

## **How Tetrabenazine Works**

The U.S. Food and Drug Administration has approved tetrabenazine for the treatment of chorea in Huntington's Disease. Tetrabenazine is marketed by Prestwick Pharmaceuticals, Inc., in Canada; Prestwick also has marketing rights in the United States.

Tetrabenazine (TBZ) is a dopamine depleter. It works by inhibiting the vesicular monoamine transporter 2 (VMAT2). Neurons are connected to each other by synapses and communicate through chemical signals called neurotransmitters. VMAT2 is responsible for regulating how much of the neurotransmitter is released across the synapse.

Since TBZ also reduces serotonin and norepinephrine, although to lesser degree than dopamine, depression is a potential side effect. In a 2006 Lighthouse interview, former Prestwick CEO, Kathleen Clarence-Smith, M.D., Ph.D., recommended that TBZ be titrated up to the individual patient's correct dose to avoid the potential side effects of depression, Parkinsonism, and sedation. About sixty percent of HD patients are already taking antidepressants. If depression occurs with TBZ, it can be treated by prescribing an antidepressant, increasing the dosage of an antidepressant the patient is already taking, or reducing the dosage of TBZ.

Tetrabenazine was first approved as a treatment for chorea in movement disorders in the United Kingdom in 1971 and in Canada in 1995. Prestwick filed a New Drug Application with the FDA in September, 2005.

TBZ is the first drug ever approved in the United States for the treatment of a Huntington's Disease symptom. Another 'first' was the inclusion of an HD family advocate on an FDA committee. Karen Milek, HDSA's 2003 HD person of the year, served on the Advisory Committee that recommended approval of tetrabenazine.

Huntington's Disease family advocates played a large role in getting the FDA to act. Letter writing campaigns were organized by Dr. Nancy Wexler of the Hereditary Disease Foundation and Barbara Boyle of the Huntington's Disease Society of America. Two hundred family members from around the country turned out for an advisory committee meeting on December 6, 2007 in Beltsville, Maryland and over a dozen spoke about the disabling effects of chorea and the importance of treating this symptom. Educating the FDA on the negative effect that chorea has on the quality of life was key to the decision.

## **References and Resources**

C. Kenney and J. Jankovic. "Tetrabenazine in the treatment of hyperkinetic movement disorders." *Expert review of neurotherapeutics*. 2006 Jan;6(1):7-17.

Huntington Study Group, (Marshall F, primary author). “Tetrabenazine as antichorea therapy in Huntington disease: A randomized controlled trial.” *Neurology* 2006;66:366-372.

FDA news release.

Prestwick's December 6, 2007 Briefing Document for the FDA and the public:  
<http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4328b1-02-Prestwick.pdf>

Prestwick website: <http://www.prestwickpharma.com/>

*Marsha L. Miller, Ph.D., August 15, 2008*