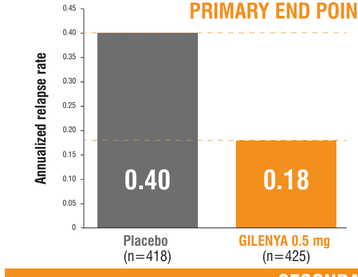
SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs PLACEBO

FREEDOMS AT THE END OF A 2-YEAR, PLACEBO-CONTROLLED STUDY IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



54%
(0.18 vs 0.40)
relative reduction in ARR
with GILENYA (n=425) vs placebo (n=418); $P<0.001$[1,5]

SECONDARY END POINTS

DISABILITY PROGRESSION*

▼30%
(18% vs 24%)
reduction in risk
with GILENYA vs placebo (HR, 0.70; 95% CI, 0.52-0.96; $P=0.02$)[1,5]
Derived from the HR.

Gd+ T1 LESIONS

▼82%
(0.2 vs 1.1)
fewer Gd+ T1 lesions
on average for GILENYA (n=425) vs placebo (n=418); $P<0.001$[1,5]

NEW OR NEWLY ENLARGING T2 LESIONS

▼74%
(2.5 vs 9.8)
fewer T2 lesions
on average for GILENYA (n=425) vs placebo (n=418); $P<0.001$[1,5]

MRI evaluations were performed at screening and at 2 years for the total population.

*Confirmed at 24 months, where 3-month confirmed disability progression was defined as an increase of 1 point in the EDSS score from baseline (or half of a point increase if the baseline EDSS score was equal to 5.5) sustained for 3 months.

More adult patients were relapse-free[2]

70% free of relapses with GILENYA 0.5 mg (n=425) vs 46% with placebo (n=418; $P<0.001$); HR, 0.48; 95% CI, 0.39-0.61; $P<0.001$

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-55 years of age, and had an EDSS score of 0.0-5.5 (median score was 2.0).

Important Safety Information (cont)

Liver Injury: Clinically significant liver injury has occurred in patients treated with GILENYA in the postmarketing setting. Signs and symptoms of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as 10 days after the first dose and also have been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

Elevation of liver enzymes (ALT, AST, and GGT) 3- and 5-fold the upper limit of normal and greater has occurred with GILENYA. The majority occurred within 6 to 9 months and returned to normal within 2 months after discontinuing GILENYA. Recurrence of liver transaminase elevations occurred with rechallenge in some patients.

Please see additional Important Safety Information on previous and following pages. Please see full Prescribing Information in pocket.

Prior to starting treatment with GILENYA (within 6 months), obtain serum transaminases (ALT and AST) and total bilirubin levels, and periodically until 2 months after GILENYA discontinuation. Patients should be monitored for signs and symptoms of any hepatic injury. Treatment with GILENYA should be interrupted if the patient is found to have an ALT greater than 3 times the reference range with serum total bilirubin greater than 2 times the reference range. Patients with severe hepatic impairment should be closely monitored, as their risk of adverse reactions is greater.

GILENYA™ (fingolimod) capsules 0.5 mg

Important Safety Information (cont)

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported with GILENYA. Symptoms reported include 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.

Respiratory Effects: Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in GILENYA patients as early as 1 month after initiation. Changes in FEV1 appear to be reversible after discontinuing GILENYA; however, there is insufficient information to determine reversibility of DLCO. Obtain spirometry and DLCO when clinically indicated.

Fetal Risk: GILENYA may cause fetal harm when administered to a pregnant woman. 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. A registry for women who become pregnant during GILENYA treatment is available. Contact the GILENYA Pregnancy Registry by calling 1-877-598-7237, sending an e-mail to gpr@quintiles.com, or visiting gilenyapregnancyregistry.com.

Severe Increase in Disability After Stopping GILENYA: Severe increase in disability accompanied by multiple new lesions on MRI has been reported following discontinuation of GILENYA in the postmarketing setting. 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.

The possibility of severe increase in disability should be considered in patients who discontinue GILENYA, including those who are pregnant or planning for pregnancy. Monitor patients for development of severe increase in disability following discontinuation of GILENYA and begin appropriate treatment as needed.

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

Increased Blood Pressure (BP): Monitor BP during treatment with GILENYA. An average increase of 3 mm Hg in systolic and 2 mm Hg in diastolic BP was observed in clinical trials versus placebo.

Malignancies: The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with GILENYA. Melanoma, squamous cell carcinoma, and Merkel cell carcinoma have been reported with GILENYA in the postmarketing setting. Monitor and evaluate suspicious skin lesions.

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. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported in the postmarketing setting.

Immune System Effects Following Discontinuation: Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts for up to 2 months following the last dose. Lymphocyte counts generally return to normal range within 1 to 2 months of stopping therapy. Initiating other drugs during this period warrants the same considerations needed for concomitant administration.

Hypersensitivity Reactions: Hypersensitivity reactions including rash, urticaria, and angioedema have been reported with GILENYA.

Drug Interactions: Closely monitor patients receiving systemic ketoconazole. The use of live attenuated vaccines should be avoided during, and for 2 months after stopping GILENYA.

Common Adverse Reactions: The most common adverse reactions with GILENYA 0.5 mg (incidence ≥10% and >placebo) were headache, liver transaminase elevations, diarrhea, nausea, cough, influenza, sinusitis, abdominal pain, back pain, and pain in extremity.

Seizure: Cases of seizures, including status epilepticus, have been reported with the use of GILENYA in clinical trials and in the postmarketing setting in adults. In adult clinical trials, the rate of seizures was 0.9% in GILENYA-treated patients and 0.3% in placebo-treated patients.

Pediatric Patients 10 Years of Age and Older: In the pediatric study, the safety profile in pediatric patients receiving GILENYA 0.25 mg or 0.5 mg daily was similar to that seen in adult patients. Cases of seizures were reported in 5.6% of GILENYA-treated patients and 0.9% of interferon beta-1a-treated patients.

References: 1. Gilenya [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; December 2019. **2.** Cohen JA, Barkhof F, Comi G, et al; for TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):402-415. **3.** Data on file. ASSESS Reference Packet. Novartis Pharmaceuticals Corp; April 2019. **4.** Data on file. CSR 2302. Novartis Pharmaceuticals Corp; July 2009. **5.** Kappos L, Radue E-W, O'Connor P, et al; for FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):387-401.

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NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 1/20 GYA-1385928

GILENYA™ (fingolimod) capsules 0.5 mg

In adult patients with RRMS at 1 year

GILENYA DEMONSTRATED SUPERIOR ARR

vs AVONEX® AND COPAXONE®[1-3]

Indication

GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

Important Safety Information

Contraindications

- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure (HF) requiring hospitalization or Class III/IV HF
- 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
- Baseline QTc interval ≥500 msec
- Cardiac arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients who have had a hypersensitivity reaction to fingolimod or any of the excipients in GILENYA. Observed reactions include rash, urticaria, and angioedema upon treatment initiation

ARR=annualized relapse rate;
RRMS=relapsing-remitting multiple sclerosis.

Please see additional Important Safety Information on the following pages. Please see full Prescribing Information in pocket.

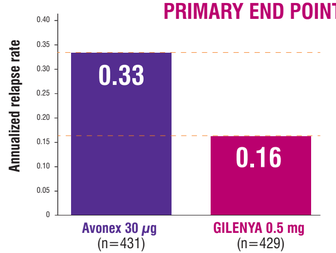
GILENYA™ (fingolimod) capsules 0.5 mg

SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs AVONEX®

TRANSFORMS

AT THE END OF A 1-YEAR, ACTIVE-CONTROLLED STUDY VS AVONEX (interferon beta-1a) INJECTION IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



52%

(0.16 vs 0.33)
relative reduction in ARR
with GILENYA (n=429) vs Avonex (n=431); $P<0.001$[1,2]

SECONDARY END POINTS

DISABILITY PROGRESSION

No significant difference in time to 3-month confirmed disability progression*

(HR, 0.71; 95% CI, 0.42-1.21; $P=0.21$) or absence of confirmed disability progression between GILENYA and Avonex at year 1 in TRANSFORMS; $P=0.25$[1,2,4]

Gd+ T1 LESIONS

▼60%

(0.2 vs 0.5)
fewer Gd+ T1 lesions
on average for GILENYA (n=429) vs Avonex (n=431); $P<0.001$[1,2]

NEW OR NEWLY ENLARGING T2 LESIONS

▼38%

(1.6 vs 2.6)
fewer T2 lesions
on average for GILENYA (n=429) vs Avonex (n=431); $P=0.002$[1,2]

MRI evaluations were performed at screening and at 1 year for the total population.

*Confirmed at 12 months, where 3-month confirmed disability progression was defined as an increase of 1 point in the EDSS score from baseline (or half of a point increase if the baseline EDSS score was equal to 5.5) sustained for 3 months.

More adult patients were relapse-free[1]

83% free of relapses with GILENYA 0.5 mg (n=429) vs 70% with Avonex (n=431); ($P<0.001$)

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-55 years of age, and had an EDSS score of 0.0-5.5 (median score was 2.0).

Important Safety Information (cont)

Bradyarrhythmia and Atrioventricular (AV) Block: Monitor patients during GILENYA initiation because of a risk of bradyarrhythmia and AV block. Prior to dosing and at the end of the observation period, obtain an electrocardiogram (ECG) in all patients (10 years of age and older). Monitor all patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure (BP) measurement.

Continue monitoring until the abnormality resolves if any of the following is present after 6 hours: (1) The heart rate (HR) 6 hours postdose is <45 bpm in adults, <55 bpm in pediatric patients 12 years of age and older, or <60 bpm in pediatric patients 10 or 11 years of age. (2) The HR 6 hours postdose is at the lowest value postdose suggesting that the maximum pharmacodynamic effect on the heart may not have occurred. (3) The ECG 6 hours postdose shows new onset second degree or higher atrioventricular (AV) block.

Begin continuous ECG monitoring in patients with symptomatic bradycardia until resolution. If pharmacological intervention is required, continue ECG monitoring overnight in a medical facility, and repeat 6-hour monitoring after the second dose. Some patients may experience a second decrease in HR within 24 hours after the first dose.

Please see additional Important Safety Information on previous and following pages. Please see full Prescribing Information in pocket.

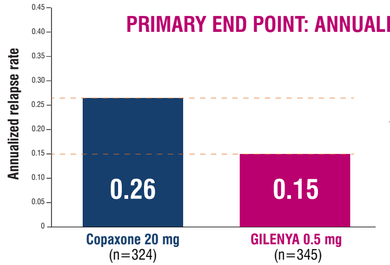
In adult patients with RRMS

SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs COPAXONE®

ASSESS

A 1-YEAR ACTIVE-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, PHASE IIIB STUDY VS COPAXONE (glatiramer acetate injection) 20 MG IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



41%

(0.15 vs 0.26)
relative reduction in ARR
with GILENYA 0.5 mg (n=345) vs Copaxone 20 mg (n=324); $P=0.0138$[3]*

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-65 years of age, and had an EDSS score of 0.0-6.0 (median score was 2.5).

Adverse Reactions

Adverse reactions with GILENYA (0.5 mg) in ASSESS were consistent with the known safety profile of GILENYA (0.5 mg)[3]

*Aggregate ARR estimate, ARR ratio, and P value are calculated using a negative binomial regression model adjusted for treatment, region, number of relapses experienced in the previous year, baseline EDSS, and baseline Gd+T1 lesion count.

EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; HR=hazard ratio; MRI=magnetic resonance imaging; NS=not significant.

Important Safety Information (cont)

Bradyarrhythmia and Atrioventricular (AV) Block (cont): Patients with pre-existing ischemic heart disease, history of MI or cardiac arrest, CHF, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia or recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block, or on concomitant drugs that slow HR or AV conduction should be evaluated by a physician and, if treated with GILENYA, monitored overnight with continuous ECG in a medical facility after first dose due to higher risk of symptomatic bradycardia or heart block. Patients with or at risk for QT prolongation or on concomitant QT-prolonging drugs with a known risk of torsades de pointes should also be monitored overnight with continuous ECG.

Repeat first-dose monitoring if GILENYA is interrupted ≥1 day within first 2 weeks or >7 days during weeks 3 and 4, or >14 days after the first month of treatment because effects on HR and AV conduction may occur upon reinitiation. First-dose monitoring is also recommended when the dose is increased in pediatric patients switching from 0.25 mg to 0.5 mg.

Please see additional Important Safety Information on previous and following pages. Please see full Prescribing Information in pocket.

Infections: GILENYA may increase risk of infections. Life threatening and fatal infections have occurred in association with GILENYA. A recent CBC should be available before initiating GILENYA. Consider suspending GILENYA if a patient develops a serious infection. Monitor for signs and symptoms of infection during treatment and up to 2 months after discontinuation. Do not start GILENYA in patients with active acute or chronic infections until infection is resolved. Two patients receiving a higher than recommended dose of GILENYA (1.25 mg) in conjunction with high-dose corticosteroid therapy died of herpetic infections. In the postmarketing setting with GILENYA, serious infections, some fatal, have been reported with opportunistic pathogens, including viruses (eg, John Cunningham virus [JCV], herpes simplex viruses 1 and 2, varicella zoster virus [VZV]), fungi (eg, cryptococci), bacteria (eg, atypical mycobacteria), and Kaposi's sarcoma. Patients with signs and symptoms consistent with any of these infections should undergo prompt diagnostic evaluation and treatment. Concomitant use with antineoplastic, immunosuppressive, or immune-modulating therapies are expected to increase the risk of additive immunosuppression. When switching to GILENYA from these types of therapies, consider their duration of effect and mode of action to avoid this risk.

STUDY DESCRIPTIONS

FREEDOMS (**F**TY720 **R**esearch **E**valuating **E**ffects of **D**aily **O**ral Therapy in **M**ultiple **S**clerosis): A 2-year, randomized, double-blind, placebo-controlled phase III study in 1272 adults with RRMS. At baseline, patients had a diagnosis of RRMS with at least 1 documented relapse during the previous year or at least 2 documented relapses during the previous 2 years, were between 18 and 55 years of age, and had a score of 0.0 to 5.5 on the EDSS (median score at baseline was 2.0). The primary end point was ARR. The key secondary end point was 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. Additional secondary end points included number of Gd+ T1 lesions, and number of new or newly enlarged lesions on T2-weighted MRI scans.[1]

TRANSFORMS (**Tr**ial **A**ssessing Injectable **I**nterferon **v**s **F**TY720 **O**ral in **R**elapsing-Remitting **M**ultiple **S**clerosis): A 1-year, randomized, double-blind, double-dummy, active-controlled (interferon beta-1a) IM injection phase III study of 1292 adults with RRMS. At baseline, patients had a diagnosis of RRMS with at least 1 documented relapse during the previous year or at least 2 documented relapses during the previous 2 years, were between 18 and 55 years of age, and had a score of 0.0 to 5.5 on the EDSS (median score at baseline was 2.0). The primary end point was ARR. The two key secondary end points were the number of new or newly enlarged hyperintense lesions on T2-weighted MRI scans at 12 months and 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.[1]

SQ=subcutaneous.

ASSESS: A 1-year, randomized, dose-blind, rater-blind, active-controlled (glatiramer acetate injection) SQ, phase IIIb study in adults with RRMS. Patients randomly assigned to receive once-daily GILENYA 0.5 mg vs once-daily subcutaneous injections of Copaxone 20 mg. At baseline, patients with RRMS between 18 and 65 years of age (median 39) had ≥1 documented relapse during the previous year or ≥2 documented relapses during the previous 2 years, and had a score of 0.0 to 6.0 on the EDSS (median score at baseline was 2.5). The primary end point was ARR.[3]

Important Safety Information (cont)

Infections (cont): Before initiating GILENYA, patients should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients is recommended prior to starting treatment. GILENYA initiation should be postponed for 1 month after vaccination. It is recommended that pediatric patients, if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating GILENYA.

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

Progressive Multifocal Leukoencephalopathy (PML): Cases of PML occurred in patients with MS who received GILENYA in the postmarketing 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 usually leads to severe disability or death. PML has occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, and who were not taking concomitant immunosuppressive or immunomodulatory medications.

Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body, clumsiness of limbs, visual disturbances, and changes in thinking, memory, and orientation, leading to confusion and personality changes.

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MRI findings may be apparent before clinical signs or symptoms. PML, diagnosed based on MRI findings and detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, has been reported in patients treated with MS medications associated with PML, including GILENYA. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful. Any suspicious findings should lead to further investigation to allow for an early diagnosis of PML. Lower PML-related morbidity and mortality 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 differences in disease in these patients.

At the first sign or symptom suggestive of PML, withhold GILENYA and perform an appropriate diagnostic evaluation.

Macular Edema: Fingolimod increases the risk of macular edema, with or without visual symptoms. Perform an exam of the fundus, including the macula, before starting GILENYA, and 3 to 4 months after initiation. Monitor visual acuity at baseline, during routine patient evaluations, and if a patient reports visual disturbances while on GILENYA. Patients with diabetes mellitus or history of uveitis are at increased risk and should have regular ophthalmologic evaluations.

GILENYA™ (fingolimod) capsules 0.5 mg

GYA-1385928
2020 Efficacy Leave Behind ASSESS Update
Presentation: Trifold brochure

Please note, this layout indicator is for illustrative purposes only and is not intended for content review

Front cover

8.5 in”

11 in”

In adult patients with RRMS at 1 year

GILENYA DEMONSTRATED
SUPERIOR ARR

vs AVONEX® AND COPAXONE®[1-3]

Indication

GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

Important Safety Information

Contraindications

- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure (HF) requiring hospitalization or Class III/IV HF
- 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
- Baseline QTc interval ≥500 msec
- Cardiac arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients who have had a hypersensitivity reaction to fingolimod or any of the excipients in GILENYA. Observed reactions include rash, urticaria, and angioedema upon treatment initiation

ARR=annualized relapse rate;
RRMS=relapsing-remitting multiple sclerosis.

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GILENYA™ (fingolimod) capsules 0.5mg

Back cover

8.5 in”

11 in”

Important Safety Information (cont)

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported with GILENYA. Symptoms reported include 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.

Respiratory Effects: Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in GILENYA patients as early as 1 month after initiation. Changes in FEV1 appear to be reversible after discontinuing GILENYA; however, there is insufficient information to determine reversibility of DLCO. Obtain spirometry and DLCO when clinically indicated.

Fetal Risk: GILENYA may cause fetal harm when administered to a pregnant woman. 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. A registry for women who become pregnant during GILENYA treatment is available. Contact the GILENYA Pregnancy Registry by calling 1-877-598-7237, sending an e-mail to gpr@quintiles.com, or visiting glenyapregnancyregistry.com.

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The possibility of severe increase in disability should be considered in patients who discontinue GILENYA, including those who are pregnant or planning for pregnancy. Monitor patients for development of severe increase in disability following discontinuation of GILENYA and begin appropriate treatment as needed.

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

Increased Blood Pressure (BP): Monitor BP during treatment with GILENYA. An average increase of 3 mm Hg in systolic and 2 mm Hg in diastolic BP was observed in clinical trials versus placebo.

Malignancies: The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with GILENYA. Melanoma, squamous cell carcinoma, and Merkel cell carcinoma have been reported with GILENYA in the postmarketing setting. Monitor and evaluate suspicious skin lesions.

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. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported in the postmarketing setting.

Immune System Effects Following Discontinuation: Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts for up to 2 months following the last dose. Lymphocyte counts generally return to normal range within 1 to 2 months of stopping therapy. Initiating other drugs during this period warrants the same considerations needed for concomitant administration.

Hypersensitivity Reactions: Hypersensitivity reactions including rash, urticaria, and angioedema have been reported with GILENYA.

Drug Interactions: Closely monitor patients receiving systemic ketoconazole. The use of live attenuated vaccines should be avoided during, and for 2 months after stopping GILENYA.

Common Adverse Reactions: The most common adverse reactions with GILENYA 0.5 mg (incidence ≥10% and >placebo) were headache, liver transaminase elevations, diarrhea, nausea, cough, influenza, sinusitis, abdominal pain, back pain, and pain in extremity.

Seizure: Cases of seizures, including status epilepticus, have been reported with the use of GILENYA in clinical trials and in the postmarketing setting in adults. In adult clinical trials, the rate of seizures was 0.9% in GILENYA-treated patients and 0.3% in placebo-treated patients.

Pediatric Patients 10 Years of Age and Older: In the pediatric study, the safety profile in pediatric patients receiving GILENYA 0.25 mg or 0.5 mg daily was similar to that seen in adult patients. Cases of seizures were reported in 5.6% of GILENYA-treated patients and 0.9% of interferon beta-1a-treated patients.

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East Hanover, New Jersey 07936-1080

Printed in USA 1/20 GYA-1385928

Outside spread

25.5 in”

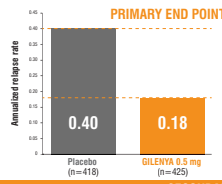
11 in”

In adult patients with RRMS

SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs PLACEBO

FREEDOMS AT THE END OF A 2-YEAR, PLACEBO-CONTROLLED STUDY IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



54% relative reduction in ARR (0.18 vs 0.40) with GILENYA (n=425) vs placebo (n=418); *P*<0.001[1,5]

SECONDARY END POINTS

DISABILITY PROGRESSION*	Gd+ T1 LESIONS	NEW OR NEWLY ENLARGING T2 LESIONS
30% reduction in risk (18% vs 24%) with GILENYA vs placebo (HR, 0.70; 95% CI, 0.52-0.96; *P*=0.02)[1,5] Derived from the HR.	**82%** fewer Gd+ T1 lesions (0.2 vs 1.1) on average for GILENYA (n=425) vs placebo (n=418); *P*<0.001[1,5]	**74%** fewer T2 lesions (2.5 vs 9.8) on average for GILENYA (n=425) vs placebo (n=418); *P*<0.001[1,5]

MRI evaluations were performed at screening and at 2 years for the total population.

*Confirmed at 24 months, where 3-month confirmed disability progression was defined as an increase of 1 point in the EDSS score from baseline (or half of a point increase if the baseline EDSS score was equal to 5.5) sustained for 3 months.

More adult patients were relapse-free[1]

70% free of relapses with GILENYA 0.5 mg (n=425) vs 46% with placebo (n=418; *P*<0.001); HR, 0.48; 95% CI, 0.39-0.61; *P*<0.001

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-55 years of age, and had an EDSS score of 0.0-5.5 (median score was 2.0).

Important Safety Information (cont)

Liver Injury: Clinically significant liver injury has occurred in patients treated with GILENYA in the postmarketing setting. Signs and symptoms of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as 10 days after the first dose and also have been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

Elevation of liver enzymes (ALT, AST, and GGT) 3- and 5-fold the upper limit of normal and greater has occurred with GILENYA. The majority occurred within 6 to 9 months and returned to normal within 2 months after discontinuing 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, and periodically until 2 months after GILENYA discontinuation. Patients should be monitored for signs and symptoms of any hepatic injury. Treatment with GILENYA should be interrupted if the patient is found to have an ALT greater than 3 times the reference range with serum total bilirubin greater than 2 times the reference range. Patients with severe hepatic impairment should be closely monitored, as their risk of adverse reactions is greater.

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GILENYA™ (fingolimod) capsules 0.5mg

Important Safety Information (cont)

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported with GILENYA. Symptoms reported include 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.

Respiratory Effects: Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in GILENYA patients as early as 1 month after initiation. Changes in FEV1 appear to be reversible after discontinuing GILENYA; however, there is insufficient information to determine reversibility of DLCO. Obtain spirometry and DLCO when clinically indicated.

Fetal Risk: GILENYA may cause fetal harm when administered to a pregnant woman. 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. A registry for women who become pregnant during GILENYA treatment is available. Contact the GILENYA Pregnancy Registry by calling 1-877-598-7237, sending an e-mail to gpr@quintiles.com, or visiting glenyapregnancyregistry.com.

Severe Increase in Disability After Stopping GILENYA: Severe increase in disability accompanied by multiple new lesions on MRI has been reported following discontinuation of GILENYA in the postmarketing setting. 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.

The possibility of severe increase in disability should be considered in patients who discontinue GILENYA, including those who are pregnant or planning for pregnancy. Monitor patients for development of severe increase in disability following discontinuation of GILENYA and begin appropriate treatment as needed.

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

Increased Blood Pressure (BP): Monitor BP during treatment with GILENYA. An average increase of 3 mm Hg in systolic and 2 mm Hg in diastolic BP was observed in clinical trials versus placebo.

Malignancies: The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with GILENYA. Melanoma, squamous cell carcinoma, and Merkel cell carcinoma have been reported with GILENYA in the postmarketing setting. Monitor and evaluate suspicious skin lesions.

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. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported in the postmarketing setting.

Immune System Effects Following Discontinuation: Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts for up to 2 months following the last dose. Lymphocyte counts generally return to normal range within 1 to 2 months of stopping therapy. Initiating other drugs during this period warrants the same considerations needed for concomitant administration.

Hypersensitivity Reactions: Hypersensitivity reactions including rash, urticaria, and angioedema have been reported with GILENYA.

Drug Interactions: Closely monitor patients receiving systemic ketoconazole. The use of live attenuated vaccines should be avoided during, and for 2 months after stopping GILENYA.

Common Adverse Reactions: The most common adverse reactions with GILENYA 0.5 mg (incidence ≥10% and >placebo) were headache, liver transaminase elevations, diarrhea, nausea, cough, influenza, sinusitis, abdominal pain, back pain, and pain in extremity.

Seizure: Cases of seizures, including status epilepticus, have been reported with the use of GILENYA in clinical trials and in the postmarketing setting in adults. In adult clinical trials, the rate of seizures was 0.9% in GILENYA-treated patients and 0.3% in placebo-treated patients.

Pediatric Patients 10 Years of Age and Older: In the pediatric study, the safety profile in pediatric patients receiving GILENYA 0.25 mg or 0.5 mg daily was similar to that seen in adult patients. Cases of seizures were reported in 5.6% of GILENYA-treated patients and 0.9% of interferon beta-1a-treated patients.

References: 1. Gilenya [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; December 2019. **2.** Cohen JA, Barkhof F, Comi G, et al; for TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):402-415. **3.** Data on file. ASSESS Reference Packet. Novartis Pharmaceuticals Corp; April 2019. **4.** Data on file. CSR 2302. Novartis Pharmaceuticals Corp; July 2009. **5.** Kappos L, Radue E-W, O'Connor P, et al; for FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):387-401.

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NOVARTIS

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Printed in USA 1/20 GYA-1385928

In adult patients with RRMS at 1 year

GILENYA DEMONSTRATED
SUPERIOR ARR

vs AVONEX® AND COPAXONE®[1-3]

Indication

GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

Important Safety Information

Contraindications

- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure (HF) requiring hospitalization or Class III/IV HF
- 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
- Baseline QTc interval ≥500 msec
- Cardiac arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients who have had a hypersensitivity reaction to fingolimod or any of the excipients in GILENYA. Observed reactions include rash, urticaria, and angioedema upon treatment initiation

ARR=annualized relapse rate;
RRMS=relapsing-remitting multiple sclerosis.

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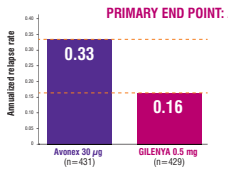
GILENYA™ (fingolimod) capsules 0.5mg

In adult patients with RRMS

SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs AVONEX®

TRANSFORMS AT THE END OF A 1-YEAR, ACTIVE-CONTROLLED STUDY VS AVONEX (interferon beta-1a) INJECTION IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



52% relative reduction in ARR (0.16 vs 0.33) with GILENYA (n=429) vs Avonex (n=431); *P*<0.001[1,2]

SECONDARY END POINTS

DISABILITY PROGRESSION	Gd+ T1 LESIONS	NEW OR NEWLY ENLARGING T2 LESIONS
No significant difference in time to 3-month confirmed disability progression* (HR, 0.71; 95% CI, 0.42-1.21; *P*=0.21) or absence of confirmed disability progression between GILENYA and Avonex at year 1 in TRANSFORMS; *P*=0.25[1,2,4]	**60%** fewer Gd+ T1 lesions (0.2 vs 0.5) on average for GILENYA (n=429) vs Avonex (n=431); *P*<0.001[1,2]	**38%** fewer T2 lesions (1.6 vs 2.6) on average for GILENYA (n=429) vs Avonex (n=431); *P*=0.002[1,2]

MRI evaluations were performed at screening and at 1 year for the total population.

*Confirmed at 12 months, where 3-month confirmed disability progression was defined as an increase of 1 point in the EDSS score from baseline (or half of a point increase if the baseline EDSS score was equal to 5.5) sustained for 3 months.

More adult patients were relapse-free[1]

83% free of relapses with GILENYA 0.5 mg (n=429) vs 70% with Avonex (n=431); (*P*<0.001)

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-55 years of age, and had an EDSS score of 0.0-5.5 (median score was 2.0).

Important Safety Information (cont)

Bradyarrhythmia and Atrioventricular (AV) Block: Monitor patients during GILENYA initiation because of a risk of bradyarrhythmia and AV block. Prior to dosing and at the end of the observation period, obtain an electrocardiogram (ECG) in all patients (10 years of age and older). Monitor all patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure (BP) measurement.

Continue monitoring until the abnormality resolves if any of the following is present after 6 hours: (1) The heart rate (HR) 6 hours postdose is <45 bpm in adults, <55 bpm in pediatric patients 12 years of age and older, or <60 bpm in pediatric patients 10 or 11 years of age. (2) The HR 6 hours postdose is at the lowest value postdose suggesting that the maximum pharmacodynamic effect on the heart may not have occurred. (3) The ECG 6 hours postdose shows new onset second degree or higher atrioventricular (AV) block.

Begin continuous ECG monitoring in patients with symptomatic bradycardia until resolution. If pharmacological intervention is required, continue ECG monitoring overnight in a medical facility, and repeat 6-hour monitoring after the second dose. Some patients may experience a second decrease in HR within 24 hours after the first dose.

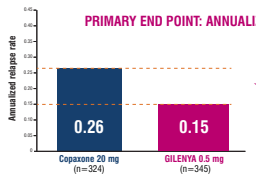
Please see additional Important Safety Information on previous and following pages. Please see full Prescribing Information in pocket.

In adult patients with RRMS

SIGNIFICANTLY LOWER ARR IN PATIENTS TREATED WITH GILENYA® (fingolimod) vs COPAXONE®

ASSESS A 1-YEAR ACTIVE-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, PHASE IIIB STUDY VS COPAXONE (glatiramer acetate injection) 20 MG IN ADULT PATIENTS WITH RRMS

PRIMARY END POINT: ANNUALIZED RELAPSE RATE



41% relative reduction in ARR (0.15 vs 0.26) with GILENYA 0.5 mg (n=345) vs Copaxone 20 mg (n=324); *P*=0.0136[3,4]

Patients had ≥1 relapse during the prior year or ≥2 relapses during the prior 2 years, were 18-65 years of age, and had an EDSS score of 0.0-6.0 (median score was 2.5).

Adverse Reactions

Adverse reactions with GILENYA (0.5 mg) in ASSESS were consistent with the known safety profile of GILENYA (0.5 mg)[3]

*Aggregate ARR estimate, ARR ratio, and *P* value are calculated using a negative binomial regression model adjusted for treatment, region, number of relapses experienced in the previous year, baseline EDSS, and baseline Gd+T1 lesion count.

EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; HR=hazard ratio; MRI=magnetic resonance imaging; NS=not significant.

Important Safety Information (cont)

Bradyarrhythmia and Atrioventricular (AV) Block (cont): Patients with pre-existing ischemic heart disease, history of MI or cardiac arrest, CHF, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia or recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block, or on concomitant drugs that slow HR or AV conduction should be evaluated by a physician and, if treated with GILENYA, monitored overnight with continuous ECG in a medical facility after first dose due to higher risk of symptomatic bradycardia or heart block. Patients with or at risk for QT prolongation or on concomitant QT-prolonging drugs with a known risk of torsades de pointes should also be monitored overnight with continuous ECG.

Repeat first-dose monitoring if GILENYA is interrupted ≥1 day within first 2 weeks or >7 days during weeks 3 and 4, or >14 days after the first month of treatment because effects on HR and AV conduction may occur upon reinitiation. First-dose monitoring is also recommended when the dose is increased in pediatric patients switching from 0.25 mg to 0.5 mg.

Infections: GILENYA may increase risk of infections. Life threatening and fatal infections have occurred in association with GILENYA. A recent CBC should be available before initiating GILENYA. Consider suspending GILENYA if a patient develops a serious infection. Monitor for signs and symptoms of infection during treatment and up to 2 months after discontinuation. Do not start GILENYA in patients with active acute or chronic infections until infection is resolved. Two patients receiving a higher than recommended dose of GILENYA (1.25 mg) in conjunction with high-dose corticosteroid therapy died of herpetic infections. In the postmarketing setting with GILENYA, serious infections, some fatal, have been reported with opportunistic pathogens, including viruses (eg, John Cunningham virus [JCV], herpes simplex viruses 1 and 2, varicella zoster virus [VZV]), fungi (eg, cryptococci), bacteria (eg, atypical mycobacteria), and Kaposi's sarcoma. Patients with signs and symptoms consistent with any of these infections should undergo prompt diagnostic evaluation and treatment. Concomitant use with antineoplastic, immunosuppressive, or immune-modulating therapies are expected to increase the risk of additive immunosuppression. When switching to GILENYA from these types of therapies, consider their duration of effect and mode of action to avoid this risk.

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GILENYA™ (fingolimod) capsules 0.5mg

STUDY DESCRIPTIONS

FREEDOMS (**F**TY720 **R**esearch **E**valuating **E**ffects of **D**aily **O**ral Therapy in **M**ultiple **S**clerosis): A 2-year, randomized, double-blind, placebo-controlled phase III study in 1272 adults with RRMS. At baseline, patients had a diagnosis of RRMS with at least 1 documented relapse during the previous year or at least 2 documented relapses during the previous 2 years, were between 18 and 55 years of age, and had a score of 0.0 to 5.5 on the EDSS (median score at baseline was 2.0). The primary end point was ARR. The key secondary end point was 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. Additional secondary end points included number of Gd+ T1 lesions, and number of new or newly enlarged lesions on T2-weighted MRI scans.[1]

SQ=subcutaneous.

TRANSFORMS (**Tr**ial **A**ssessing Injectable **I**nterferon vs **F**TY720 **O**ral in **R**elapsing-Remitting **M**ultiple **S**clerosis): A 1-year, randomized, double-blind, double-dummy, active-controlled (interferon beta-1a) IM injection phase III study of 1292 adults with RRMS. At baseline, patients had a diagnosis of RRMS with at least 1 documented relapse during the previous year or at least 2 documented relapses during the previous 2 years, were between 18 and 55 years of age, and had a score of 0.0 to 5.5 on the EDSS (median score at baseline was 2.0). The primary end point was ARR. The two key secondary end points were the number of new or newly enlarged hyperintense lesions on T2-weighted MRI scans at 12 months and 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.[1]

ASSESS: A 1-year, randomized, dose-blind, rater-blind, active-controlled (glatiramer acetate injection) SQ, phase IIIb study in adults with RRMS. Patients randomly assigned to receive once-daily GILENYA 0.5 mg vs once-daily subcutaneous injections of Copaxone 20 mg. At baseline, patients with RRMS between 18 and 65 years of age (median 39) had ≥1 documented relapse during the previous year or ≥2 documented relapses during the previous 2 years, and had a score of 0.0 to 6.0 on the EDSS (median score at baseline was 2.5). The primary end point was ARR.[3]

MRI findings may be apparent before clinical signs or symptoms. PML, diagnosed based on MRI findings and detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, has been reported in patients treated with MS medications associated with PML, including GILENYA. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful. Any suspicious findings should lead to further investigation to allow for an early diagnosis of PML. Lower PML-related morbidity and mortality 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 differences in disease in these patients.

At the first sign or symptom suggestive of PML, withhold GILENYA and perform an appropriate diagnostic evaluation.

Important Safety Information (cont)

Infections (cont): Before initiating GILENYA, patients should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients is recommended prior to starting treatment. GILENYA initiation should be postponed for 1 month after vaccination. It is recommended that pediatric patients, if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating GILENYA.

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

Progressive Multifocal Leukoencephalopathy (PML): Cases of PML occurred in patients with MS who received GILENYA in the postmarketing 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 usually leads to severe disability or death. PML has occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, and who were not taking concomitant immunosuppressive or immunomodulatory medications.

Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body, clumsiness of limbs, visual disturbances, and changes in thinking, memory, and orientation, leading to confusion and personality changes.

Macular Edema: Fingolimod increases the risk of macular edema, with or without visual symptoms. Perform an exam of the fundus, including the macula, before starting GILENYA, and 3 to 4 months after initiation. Monitor visual acuity at baseline, during routine patient evaluations, and if a patient reports visual disturbances while on GILENYA. Patients with diabetes mellitus or history of uveitis are at increased risk and should have regular ophthalmologic evaluations.

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GILENYA™ (fingolimod) capsules 0.5mg

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