 0.1, and 0.3 mg/kg/day or 0, 1, 3, and 10 mg/kg/day), increased incidences of fetal malformations and embryofetal deaths were observed at all but the lowest dose tested (0.03 mg/kg/day), which is less than the recommended human dose (RHD) on a mg/m^2 basis. Oral administration to pregnant rabbits during organogenesis (0, 0.5, 1.5, and 5 mg/kg/day) resulted in increased incidences of embryofetal mortality and fetal growth retardation at the mid and high doses. The no-effect dose for these effects in rabbits (0.5 mg/kg/day) is approximately 20 times the RHD on a mg/m^2 basis.

When fingolimod was orally administered to female rats during pregnancy and lactation (0, 0.05, 0.15, and 0.5 mg/kg/day), pup survival was decreased at all doses and a neurobehavioral (learning) deficit was seen in offspring at the high dose. The low-effect dose of 0.05 mg/kg/day is similar to the RHD on a mg/m^2 basis.

10.2 Lactation

Risk Summary

There are no data on the presence of fingolimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Fingolimod is excreted in the milk of treated rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GILENYA and any potential adverse effects on the breastfed infant from GILENYA or from the underlying maternal condition.

10.3 Females and Males of Reproductive Potential

Pregnancy Testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with GILENYA *[see Use in Specific Populations (10.1)]*.

Contraception

Before initiation of GILENYA treatment, females of reproductive potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with GILENYA *[see Warnings and Precautions (7.8) and Use in Specific Populations (10.1)]*. Since it takes approximately 2 months to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use

effective contraception during this period *[see Warnings and Precautions (7.8, 7.13)]*.

10.4 Pediatric Use

Gilenya is not indicated for use in pediatric patients.

Juvenile Animal Toxicity Data

In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis.

When fingolimod (0.5 or 5 mg/kg/day) was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment.

Overall, a no-effect dose for adverse developmental effects in juvenile animals was not identified.

10.5 Geriatric Use

Clinical MS studies of GILENYA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.

10.6 Hepatic Impairment

Because fingolimod, but not fingolimod-phosphate, exposure is doubled in patients with severe hepatic impairment, patients with severe hepatic impairment should be closely monitored, as the risk of adverse reactions may be greater *[see Warnings and Precautions* (*7.5), Clinical Pharmacology (13.3)]*.

No dose adjustment is needed in patients with mild or moderate hepatic impairment.

10.7 Renal Impairment

The blood level of some GILENYA metabolites is increased (up to 13-fold) in patients with severe renal impairment *[see Clinical Pharmacology (13.3)]*. The toxicity of these metabolites has not been fully explored. The blood level of these metabolites has not been assessed in patients with mild or moderate renal impairment.

11 OVERDOSAGE

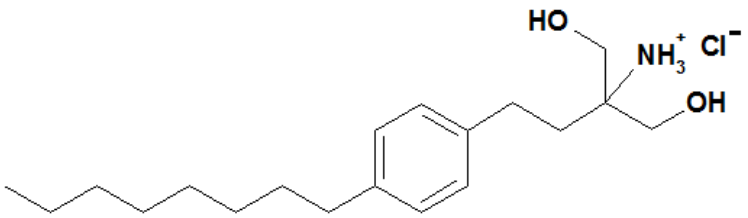
GILENYA can induce bradycardia as well as AV conduction blocks (including complete AV block). The decline in heart rate usually starts within 1 hour of the first dose and is maximal within 6 hours in most patients *[see Warnings and Precautions (7.1)]*. In case of GILENYA overdosage, observe patients overnight with continuous ECG monitoring in a medical facility, and obtain regular measurements of blood pressure *[see Dosage and Administration (5.4)]*.

Neither dialysis nor plasma exchange results in removal of fingolimod from the body.

12 DESCRIPTION

Fingolimod is a sphingosine 1-phosphate receptor modulator.

Chemically, fingolimod is 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride. Its structure is shown



below:

Fingolimod hydrochloride is a white to practically white powder that is freely soluble in water and alcohol and soluble in propylene glycol. It has a molecular weight of 343.93 g/mol.

Each GILENYA 0.5 mg capsule contains the following inactive ingredients: mannitol, magnesium stearate. Empty capsule shell: gelatin, titanium dioxide, yellow iron oxide. Printing inks black and yellow: shellac (E904), dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, black iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), dimethicone.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

13.2 Pharmacodynamics

Heart Rate and Rhythm

Fingolimod causes a transient reduction in heart rate and AV conduction at treatment initiation *[see Warnings and Precautions (7.1)]*.

Heart rate progressively increases after the first day, returning to baseline values within 1 month of the start of chronic treatment.

Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise, are not affected by fingolimod treatment.

Fingolimod treatment is not associated with a decrease in cardiac output.

Potential to Prolong the QT Interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTc, with the upper boundary of the 90% confidence interval (CI) of 14.0 msec. There is no consistent signal of increased incidence of QTc outliers, either absolute or change from baseline, associated with fingolimod treatment. In MS studies, there was no clinically relevant prolongation of the QT interval, but patients at risk for QT prolongation were not included in clinical studies.

Immune System

Effects on Immune Cell Numbers in the Blood

In a study in which 12 adult subjects received GILENYA 0.5 mg daily, the lymphocyte count decreased to approximately 60% of baseline within 4 to 6 hours after the first dose. With continued daily dosing, the lymphocyte count continued to decrease over a 2-week period, reaching a nadir count of approximately 500 cells/mcL or approximately 30% of baseline. In a placebo-controlled study in 1272 MS patients (of whom 425 received fingolimod 0.5 mg daily and 418 received placebo), 18% (N = 78) of patients on fingolimod 0.5 mg reached a nadir of < 200 cells/mcL on at least 1 occasion. No patient on placebo reached a nadir of < 200 cells/mcL. Low lymphocyte counts are maintained with chronic daily dosing of GILENYA 0.5 mg daily.

Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within 1 to 2 months.

Effect on Antibody Response

GILENYA reduces the immune response to vaccination, as evaluated in 2 studies.

In the first study, the immunogenicity of keyhole limpet hemocyanin (KLH) and pneumococcal polysaccharide vaccine (PPV-23) immunization were assessed by IgM and IgG titers in a steady-state, randomized, placebo-controlled study in healthy adult volunteers. Compared to placebo, antigen-specific IgM titers were decreased by 91% and 25% in response to KLH and PPV-23, respectively, in subjects on GILENYA 0.5 mg. Similarly, IgG titers were decreased by 45% and 50%, in response to KLH and PPV-23, respectively, in subjects on GILENYA 0.5 mg daily compared to placebo. The responder rate for GILENYA 0.5 mg as measured by the number of subjects with a > 4-fold increase in KLH IgG was comparable to placebo and 25% lower for PPV-23 IgG, while the number of subjects with a > 4-fold increase in KLH and PPV-23 IgM was 75% and 40% lower, respectively, compared to placebo. The capacity to mount a skin delayed-type hypersensitivity reaction to *Candida* and tetanus toxoid was decreased by approximately 30% in subjects on GILENYA 0.5 mg daily, compared to placebo. Immunologic responses were further decreased with fingolimod 1.25 mg (a dose higher than recommended in MS) *[see Warnings and Precautions (7.2)]*.

In the second study, the immunogenicity of Northern hemisphere seasonal influenza and tetanus toxoid vaccination was assessed in a 12-week steady-state, randomized, placebo-controlled study of GILENYA 0.5 mg in adult multiple sclerosis patients (n = 136). The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥ 4-fold increase in antibody directed against at least 1 of the 3 influenza strains, was 54% for GILENYA 0.5 mg and 85% in the placebo group. The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥ 4-fold increase in antibody directed against tetanus toxoid was 40% for GILENYA 0.5 mg and 61% in the placebo group.

Pulmonary Function

Single fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. In a 14-day study of 0.5, 1.25, or 5 mg/day, fingolimod was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment had a normal bronchodilator response to inhaled beta-agonists.

In a 14-day placebo-controlled study of adult patients with moderate asthma, no effect was seen for GILENYA 0.5 mg (recommended dose in MS). A 10% reduction in mean FEV1 at 6 hours after dosing was observed in adult patients receiving fingolimod 1.25 mg (a dose higher than recommended for use in MS) on Day 10 of treatment. Fingolimod 1.25 mg was associated with a 5-fold increase in the use of rescue short-acting beta-agonists.

13.3 Pharmacokinetics

Absorption

The T_{max} of fingolimod is 12–16 hours. The apparent absolute oral bioavailability is 93%.

Food intake does not alter C_{max} or (AUC) of fingolimod or fingolimod-phosphate. Therefore, GILENYA may be taken without regard to meals.

Steady-state blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Distribution

Fingolimod highly (86%) distributes in red blood cells. Fingolimod-phosphate has a smaller uptake in blood cells of < 17%. Fingolimod and fingolimod-phosphate are > 99.7% protein bound. Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200 ± 260 L.

Metabolism

The biotransformation of fingolimod in humans occurs by 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative biotransformation catalyzed mainly by the cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive

non-polar ceramide analogs of fingolimod.

Inhibitors or inducers of CYP4F2 and possibly other CYP4F isozymes might alter the exposure of fingolimod or fingolimod-phosphate. *In vitro* studies in hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 816 hours post-dose of total radiolabeled components, are fingolimod itself (23.3%), fingolimod-phosphate (10.3%), and inactive metabolites [M3 carboxylic acid metabolite (8.3%), M29 ceramide metabolite (8.9%), and M30 ceramide metabolite (7.3%)].

Elimination

Fingolimod blood clearance is 6.3 ± 2.3 L/h, and the average apparent terminal half-life ($t_{1/2}$) is 6 to 9 days. Blood levels of fingolimod-phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both.

After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the feces with amounts of each representing less than 2.5% of the dose.

Specific Populations

Pediatric Patients

Gilenya is not indicated for use in pediatric patients.

Geriatric Patients

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 65 years is limited.

Gender

Gender has no clinically significant influence on fingolimod and fingolimod-phosphate pharmacokinetics.

Race

The effects of race on fingolimod and fingolimod-phosphate pharmacokinetics cannot be adequately assessed due to a low number of non-white patients in the clinical program.

Renal Impairment

In adult patients with severe renal impairment, fingolimod C_{max} and AUC are increased by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC are increased by 25% and 14%, respectively, with no change in apparent elimination half-life. Based on these findings, the GILENYA 0.5 mg dose is appropriate for use in adult patients with renal impairment. The systemic exposure of 2 metabolites (M2 and M3) is increased by 3- and 13-fold, respectively. The toxicity of these metabolites has not been fully characterized.

A study in patients with mild or moderate renal impairment has not been conducted.

Hepatic Impairment

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod $AUC_{0-\infty}$ was increased respectively by 12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22% and $AUC_{0\text{-}96\ hours}$ was decreased by 29%. The pharmacokinetics of fingolimod-phosphate was not evaluated in patients with mild or moderate hepatic impairment. The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored, as the risk of adverse reactions is greater *[see Warnings and Precautions (7.5)]*.

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B).

Drug Interactions

Ketoconazole

The coadministration of ketoconazole (a potent inhibitor of CYP3A and CYP4F) 200 mg twice-daily at steady-state and a single dose of fingolimod 5 mg led to a 70% increase in AUC of fingolimod and fingolimod-phosphate. Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater *[see Drug Interactions (9.2)]*.

Carbamazepine

The coadministration of carbamazepine (a potent CYP450 enzyme inducer) 600 mg twice-daily at steady-state and a single dose of fingolimod 2 mg decreased blood concentrations (AUC) of fingolimod and fingolimod-phosphate by approximately 40%. The clinical impact of this decrease is unknown.

Other strong CYP450 enzyme inducers, e.g., rifampicin, phenytoin, phenobarbital, and St. John's wort, may also reduce AUC of fingolimod and fingolimod-phosphate. The clinical impact of this potential decrease is unknown.

Potential of Fingolimod and Fingolimod-phosphate to Inhibit the Metabolism of Comedications

In vitro inhibition studies using pooled human liver microsomes and specific metabolic probe substrates demonstrate that fingolimod has little or no capacity to inhibit the activity of the following CYP enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 (fingolimod only), and similarly fingolimod-phosphate has little or no capacity to inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations up to 3 orders of magnitude of therapeutic concentrations. Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major CYP isoenzymes described above.

Potential of Fingolimod and Fingolimod-phosphate to Induce its Own and/or the Metabolism of Comedications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and MDR1 (P-glycoprotein) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce mRNA or activity of the different CYP enzymes and MDR1 with respect to the vehicle control; therefore, no clinically relevant induction of the tested CYP enzymes or MDR1 by fingolimod are expected at therapeutic concentrations. Fingolimod-phosphate was also examined for its potential to induce mRNA and/or activity of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP4F2, CYP4F3B, and CYP4F12. Fingolimod-phosphate is not expected to have clinically significant induction effects on these enzymes at therapeutic doses of fingolimod. *In vitro* experiments did not provide an indication of CYP induction by fingolimod-phosphate.

Transporters

Based on *in vitro* data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of comedications and/or biologics transported by the organic anion transporting polypeptides OATP1B1, OATP1B3, or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of comedications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2), or P-glycoprotein (P-gp) at therapeutic concentrations.

Oral Contraceptives

The coadministration of fingolimod 0.5 mg daily with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any clinically significant change in oral contraceptives exposure. Fingolimod and fingolimod-phosphate exposure were consistent with those from previous studies. No interaction studies have been performed with oral contraceptives containing other progestagens; however, an effect of fingolimod on their exposure is not expected.

Cyclosporine

The pharmacokinetics of single-dose fingolimod was not altered during coadministration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by fingolimod. These data indicate that GILENYA is unlikely to reduce or increase the clearance of drugs cleared mainly by CYP3A4. Potent inhibition of transporters MDR1 (P-gp), MRP2, and OATP-1B1 does not influence fingolimod disposition.

Isoproterenol, Atropine, Atenolol, and Diltiazem

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by coadministered isoproterenol or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the coadministration of the latter 2 drugs individually with fingolimod.

Population Pharmacokinetics Analysis

A population pharmacokinetics evaluation performed in MS patients did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) on fingolimod or fingolimod-phosphate predose concentrations. In addition, the following commonly coprescribed substances had no clinically relevant effect (< 20%) on fingolimod or fingolimod-phosphate predose concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, and corticosteroids.

14 NON CLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of fingolimod were conducted in mice and rats. In mice, fingolimod was administered at oral doses of 0, 0.025, 0.25, and 2.5 mg/kg/day for up to 2 years. The incidence of malignant lymphoma was increased in males and females at the mid and high dose. The lowest dose tested (0.025 mg/kg/day) is less than the RHD of 0.5 mg/day on a body surface area (mg/m^2) basis. In rats, fingolimod was administered at oral doses of 0, 0.05, 0.15, 0.5, and 2.5 mg/kg/day. No increase in tumors was observed. The highest dose tested (2.5 mg/kg/day) is approximately 50 times the RHD on a mg/m^2 basis.

Fingolimod was negative in a battery of *in vitro* (Ames, mouse lymphoma thymidine kinase, chromosomal aberration in mammalian cells) and *in vivo* (micronucleus in mouse and rat) assays.

When fingolimod was administered orally (0, 1, 3, and 10 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested (10 mg/kg), which is approximately 200 times the RHD on a mg/m^2 basis.

14.2 Animal Toxicology and/or Pharmacology

Lung toxicity was observed in 2 different strains of rats and in dogs and monkeys. The primary findings included increase in lung weight, associated with smooth muscle hypertrophy, hyperdistention of the alveoli, and/or increased collagen. Insufficient or lack of pulmonary collapse at necropsy, generally correlated with microscopic changes, was observed in all species. In rats and monkeys, lung toxicity was observed at all oral doses tested in chronic studies. The lowest doses tested in rats (0.05 mg/kg/day in the 2-year carcinogenicity study) and monkeys (0.5 mg/kg/day in the 39-week toxicity study) are similar to and approximately 20 times the RHD on a mg/m^2 basis, respectively.

In the 52-week oral study in monkeys, respiratory distress associated with ketamine administration was observed at doses of 3 and 10 mg/kg/day; the most affected animal became hypoxic and required oxygenation. As ketamine is not generally associated with respiratory depression, this effect was attributed to fingolimod. In a subsequent study in rats, ketamine was shown to potentiate the bronchoconstrictive effects of fingolimod. The relevance of these findings to humans is unknown.

15 CLINICAL STUDIES

15.1 Adults

The efficacy of GILENYA was demonstrated in 2 studies that evaluated once-daily doses of GILENYA 0.5 mg and 1.25 mg in patients with relapsing-remitting MS (RRMS). Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Study 1 was a 2-year randomized, double-blind, placebo-controlled study in patients with RRMS who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at screening, Month 6, Month 12, and Month 24. The primary endpoint was the annualized

relapse rate.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (N = 425), 1.25 mg (N = 429), or placebo (N = 418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg, and 719 days on placebo.

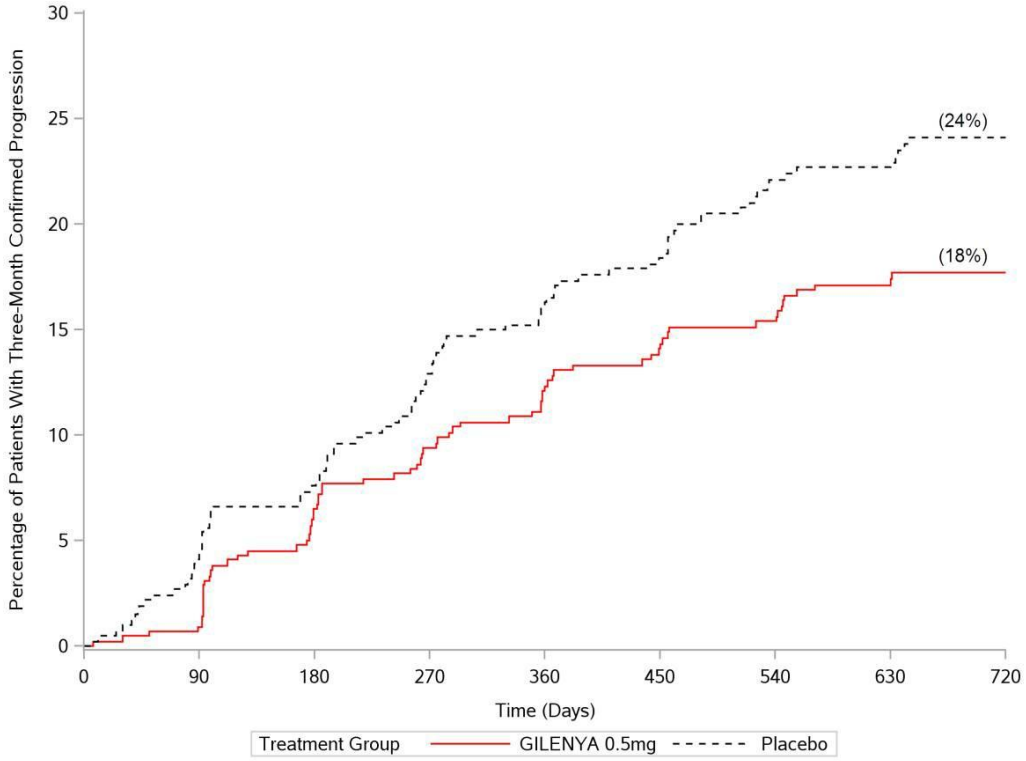
The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received placebo. The secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with GILENYA treatment compared to placebo. The 1.25 mg dose resulted in no additional benefit over the GILENYA 0.5 mg dose. The results for this study are shown in Table 2 and Figure 1.

Table 2: Clinical and MRI Results of Study 1

	GILENYA 0.5 mg N = 425	**Placebo N = 418**	**p-value**
Clinical Endpoints			
Annualized relapse rate (primary endpoint)	0.18	0.40	< 0.001
Percentage of patients without relapse	70%	46%	< 0.001
Hazard ratio‡ of disability progression (95% CI)	0.70 (0.52, 0.96)		0.02
MRI Endpoint			
Mean (median) number of new or newly enlarging T2 lesions over 24 months	2.5 (0)	9.8 (5.0)	< 0.001
Mean (median) number of T1 Gd-enhancing lesions at Month 24	0.2 (0)	1.1 (0)	< 0.001

All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.
‡Hazard ratio is an estimate of the relative risk of having the event of disability progression on GILENYA as compared to placebo.

Figure 1: Time to 3-Month Confirmed Disability Progression – Study 1 (ITT population)



Study 2 was a 1-year randomized, double-blind, double-dummy, active-controlled study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted.

Neurological evaluations were performed at screening, every 3 months, and at the time of suspected relapses. MRI evaluations were performed at screening and at Month 12. The primary endpoint was the annualized relapse rate.

Median age was 36 years, median disease duration was 5.9 years, and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (N = 431), 1.25 mg (N = 426), or interferon beta-1a, 30 mcg via the intramuscular route (IM) once-weekly (N = 435) for up to 12 months. Median time on study drug was 365 days on GILENYA 0.5 mg, 354 days on 1.25 mg, and 361 days on interferon beta-1a IM.

The annualized relapse rate was significantly lower in patients treated with GILENYA 0.5 mg than in patients who received interferon beta-1a IM. The key secondary endpoints were number of new and newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5-point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new and newly enlarging T2 lesions was significantly lower in patients treated with GILENYA than in patients who received interferon beta-1a IM. There was no significant difference in the time to 3-month confirmed disability progression between GILENYA and interferon beta-1a-treated patients at 1 year. The 1.25 mg dose resulted in no additional benefit over the GILENYA 0.5 mg dose. The results for this study are shown in Table 3.

Table 3: Clinical and MRI Results of Study 2

	GILENYA 0.5 mg N = 429	**Interferon beta-1a IM 30 mcg N = 431**	**p-value**
Clinical Endpoints			

Annualized relapse rate (primary endpoint)	0.16	0.33	< 0.001
Percentage of patients without relapse	83%	70%	< 0.001
Hazard ratio‡ of disability progression	0.71		0.21
(95% CI)	(0.42, 1.21)		
MRI Endpoint			
Mean (median) number of new or newly enlarging T2 lesions over 12 months	1.6 (0)	2.6 (1.0)	0.002
Mean (median) number of T1 Gd-enhancing lesions at Month 12	0.2 (0)	0.5 (0)	< 0.001

All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.
‡ Hazard ratio is an estimate of the relative risk of having the event of disability progression on GILENYA as compared to control.

Pooled results of study 1 and study 2 showed a consistent and statistically significant reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior MS therapy, and disease activity.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Blister packs of 7 or 28 capsules.

Not all pack sizes may be marketed.

16.2 Storage and Handling

Store below 25°C.

Protect from moisture.

17 REGISTRATION HOLDER and IMPORTER

Novartis Israel Ltd., P.O.B. 7126, Tel Aviv.

18 REGISTRATION NUMBER

145-78-33270

Revised in November 2020.

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו - 1986
התרופה משווקת על פי מרשם רופא בלבד

גילניה 0.5 מ"ג
כמוסות קשות

החומר הפעיל
כל כמוסה מכילה: פינגולימוד (כהידרוכלוריד) 0.5 מ"ג (Fingolimod (as hydrochloride

חומרים בלתי פעילים:
ראה סעיף 6 'מידע נוסף'

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה.
אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם דומה.

נטילת המנה הראשונה:
לאחר נטילת המנה הראשונה של גילניה נדרשת השגחה על ידי איש צוות רפואי במשך שש שעות לפחות.
המלצה זו מתאימה גם אם אתה מתחיל שוב טיפול לאחר הפסקה בטיפול בגילניה.
ההוראות המלאות לגבי נטילת המנה הראשונה מפורטות בסעיף 'אזהרות מיוחדות הנוגעות לשימוש בתרופה'.

1. למה מיועדת התרופה?

גילניה מיועדת לטיפול בצורות התקפיות של מחלת הטרשת הנפוצה, להפחית את מספר ההתקפים ולהאט את ההתפתחות של בעיות גופניות (נכות) הנגרמות מהמחלה.

קבוצה תרפויטית:
מדכא סלקטיבי של מערכת החיסון.
מווסת של הקולטן ספינגוזין-1-פוספט.

<u>מהי טרשת נפוצה</u>
מחלת הטרשת הנפוצה זו מחלה כרונית המשפיעה על מערכת העצבים המרכזית הכוללת את המוח וחוט השדרה. בטרשת נפוצה התהליך הדלקתי הורס את המעטפת המגינה (הנקראת מיאלין) הנמצאת סביב העצבים במערכת העצבים המרכזית ומונעת פעילות רגילה של העצבים (demyelination).

טרשת נפוצה מסוג התקפית הפוגתית (relapsing-remitting) מאופינת בהתקפים חוזרים (relapses) של תסמינים של מערכת העצבים, המשקפים דלקת במערכת העצבים המרכזית.
למטופלים שונים יתכנו תסמינים שונים אך תסמינים אופיניים הם: קשיים בהליכה, חוסר תחושה, בעיות בראייה או בעיות בשיווי המשקל.
התסמינים של התקף חוזר (relapse) עשויים להעלם לגמרי כשההתקף נגמר אך בעיות מסוימות עשויות להשאר.

<u>כיצד פועלת גילניה</u>
גילניה עוזרת להגן על מערכת העצבים המרכזית מפני תקיפה של המערכת החיסונית בגוף על ידי הפחתת היכולת של תאי דם לבנים מסוימים (לימפוציטים) לנוע בחופשיות בגוף ומניעת הגעתם למוח ולחוט השדרה. דבר זה מגביל את הנזק לעצבים הנגרם על ידי הטרשת הנפוצה. גילניה גם מפחיתה חלק מהתגובה החיסונית של הגוף.

2. לפני השימוש בתרופה

אין להשתמש בתרופה אם:

- סבלת מהתקף לב, מתעוקת לב בלתי יציבה (unstable angina), משבץ מוחי או ארוע מוחי חולף או מסוגים מסויימים של אי ספיקת לב ב- 6 החודשים האחרונים.
- אתה סובל או סבלת בעבר מסוגים מסויימים של קצב לב לא סדיר או לא רגיל (הפרעות קצב), כולל מטופלים שבהם ממצא לבבי בשם QT מוארך נראה באק״ג לפני תחילת הטיפול בגילניה.
- יש לך בעיה בקצב הלב המצריכה טיפול בתרופות מסויימות.
- אתה אלרגי (בעל רגישות יתר) לפינגולימוד או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה, המפורטים בסעיף 6 ׳מידע נוסף׳. התסמינים של תגובה אלרגית עשויים לכלול: פריחה, סרפדת מגרדת (hives) או נפיחות של השפתיים, הלשון או הפנים.

שוחח עם הרופא שלך לפני שאתה נוטל גילניה אם יש לך את אחד מהמצבים האלה או אם אינך יודע אם יש לך אותם.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

- **נטילת המנה הראשונה:**

גילניה יכולה לגרום לקצב הלב שלך להאט, במיוחד לאחר שאתה נוטל את המנה הראשונה. אתה תעבור בדיקה הנקראת אלקטרוקרדיוגרם (אק״ג) לבדיקת הפעילות החשמלית של הלב לפני שאתה נוטל את המנה הראשונה של גילניה.
כל המטופלים יישארו בהשגחה של איש צוות רפואי למשך 6 שעות לפחות לאחר נטילת המנה הראשונה של גילניה.
לאחר שאתה נוטל את המנה הראשונה של גילניה:

- יש לבדוק את הדופק ואת לחץ הדם שלך בכל שעה
- עליך להיות בהשגחה של איש צוות רפואי כדי לראות אם יש לך תופעות לוואי רציניות כלשהן. אם קצב הלב שלך מאט יותר מדי, יתכן שיהיו לך תסמינים כגון:
  - סחרחורת
  - עייפות
  - הרגשה כאילו הלב שלך פועם באיטיות או מחסיר פעימות
  - כאב בחזה
- אם יש לך אחד או יותר מהתסמינים של קצב לב איטי, הם בדרך כלל יתרחשו במהלך 6 השעות הראשונות לאחר נטילת המנה הראשונה של גילניה. התסמינים יכולים להתרחש עד 24 שעות לאחר שאתה נוטל את המנה הראשונה של גילניה.
- 6 שעות לאחר שאתה נוטל את המנה הראשונה של גילניה, תעבור אק״ג נוסף. אם האק״ג מראה בעיות לב כלשהן או אם קצב הלב שלך עדיין נמוך מדי או ממשיך לרדת, אתה תמשיך להיות בהשגחה.
- אם יש לך תופעות לוואי רציניות כלשהן לאחר נטילת המנה הראשונה של גילניה, בעיקר כאלה שדורשות טיפול בתרופות אחרות, אתה תישאר במרכז הרפואי להשגחה במשך הלילה. בנוסף, תהיה בהשגחה לתופעות לוואי רציניות כלשהן למשך 6 שעות לפחות לאחר שאתה נוטל את המנה השניה של גילניה ביום שלמחרת.
- אם יש לך סוגים מסויימים של בעיות לב, או אם אתה נוטל סוגים מסויימים של תרופות שיכולות להשפיע על הלב שלך, אתה תישאר במרכז הרפואי בהשגחת איש צוות רפואי במשך הלילה לאחר נטילת המנה הראשונה של גילניה.

קצב הלב האיטי שלך יחזור למצב רגיל בדרך כלל בתוך חודש אחד לאחר שהתחלת ליטול גילניה. פנה מיד לרופא שלך או לחדר מיון בבית החולים הקרוב אם יש לך תסמינים כלשהם של קצב לב איטי.

אם החמצת מנה אחת או יותר של גילניה, יתכן שתצטרך להיות בהשגחה של איש צוות רפואי כאשר תיטול את המנה הבאה. פנה לרופא שלך אם החמצת מנה של גילניה. ראה גם ׳כיצד תשתמש בתרופה?׳.

יש לידע את הרופא לגבי כל המצבים הרפואיים שלך לפני נטילת גילניה, כולל אם היו לך או אם יש לך כעת:

- קצב לב לא סדיר או לא רגיל (הפרעת קצב)

- הסטוריה של שבץ או אירוע מוחי חולף
- בעיות לב, כולל התקף לב או תעוקת לב
- הסטוריה של התעלפויות חוזרות (איבוד הכרה)
- חום או זיהום, או אם אתה לא מסוגל להלחם בזיהומים בגלל מחלה או נוטל או נטלת בעבר תרופות המחלישות את מערכת החיסון שלך
- לאחרונה קיבלת חיסון או שאתה עומד לקבל חיסון
- אבעבועות רוח או אם קיבלת חיסון לאבעבועות רוח. יתכן שהרופא יבצע בדיקת דם לנגיף אבעבועות הרוח. יתכן שתצטרך לקבל את כל סדרת החיסונים לאבעבועות רוח ואז להמתין חודש אחד לפני שאתה מתחיל את הטיפול בגילניה
- בעיות בעיניים, במיוחד דלקת בעין שנקראת דלקת הענביה (אובאיטיס)
- סוכרת
- בעיות נשימה, כולל בזמן השינה
- בעיות בכבד
- לחץ דם גבוה
- סוגים של סרטן העור הנקראים קרצינומה של תאי הבסיס (BCC) או מלאנומה
- אנא התייעצי עם הרופא שלך לפני כניסה להריון. עלייך להמנע מכניסה להריון במהלך נטילת גילניה או במהלך החודשיים לאחר שהפסקת, בשל הסיכון לפגוע בעובר. ראי סעיף 'הריון והנקה' בהמשך.

מטופלים קשישים (מעל גיל 65)
הניסיון עם טיפול בגילניה באנשים קשישים מוגבל.
יש להשתמש בגילניה בזהירות במטופלים בגיל 65 ומעלה.

ילדים ומתבגרים
התרופה אינה מיועדת לילדים ולמתבגרים מתחת לגיל 18.

בדיקות ומעקב
לפני תחילת הטיפול:
בדיקת כדוריות דם לבנות, בדיקת ראייה, בדיקת דם לבדיקת תפקודי כבד – כמפורט בפרק תופעות הלוואי.
יתכן שהרופא יבצע בדיקת דם לנגיף אבעבועות הרוח.

לבדיקות הנדרשות בנטילת המנה הראשונה של גילניה – ראה סעיף 'נטילת המנה הראשונה' לעיל.

במהלך הטיפול:
בדיקות לחץ דם, בדיקת העור, בדיקת ראייה 3 עד 4 חודשים לאחר התחלת הטיפול, בדיקת דם לבדיקת תפקודי כבד – כמפורט בפרק תופעות הלוואי.
יש להיוועץ לגבי בדיקה שגרתית של משטח צוואר הרחם (משטח פאפ) - כמפורט בפרק תופעות הלוואי.

אינטראקציות/תגובות בין תרופתיות
השימוש בגילניה יחד עם תרופות אחרות עלול לגרום לתופעות לוואי רציניות.
אם אתה לוקח, או אם לקחת לאחרונה תרופות אחרות כולל תרופות ללא מרשם, ויטמינים ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד אם אתה לוקח:

- **תרופות המאריכות מקטע QT** כגון ציטלופראם, כלורפרומאזין, הלופרידול, מתאדון, אריתרומיצין, מכיוון שהתחלת טיפול בגילניה גורמת לירידה בקצב הלב ועשויה להאריך מקטע QT.
- **קטוקונאזול** – תרופה לטיפול בזיהומים פטרייתיים. מטופל המשתמש בגילניה ובקטוקונזול בו זמנית צריך להיות במעקב צמוד מכיוון שהסיכון לתופעות לוואי גדול יותר.
- **חיסונים** - אם אתה צריך לקבל חיסון, פנה קודם לקבלת ייעוץ מהרופא שלך. במהלך הטיפול ועד לחודשיים לאחר הטיפול בגילניה, אתה לא תוכל לקבל חיסונים מסוימים המכילים נגיף חי (חיסונים מוחלשים חיים) מכיוון שהם עלולים לגרום לזיהום שהחיסון אמור למנוע. גם חיסונים אחרים עלולים לא לפעול כרגיל אם יינתנו במהלך התקופה הזו.

- **תרופות אנטי-ניאופלסטיות, תרופות המדכאות או המווסתות את המערכת החיסונית** (כולל קורטיקוסטרואידים) – צפויות להגביר את הסיכון לדיכוי המערכת החיסונית ויש להתחשב בסיכון להשפעה נוספת על המערכת החיסונית אם תרופות אלה ניתנות ביחד עם גילניה. כאשר מחליפים את הטיפול מתרופות עם השפעה מתמשכת על מערכת החיסון כגון נטליזומאב, טריפלונומיד או מיטוקסנטרון, יש להתחשב במשך זמן ואופן הפעולה של התרופות האלה כדי להמנע מהשפעה נוספת ולא מכוונת של דיכוי חיסוני כאשר מתחילים גילניה.
- **תרופות המאטות את קצב הלב ואת ההולכה הפרוזדורית-חדרית** כגון חוסמי-בטא, דיגוקסין או חוסמי תעלת הסידן כגון דילתיאזם או וראפאמיל. לפני שמתחילים את הטיפול בגילניה, יש להיוועץ ברופא שרשם לך את התרופות האלה לגבי האפשרות להחליף לתרופות שלא מאטות את קצב הלב ואת ההולכה הפרוזדורית-חדרית.

שימוש בגילניה ומזון
ניתן ליטול גילניה עם אוכל או ללא אוכל.

הריון והנקה
יש ליידע את הרופא שלך לפני נטילת גילניה, אם את בהריון או מתכננת להכנס להריון.
גילניה עלולה לפגוע בעובר שלך.
ספרי מיד לרופא שלך אם נכנסת להריון במהלך הטיפול בגילניה או אם נכנסת להריון בתוך חודשיים מהפסקת הטיפול בגילניה.

- עלייך להפסיק נטילת גילניה חודשיים לפני שאת מנסה להכנס להריון.
- אם את יכולה להרות, עלייך להשתמש באמצעי מניעה יעיל במהלך הטיפול בגילניה ובמשך חודשיים לפחות לאחר הפסקת הטיפול.

יש ליידע את הרופא שלך לפני נטילת גילניה אם את מיניקה או אם את מתכננת להיניק.

לא ידוע אם גילניה עוברת לחלב אם. היוועצי ברופא שלך לגבי הדרך הטובה ביותר להאכיל את תינוקך אם את נוטלת גילניה.

נהיגה ושימוש במכונות
הרופא יאמר לך אם מחלתך מאפשרת לך לנהוג ברכב, כולל רכיבה באופניים, ולהשתמש במכונות באופן בטוח. לגילניה לא צפויה שתהיה השפעה על היכולת שלך לנהוג ולהשתמש במכונות.
עם זאת, לאחר נטילת המנה הראשונה של גילניה, עליך להשאר למשך 6 שעות בהשגחת איש צוות רפואי. במהלך הזמן הזה ופוטנציאלית גם לאחר מכן, היכולת שלך לנהוג ולהשתמש במכונות עשויה להיות לקויה.

3. כיצד תשתמש בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.

מינון
המינון ואופן הטיפול יקבעו על ידי הרופא בלבד. המינון המקובל בדרך כלל הוא:
כמוסה אחת ביום (0.5 מ״ג פינגולימוד).
אין לעבור על המנה המומלצת.

צורת הנטילה
למתן דרך הפה.
יש ליטול גילניה פעם אחת ביום, עם כוס מים.
נטילת גילניה באותה השעה בכל יום תסייע לזכור מתי יש ליטול את התרופה.
אין מידע לגבי פתיחת הכמוסה ופיזור התוכן שלה.

נטילת גילניה יותר מהנדרש
אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית-חולים והבא אריזת התרופה איתך.

אם שכחת ליטול גילניה
אם שכחת מנה של גילניה, פנה לרופא מיד. יתכן שתצטרך להיות במעקב של איש צוות רפואי במשך 6 שעות לפחות כאשר תיקח את המנה הבאה. אם תצטרך להיות במעקב של איש צוות רפואי כאשר תיקח את המנה הבאה של גילניה, אתה תעבור:

- בדיקת אק״ג לפני נטילת המנה
- בדיקות דופק ולחץ דם בכל שעה לאחר נטילת המנה
- בדיקת אק״ג 6 שעות לאחר נטילת המנה

הפסקת הטיפול
יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.
גם אם חל שיפור במצב בריאותך, אין להפסיק את הטיפול בתרופה ללא התיעצות עם הרופא.
אם אתה מפסיק את נטילת התרופה, תסמיני הטרשת הנפוצה עלולים לחזור ולהחמיר – ראה סעיף ׳החמרה קשה בטרשת הנפוצה לאחר הפסקת גילניה׳ בפרק תופעות הלוואי.

אין ליטול תרופות בחושך! בדוק התווית והמנה <u>בכל פעם</u> שהנך נוטל תרופה.
הרכב משקפיים אם הנך זקוק להם.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

4. תופעות לוואי

כמו בכל תרופה, השימוש בגילניה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תבהל למקרא רשימת תופעות הלוואי, יתכן שלא תסבול מאף אחת מהן.

גילניה עשויה לגרום לתופעות לוואי רציניות, כולל:

- **קצב לב איטי (ברדיקרדיה או ברדיאריתמיה) כאשר אתה מתחיל ליטול גילניה**

גילניה יכולה לגרום להאטה בקצב הלב שלך, במיוחד לאחר שאתה נוטל את המנה הראשונה. ראה פירוט בסעיף ׳אזהרות מיוחדות הנוגעות לשימוש בתרופה׳, תת-סעיף ׳נטילת המנה הראשונה׳.

- **זיהומים**

גילניה יכולה להגביר את הסיכון שלך לזיהומים רציניים שעשויים להיות מסכני חיים ולגרום למוות. אין לקבל חיסונים **חיים** במהלך הטיפול בגילניה ובמשך חודשיים לאחר שהפסקת ליטול גילניה. דבר עם הרופא שלך לפני שאתה מקבל חיסון בזמן הטיפול ובמשך חודשיים לאחר הטיפול בגילניה. אם אתה מקבל חיסון חי, אתה עשוי לקבל את הזיהום שהחיסון היה אמור למנוע.
חיסונים עשויים להיות פחות יעילים כאשר הם ניתנים בזמן הטיפול בגילניה.
וירוס הפפילומה (HPV) – עקב הסיכון לזיהום וירוס הפפילומה יש להיוועץ ברופא שלך לגבי בדיקה שגרתית של משטח צוואר הרחם (משטח פאפ).

גילניה מפחיתה את מספר תאי הדם הלבנים (לימפוציטים) בדם שלך. זה יחזור לרמה הרגילה בדרך כלל בתוך חודשיים מהפסקת הטיפול. יתכן שהרופא שלך יבצע בדיקת דם לבדיקת תאי הדם הלבנים שלך לפני שאתה מתחיל ליטול גילניה. פנה מיד לרופא שלך אם יש לך תסמינים כלשהם של זיהום במשך טיפול בגילניה ולמשך חודשיים לאחר המנה האחרונה של גילניה:

- חום
- עייפות
- כאבים בגוף
- צמרמורות
- בחילות
- הקאות
- כאב ראש המלווה בחום, נוקשות בצוואר, רגישות לאור, בחילות או בלבול (אלה עשויים להיות תסמינים של דלקת קרום המוח, זיהום של הקרומים סביב המוח ועמוד השידרה).

- **Progressive Multifocal Leukoencephalopathy (PML)**

PML זה זיהום נדיר במח אשר מוביל בדרך כלל למוות או לנכות חמורה. אם PML מתרחש, זה קורה בדרך כלל באנשים עם מערכת חיסונית מוחלשת אך קרה גם באנשים שהמערכת החיסונית שלהם לא מוחלשת. התסמינים של PML מחמירים במשך ימים עד שבועות. פנה מיד לרופא שלך אם יש לך תסמינים של PML, חדשים או מחמירים, אשר נמשכים מספר ימים, כולל:

- חולשה של צד אחד של הגוף
- איבוד תיאום התנועות (הקואורדינציה) בזרועות וברגליים
- ירידה בכוח

- בעיות בשיווי המשקל
- שינויים בראייה
- שינויים בחשיבה או בזיכרון
- בלבול
- שינויים באישיות

- **בעיה בראייה הנקראת בצקת מאקולרית**

בצקת מאקולרית עשויה לגרום לחלק מאותם תסמינים הקשורים בראייה כמו התקף של טרשת נפוצה (דלקת בעצב הראיה). יתכן שלא תבחין בתסמינים כלשהם עם בצקת מאקולרית. אם מתרחשת בצקת מאקולרית, היא בדרך כלל מתחילה במהלך 3 עד 4 החודשים הראשונים לאחר התחלת הטיפול בגילניה. על הרופא שלך לבדוק את הראיה שלך לפני תחילת הטיפול בגילניה ו- 3 עד 4 חודשים לאחר תחילת הטיפול, או בכל זמן בו אתה מבחין בשינויים בראיה במהלך הטיפול בגילניה. הסיכון שלך לבצקת מאקולרית גבוה יותר אם יש לך סוכרת או אם היתה לך דלקת בעין הנקראת דלקת הענבייה (אובאיטיס).

פנה מיד לרופא אם יש לך אחד או יותר מהבאים:

- ערפול או צללים במרכז הראיה שלך
- כתם עיוור במרכז הראיה שלך
- רגישות לאור
- ראיית צבעים (גוונים) חריגה

תופעות לוואי רציניות נוספות:

- **התנפחות והיצרות של כלי הדם במח שלך.** מצב הנקרא PRES (Posterior Reversible Encephalopathy Syndrome) התרחש באופן נדיר במטופלים הנוטלים גילניה.
התסמינים של PRES משתפרים בדרך כלל כאשר מפסיקים ליטול גילניה. אולם ללא טיפול, עלולים להוביל לשבץ. פנה מיד לרופא אם יש לך אחד או יותר מהתסמינים הבאים:
  - כאב ראש חמור פתאומי
  - בלבול פתאומי
  - איבוד פתאומי של הראייה או שינויים אחרים בראייה שלך
  - פרכוסים
- **נזק לכבד.** גילניה עשויה לגרום לנזק לכבד. על הרופא שלך לבצע בדיקות דם כדי לבדוק את הכבד שלך לפני שאתה מתחיל ליטול גילניה ובאופן תקופתי במהלך הטיפול. פנה לרופא שלך מיד אם יש לך אחד או יותר מהתסמינים הבאים של נזק לכבד:
  - בחילות
  - הקאות
  - כאב בטן
  - עייפות
  - איבוד התאבון
  - הצהבה של העור או של לובן העיניים
  - שתן כהה
- **בעיות נשימה.** לאנשים מסויימים הנוטלים גילניה יש קוצר נשימה. פנה לרופא מיד אם יש לך בעיות נשימה חדשות או מחמירות.
- **החמרה קשה בטרשת הנפוצה לאחר הפסקת גילניה.**

בהפסקת גילניה, תסמיני טרשת נפוצה עלולים לחזור ולהחמיר בהשוואה למה שהיה לפני הטיפול או במהלכו. אנשים רבים עם החמרה בתסמיני טרשת נפוצה שהתרחשה לאחר הפסקת גילניה לא חוזרים לרמת התפקוד שהיתה להם לפני הפסקת גילניה. החמרה זו מתרחשת לרוב תוך 12 שבועות לאחר הפסקת גילניה אך עשויה להתרחש מאוחר יותר. דבר עם הרופא שלך תמיד לפני שאתה מפסיק ליטול גילניה מכל סיבה שהיא. ספר לרופא שלך אם יש החמרה בתסמיני הטרשת הנפוצה לאחר הפסקת גילניה.

- **לחץ דם גבוה.** על הרופא שלך לבדוק את לחץ הדם שלך במהלך הטיפול בגילניה.
- **סוגים של סרטן העור הנקראים קרצינומה של תאי הבסיס (BCC) ומלאנומה.** ספר לרופא שלך אם יש שינויים כלשהם במראה העור שלך כולל שינויים בשומה, אזור כהה חדש על העור שלך, פצע שאינו מחלים או גידולים על העור שלך כגון בליטה שעשויה להיות מבריקה, לבן פנינה, בצבע העור או ורודה. על הרופא שלך לבדוק את העור שלך

לראות אם יש שינויים כלשהם במהלך הטיפול בגילניה. עליך להגביל את זמן השהייה באור שמש ובאור אולטרה-סגול (UV). לבש בגדים מגנים והשתמש בקרם הגנה עם מקדם הגנה גבוה.

- **תגובות אלרגיות**. פנה לרופא שלך אם יש לך תסמינים של תגובה אלרגית, כולל פריחה, סרפדת מגרדת או התנפחות של השפתיים, הלשון או הפנים.

<u>תופעות הלוואי השכיחות ביותר של גילניה כוללות (מופיעות ביותר ממשתמש אחד מעשרה):</u>

- כאב ראש
- בדיקות כבד לא תקינות
- שלשול
- שיעול
- שפעת
- דלקת בסינוסים (סינוסיטיס)
- כאב גב
- כאב באזור הבטן
- כאב בזרועות או ברגליים

<u>תופעות לוואי שכיחות (מופיעות ב- 1-10 משתמשים מתוך 100):</u>

- דלקת הסימפונות (ברונכיטיס)
- שלבקת חוגרת (הרפס זוסטר)
- פטריית שמש
- מיגרנה
- בחילות
- חולשה
- נשירת שיער
- קרנת אקטינית - גידול טרום-סרטני (actinic keratosis)
- עליה ברמות הטריגליצרידים בדם
- ראיה מעורפלת
- מיעוט לימפוציטים (לימפופניה)
- מיעוט תאי דם לבנים (לויקופניה)
- פפילומה של העור - גידול שפיר על פני העור

תופעות לוואי נוספות שדווחו כוללות פרכוסים, סחרחורת, דלקת ריאות, אקזמה וגרד.

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם הרופא.

<u>דיווח על תופעות לוואי</u>

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי או ע"י כניסה לקישור:
https://sideeffects.health.gov.il

5. איך לאחסן את התרופה?

מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.

אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.

תנאי איחסון

יש לאחסן את התרופה מתחת ל - 25°C, יש להגן מלחות.

6. מידע נוסף

נוסף על המרכיב הפעיל התרופה מכילה גם:

Mannitol, magnesium stearate.

מרכיבי הכמוסה הריקה:

Gelatin, titanium dioxide (C.I. 77891, E171), yellow iron oxide (C.I. 77492, E172), printing ink black, printing ink yellow.

מרכיבי הדיו המוטבע על הכמוסה:

Shellac (E904), dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, black iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), dimethicone.

כיצד נראית התרופה ומה תוכן האריזה

התרופה גילניה משווקת ככמוסות קשות לשימוש פומי (מתן דרך הפה). לכמוסות הקשות גוף לבן אטום עם הדפסת שני פסים בצהוב ומכסה צהוב בהיר אטום עם הדפסת FTY 0.5 mg בשחור.
תכולת הכמוסות: אבקה בצבע לבן עד כמעט לבן.

גודל האריזה: 7 או 28 כמוסות. (יתכן שלא כל גדלי האריזה משווקים).

בעל הרישום והיבואן וכתובתו: נוברטיס ישראל בע"מ, ת.ד. 7126 תל אביב

נערך בנובמבר 2020

מס' רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:
גילניה 0.5 מ"ג - 145 78 33270

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.