Gilenya™ Mechanism of Action

(4.5 minute animation)

Multiple sclerosis (MS) is a progressive, debilitating, chronic disease that affects roughly 400,000 Americans. The hallmark of MS is an immune-mediated demyelination of the neurons in the brain and spinal cord.
[Ref 1. Frohman, E.M., et al. *Arch Neurol* 2005;62:1345, A 1 - B,1 & 2] [Ref 2.NMS website. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx. Accessed July 9, 2010: 2, Section 1][Ref 3. Compston, A and Coles, A. Lancet 2002;359:1225, A, 3 & B,1,2]

Gilenya™, fingolimod, is a sphingosine 1-phosphate receptor modulator indicated to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability in patients with relapsing forms of MS, provided in an oral formulation.
[Ref 4. Gilenya Prescribing Information. 09/2010. Section 1 & Section 5.2 and 5.8.][Ref 5. Baumruker T, et al. Expert Opin Investig Drugs. 2007;16:283, A, 3] [Ref 6. Brinkmann, V and Lynch, KR. *Curr Opin Immunol* 2002; 14:570, A, 2]

LYMPHOCYTES AND MS

As Gilenya is an immune modulating drug, let's first consider the immune system and its role in MS.
[Ref 4. Gilenya Prescribing Information. 09/2010. Section 1 & Section 5.2.]

Lymphocytes are the immune cells primarily responsible for acquired immune response. Most of these cells reside in the lymph nodes, while other lymphocytes are found in circulating blood. Of these lymphocytes in circulation, a subset regularly migrates between the lymph nodes and the bloodstream. This subset is thought to include the T cells which migrate into the central nervous system (CNS) and contribute to MS pathology.
[Ref 7. Westermann J, et al. Clin Investig. 1992;70:541, Fig 2. & B, 2][Ref 8. Janeway CA, *Immunobiology. The Immune System in Health and Disease.* 5th ed. 2001: 2, A, 5; 3, Fig. 1.3; 6, A,3; 8, A,3 and 12, A, 1] [Ref 9. Chun J, et al. *Clin Neuropharmacol.* 2010;33:92, B, 2; 93, B, 3]

HOW DO THE LYMPHOCYTES MIGRATE FROM THE LYMPH NODES TO THE CNS?

The egress of circulating lymphocytes from lymph nodes into the blood is controlled by receptors on T cells, called $S1P_1$ receptors. When these receptors are stimulated by the ligand Sphingosine1-phospate (S1P) the T cells are then able to exit the lymph node into the circulation. In MS, some of these T cells migrate to the CNS and are thought to react to and damage the myelin.
[Ref 10. Matloubian M, et al. Nature. 2004;427:355, A, abstract; 357, B, 1; 358, A, 2 and Fig. 4.][Ref 4. Gilenya Prescribing Information. 09/2010. Section 12.1][Ref 9. Chun J, et al. *Clin Neuropharmacol.* 2010;33: 95, A, 2-5] [Ref 11. Brinkmann V. *Br J Pharmacol.* 2009;158:1174, B, 3; 1175, Fig. 1 and A, 1; 1176, A,1]

LYMPHOCYTE SEQUESTRATION

Gilenya reversibly sequesters circulating T cells in lymph nodes. Although the mechanism by which Gilenya exerts therapeutic effects in MS is unknown, based on animal model data, it is thought that the sequestration reduces T cell migration to the CNS. **[Ref 4. Gilenya Prescribing Information. 09/2010. Section 12.1]**

Here's how it's thought to work:

In the bloodstream, Gilenya diffuses through the membrane of the T cell to its interior. Once inside the T cell, it is rapidly phosphorylated to its active state–called fingolimod phosphate–which closely resembles the ligand S1P. Fingolimod phosphate is then transported outside of the cell where it binds to $S1P_1$ receptors on the T cell. Its binding causes the internalization of the $S1P_1$ receptors and therefore their removal from the cell surface, preventing interaction of the S1P ligand with $S1P_1$ receptors on the T cell surface. Consequently, the T cell becomes insensitive to the S1P signaling necessary for its egress from the lymph node. This redistribution of lymphocytes may reduce migration of T cells to the CNS. **[Ref 10. Matloubian M, et al. Nature. 2004;427:355, A, abstract; 357, B, 1; 358, A, 2 and Fig. 4.][Ref 4. Gilenya Prescribing Information. 09/2010. Section 12.1][Ref 9. Chun J, et al. *Clin Neuropharmacol.* 2010;33: 95, A, 2-5] [Ref 11. Brinkmann V. *Br J Pharmacol.* 2009;158:1174, B, 3; 1175, Fig. 1 and A, 1; 1176, A, 1]**

GILENYA™ (FINGOLIMOD) REVERSIBLE SEQUESTRATION

Since Gilenya does not destroy, but sequesters T cells, lymphocyte circulation returns to normal generally within 1-2 months of stopping Gilenya treatment.
[Ref 5. Baumruker T, et al. *Expert Opin Investig Drugs.* 2007;16: 286, B, 3 ; 284, B,1][Ref 13. Mehling M, et al. *Neurology*. 2008;71:1261, A, 4-5; 1263, B,6 1265, B,2; 1266, B,1] [Ref 9. Chun J, et al. *Clin Neuropharmacol.* 2010;33: 94, A, 1 – B,3 ; 95, A, 1-3 and B, 2][Ref 12. Brinkmann V, et al. *Am J Transplant.* 2004;4:1022, A, 1] [Ref 11. Brinkmann V. *Br J Pharmacol.* 2009;158:1176, B, 2 – 1177, A,1; 1175, B,1] [Ref 4. Gilenya Prescribing Information. 09/2010. Section 5.8 and 12.2]
Gilenya has a unique mechanism of action and is an important therapeutic option for patients with relapsing forms of MS.
[Ref 4. Gilenya Prescribing Information. 09/2010. Section 12.1][Ref 9. Chun J, et al. *Clin Neuropharmacol.* 2010;33:91, A, abstract] [Ref 12. Brinkmann V, et al. *Am J Transplant.* 2004;4:1023, A, 2] [Ref 14. Kimura et al. Stem Cells 2007;25;123, A, 1]

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