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ACS Chemical Neuroscience Molecule Spotlight on Gilenya (Fingolimod; FTY720)

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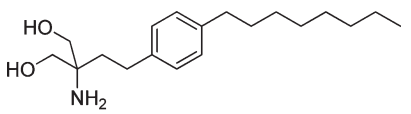

Gilenya® (Fingolimod; FTY720)
Sphingosine 1-phosphate (S1P) receptor modulator

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) that is the leading cause of neurological disability in young and middle-aged adults, affecting approximately 2.5 million people worldwide (a lifetime risk of 1 in 400) (*1*). MS is characterized by inflammatory processes followed by atrogliosis, demyelination of the myelin sheath, and loss of oligodendrocytes and neurons (*1*). MS is diagnosed, generally, between the ages of 20 and 40 years old with women targeted more than men (2:1). Although MS is a worldwide disease, the greatest prevalence is found in caucasians and high rates are noted in Europe, North America, Australia, New Zealand, and northern Asia (*2*). A large proportion of new diagnoses are relapsing−remitting multiple sclerosis (RRMS), which is noted by relapses (exacerbations) of new symptoms and appearance of old symptoms worsening. During relapses, the myelin sheath that protects neurons is damaged via an inflammatory response by the body's immune system. These relapses are followed by periods of remission during which time the patient can recover fully, or partially, which can lead to permanent disability (*3*). Relapses can be of varying time periods (days/weeks/months) with recovery also being of varying time lengths (slow or instantaneous). After a short time period after initial diagnosis (6−10 years), a significant number of patients with RRMS (∼40%) progress to secondary progressive MS (SPMS). SPMS is characterized by steady progression of disease without the relapses/remission seen in the previous stage of the disease. The majority of patients with RRMS will eventually develop SPMS. Current state-of-the art treatments for MS involve injectable drugs: subcutaneous (Rebif, Copaxone), intramuscular (Avonex), and intraveneous (Tysabri)) which target lymphocytes with the aim of slowing the autoimmune dysfunction, without acting directly on the CNS (*4*). Due to limitations of the current treatments to injectable forms, there has been significant research in the area of an orally bioavaible drug, culminating with the approval of Gilenya.

Gilenya (fingolimod; FTY720) is a newly approved, orally bioavaible disease modifying drug to reduce relapses and delay disability progression in patients with relapsing forms of multiple sclerosis (MS) (approved September 22, 2010) (*5*). Fingolimod is a structural analogue of the natural product sphingosine and exerts its biological action in vivo by undergoing rapid phosphorylation by sphingosine kinase 2, producing fingolimod phosphate which then binds to the S1P receptors (S1P$_{1,3-5}$). After oral administration, fingolimod crosses the blood−brain barrier (BBB) into the CNS where endogenous sphingosine activity converts fingolimod to the active form; levels of both the parent and the active substance have been shown to be higher in the brain compared to blood (*6*). The S1P receptors play key roles in the immune system including regulating lymphocyte migration from lymphoid tissue into circulation. By binding the S1P receptor, fingolimod prevents the lymphocyte egress which reduces the lymphocyte infiltration into the CNS (*6*). Distinguishing features of fingolimod are two-fold: first, fingolimod is an orally dosed drug, and second, fingolimod readily crosses the BBB and therefore may have direct CNS effects.

Clinical trials of oral fingolimod have shown that it improved the relapse rate and risk of disability progression (*7*). This study was a 24-month, double-blind, randomized study which looked at 1272 patients with RRMS at two doses of fingolimod (0.5 and 1.25 mg, daily). The annualized relapse rate of 0.5 mg and 1.25 mg fingolimod was 0.18 and 0.16, respectively, compared to 0.4 for placebo. Both doses reduced the risk of disability progression over the 24-month period, and both doses were superior to placebo with regard to magnetic resonance imaging (MRI) measures (no. of new or enlarged lesions on T_2-weighted images, gadolinium-enhancing lesions, and brain-volume loss) (*7*). The most common reported adverse events (AEs) were bradycardia, atrioventricular conduction block (at initiation of treatment), macular edema, elevated liver enzymes, and mild hypertension (*7*). In addition, fingolimod can increase the risk of serious infections.

With the approval of Gilenya (fingolimod; FTY720) physicians now have a noninjectable option in the

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treatment of RRMS, representing the first orally bioavaible disease modifying drug for MS patients.

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