Fingolimod (Gilenya) Capsules

Manufacturer: Novartis, Florham Park, N.J.

Indication: Fingolimod is indicated for the treatment of relapsing forms of multiple sclerosis (MS) in order to reduce the frequency of clinical exacerbations and to delay the progression of physical disability.

Drug Class: Fingolimod is a sphingosine 1-phosphate receptor modulator. The chemical formula is 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol HCl, and the molecular weight is 343.93. The product is provided as 0.5-mg hard gelatin capsules for oral use.

Uniqueness of Drug: Metabolized by sphingosine kinase to the active metabolite (fingolimod-phosphate), fingolimod 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, thus reducing the number of lymphocytes in peripheral blood. The mechanism by which these therapeutic effects occur in MS is unknown, but it may involve reduction of lymphocyte migration into the central nervous system (CNS).

Warnings and Precautions:

Reduction in heart rate. Initiating treatment results in a decreased heart rate. All patients should be observed for a period of six hours for signs and symptoms of bradycardia. If bradycardia-related symptoms occur after the dose is given, appropriate management should be instituted and the patient should be observed until the symptoms have resolved.

Underlying risk factors for bradycardia and atrioventricular (AV) block should be identified. If a recent electrocardiogram (ECG) (performed within the previous six months) is not available, one should be obtained in patients who are taking antiarrhythmic agents (including beta blockers and calcium-channel blockers), who have cardiac risk factors, and who have a slow or irregular heartbeat before starting therapy.

After the first dose is given, the heart rate starts to decrease within an hour; the decline on day 1 is maximal at approximately six hours. Following the second dose, a further decrease in heart rate may occur when compared with the rate prior to the second dose; however, this change is smaller than that occurring after the first dose. With continued dosing, the heart rate returns to the baseline level within one month of chronic treatment.

Atrioventricular blocks. Initiating fingolimod treatment has resulted in transient AV conduction delays. In controlled clinical trials, adverse drug reactions of first-degree AV block (a prolonged PR interval on the ECG) after the first dose were reported in 0.1% of patients receiving fingolimod 0.5 mg, but they did not occur with placebo. Second-degree AV blocks following the first dose were also identified in 0.1% of patients receiving the 0.5-mg dose but in none of the patients receiving placebo.

Reinitiating therapy following discontinuation. If fingolimod therapy is discontinued for more than two weeks, the effects on heart rate and AV conduction may recur on restarting the treatment. The same precautions should apply as in the initial dosing.

Risk of infection. Fingolimod causes a dose-dependent reduction in the peripheral lymphocyte count to 20% to 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. The drug may thus increase the risk of infections, some serious in nature. Treatment should be suspended if a serious infection develops, and the benefits and risks should be considered before the patient begins therapy again. In controlled studies, the overall rate of infection (72%) and serious infection (2%) with fingolimod 0.5 mg was similar to that of placebo. However, pneumonia and, to a lesser extent, pneumonia were more common in fingolimod-treated patients.

Concomitant uses. Fingolimod has not been administered concomitantly with antineoplastic, immunosuppressive, or immune-modulating therapies for MS. The concomitant use of fingolimod with any of these agents would be expected to increase the risk of immunosuppression.

Varicella zoster virus antibody testing and vaccination. As with patients taking any immune-modulating drug, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before they begin taking fingolimod. VZV vaccination of antibody-negative patients should be considered before therapy begins. Afterward, the initiation of treatment with fingolimod should be postponed for one month to allow the full effect of vaccination to occur.

Macular edema. In clinical trials, macular edema occurred in 0.4% of patients receiving fingolimod 0.5 mg. An adequate ophthalmologic evaluation should be performed at baseline and at three to four months after treatment begins. Macular edema generally improved or resolved with or without treatment after the drug was discontinued, but some patients had residual visual acuity loss even after resolution of macular edema. Patients with a history of uveitis and patients with diabetes mellitus are at an increased risk of macular edema during fingolimod therapy. Fingolimod has not been tested in MS patients with diabetes mellitus.

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 as early as one month after treatment with fingolimod began. At month 24, the reduction from baseline in the percentage of predicted values for FEV1 was 3.1% for fingolimod 0.5 mg and 2% for placebo. For DLCO, the reductions from baseline in percentage of predicted values at month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo. The changes...
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Pegloticase (Krystexxa)

**Manufacturer**: Savient, East Brunswick, N.J.

**Indication**: Pegloticase is indicated for the treatment of chronic gout that is refractory to conventional therapy. The drug is designed for intravenous (IV) infusion.

**Biologic Class**: A uric acid–specific enzyme, pegloticase is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to mono-methoxy polyethylene glycol (mPEG). The molecular weight is 10 kDa. The complementary DNA coding for uricase is based on mammalian sequences. The molecular weight is approximately 34 kDa per uricase subunit.

**Uniqueness of Biologic Product**: As a recombinant uricase, pegloticase achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid levels. Allantoin is an inert and water-soluble purine metabolite. It is readily eliminated, primarily by renal excretion.

**Boxed Warning**: Anaphylactic and infusion reactions have occurred during and after administration of pegloticase. Anaphylaxis may occur with any infusion, including a first infusion, and is generally manifested within two hours. Delayed-type hypersensitivity reactions have also been reported. Pegloticase should be given in a health care setting that is set up to manage anaphylactic and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids, and they should be closely monitored for an appropriate period of time to guard against anaphylaxis. Serum uric acid levels should be monitored prior to any infusions. Discontinuing treatment should be considered if uric acid levels rise to above 6 mg/dL, particularly if two consecutive readings exceed this level.

**Warnings and Precautions**: Anaphylaxis. Anaphylaxis may occur with any infusion, including a first infusion, and is usually manifested within two hours of the infusion. Delayed-type hypersensitivity reactions have also been observed.

Infusion reactions. Infusion reactions have occurred with pegloticase therapy. The drug should be administered in health care settings and by health care providers prepared to manage anaphylaxis. Patients should be premedicated with antihistamines and corticosteroids. If an infusion reaction occurs, the infusion should be slowed or stopped and restarted at a slower rate. If a severe infusion reaction occurs, infusion should be stopped and treatment instituted as needed.

Gout flares. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic agents, including pegloticase. If a gout flare occurs during treatment, therapy does not need to be discontinued. Gout care prophylaxis, such as with nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine (Colcrys, AR Scientific/URL Pharma) upon initiation of treatment, is recommended for at least the first six months of therapy unless these agents are medically contraindicated or not tolerated.

Sources: www.pharma.us.novartis.com; www.fda.gov

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**Congestive heart failure.** Pegloticase has not been formally studied in patients with congestive heart failure, but some patients have experienced exacerbations. Caution should be exercised if congestive heart failure is present, and patients should be monitored closely.

**Dosage and Administration:** For adults, the recommended dose of pegloticase is 8 mg, given as an IV infusion every two weeks. The drug should not be given as an IV push or as a bolus. Uric acid levels should be checked before each infusion. Premedication with antihistamines and corticosteroids is required. A health care professional should be available in case of an anaphylactic reaction. The pegloticase admixture should be administered only by IV infusion over no less than 120 minutes via a gravity-fed pump, a syringe-type pump, or an infusion pump.

**Commentary:** Gout is a sudden, painful joint inflammation that usually affects the big toe. Because of the increase in the uric acid level in the blood, and then in the joints, urate crystals form on the joint and make it painful to move or touch the toe. A sudden attack of gout can sometimes be followed years later by chronic gout, which affects both the small and large joints of hands and feet.

Pegloticase converts the urate crystals to a substance that will not form on the joints and might also enable the body to manage the urate crystals that have already built up on the joint. Pegloticase is the first medication approved for adults with chronic gout that is refractory to conventional therapy.

A statistically significant proportion of patients achieved reductions of serum uric acid levels with pegloticase 8 mg, administered every two weeks. Within six months of treatment, patients also experienced positive clinical improvement, reversing the course of this debilitating disease and achieving a complete response for the resolution of tophi within the first six months of therapy.

**Source:** www.krystexxa.com

**Drospirenone/Ethinyl Estradiol/Levomefolate Calcium Tablets (Beyaz)**

**Manufacturer:** Bayer HealthCare, Wayne, N.J.

**Indication:** Beyaz is the first oral contraceptive (OC) approved by the FDA for four indications:

- preventing pregnancy (it is 99% effective when taken as directed)
- treating symptoms of premenstrual dyshoric disorder in women who choose an OC for birth control
- treating moderate acne for girls at least 14 years of age, who choose an OC for birth control and who have started having menstrual periods
- raising folate levels in women who choose an OC for birth control in order to reduce the risk of a neural tube defect if a pregnancy occurred during Beyaz therapy or shortly after they discontinued therapy

**Drug Class:** Beyaz combines the hormone ingredients contained in another OC, Yaz (Berlex/Bayer Schering). Yaz is composed of drospirenone 3 mg/ethinyl estradiol 20 mcg; Beyaz contains these ingredients plus 0.451 mcg of levomefolate calcium (a B vitamin).

**Uniqueness of Drug:** Beyaz is the first OC approved to raise folate levels in women who choose an OC for birth control. The medication raises folate levels for the purpose of reducing the risk of a neural tube defect in a fetus that was conceived while the patient was taking Beyaz treatment or shortly after she stopped taking it. Combined OCs lower the risk of pregnancy primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

**Boxed Warning:**

- **Cigarette smoking and serious cardiovascular events.** Women older than 35 years of age who smoke should not use Beyaz. Cigarette smoking increases the risk of serious cardiovascular (CV) events from combination OC use.

**Warnings and Precautions:**

- **Thromboembolic disorders and other vascular problems.** Beyaz therapy should be stopped if an arterial or deep venous thrombotic event occurs. OCs must be used with caution in women with risk factors for CV disease.
- **Hyperkalemia.** Beyaz should not be used in patients with conditions that predispose them to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction, and adrenal insufficiency).
- **Carcinoma of the breasts and reproductive organs.** Women who currently have or who have had breast cancer should not use Beyaz because breast cancer is usually a hormonally sensitive tumor.
- **Liver disease.** Beyaz should be discontinued if jaundice develops. Hepatic adenomas are associated with combination OCs.
- **Hypertension.** For women with well-controlled hypertension, blood pressure (BP) should be monitored. Therapy with Beyaz should be stopped if BP rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use combination OCs.
- **Gallbladder disease.** Studies suggest a small increased relative risk of gallbladder disease among users of combination OCs.
- **Carbohydrate and lipid metabolic effects.** Prediabetic and diabetic women who are taking Beyaz should be monitored. Combined OCs may decrease glucose tolerance in a dose-related fashion.
- **Headache.** If new headaches become recurrent, persistent, or severe while a patient is taking Beyaz, the cause should be evaluated and the drug should be discontinued if indicated.
- **Bleeding irregularities.** Breakthrough or intracyclic bleeding and spotting sometimes occur in patients taking combined OCs, especially during the first three months of use.
- **Contraceptive use before or during early pregnancy.** Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used OCs prior to pregnancy.
- **Depression.** Women with a history of depression should be carefully observed, and Beyaz should be discontinued if depression recurs to a serious degree.
- **Other conditions.** In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of this condition.

**Dosage and Administration:** One tablet should be taken
by mouth at the same time every day. The failure rate may increase when a tablet is missed or taken incorrectly. To achieve maximum effectiveness for contraception and premenstrual dysmorphic disorder, this medication must be taken as directed. A single missed dose should be taken as soon as the patient remembers it. The patient should be instructed to begin taking Beyaz either on the first day of her menstrual period (day 1 start) or on the first Sunday after the onset of her menstrual period (Sunday start).

Beyaz is available in blister packs. Each pack contains 28 film-coated tablets in the following order:

- 24 pink tablets, each containing 3 mg of drospirenone, 0.02 mg of ethinyl estradiol as betadex clathrate, and 0.451 mg of levomefolate calcium
- 4 light orange tablets, each containing 0.451 mg of levomefolate calcium

**Commentary:** Beyaz is based on the FDA-approved OC, Yaz, which contains the same doses of estrogen and progestin; however, Beyaz also includes levomefolic acid (methylfolin), a stable form of the naturally occurring folate found predominantly in food. Folates belong to the group of B vitamins.

Beyaz is indicated for preventing pregnancy, treating premenstrual dysphoric disorder, and treating moderate acne vulgaris in females who are at least 14 years of age (only if they desire an OC for birth control). Beyaz is also approved for women using an OC who wish to raise folate levels in order to reduce the risk of a neural tube defect if a pregnancy occurred while they were taking the product or shortly after they discontinued taking it. This is the only OC that is approved to increase folate in women who choose an OC for birth control.