Leteprinim Potassium (Neotrofin®) and Alzheimer’s disease

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Leteprinim potassium (Neotrofin®) is a drug under development by NeoTherapeutics of Irvine, Calif., to repair and regenerate nerve cells damaged by spinal cord injury, Parkinson’s disease, the effects of some chemotherapy drugs, and, until recently, Alzheimer’s disease. In preclinical studies, leteprinim showed promise in restoring nerve function in animal models of aging, memory decline, and brain and spinal cord injury. Phase I trials enrolling small numbers of people offered preliminary evidence that leteprinim is safe and well tolerated in human recipients.

NeoTherapeutics then advanced leteprinim to Phase II trials to assess effectiveness, determine optimal dosage and gain further safety data. In April 2001, the company began recruiting participants for a large U.S. Phase II study enrolling 500 people with mild to moderate Alzheimer’s at 52 locations nationwide. On April 30, 2002, the company announced that preliminary analysis of study data revealed that some individuals taking leteprinim showed improvement on tests of mental status and general functioning. However, overall, leteprinim did not perform well enough compared to a placebo (inactive treatment) to meet U.S. Food and Drug Administration (FDA) standards for approving a drug as an Alzheimer treatment.

As a result, the company says that it will suspend all further tests of leteprinim in people with Alzheimer’s until it can find a partner to help underwrite such studies. Alvin J. Glasky, Ph.D., chairman and chief executive officer of NeoTherapeutics, expressed optimism that future trials involving different doses of medication or timing of doses might document a more robust effect of leteprinim as an Alzheimer treatment. In the meantime, NeoTherapeutics will continue studies exploring leteprinim as a treatment for Parkinson’s disease, spinal cord injury and chemotherapy-induced nerve damage.

How does leteprinim work?
Nerve cells produce nerve growth factors, proteins that regulate cell maturation during prenatal development and also play an important role in cell survival, repair and regeneration during adult life. Because of their significance in cell maintenance and repair, these factors have attracted attention as potential treatments in Alzheimer’s disease, stroke, spinal cord injury and other neurodegenerative conditions. However, nerve growth factors are too large to cross the blood-brain barrier, a protective shield that restricts passage of molecules to the brain. Scientists seek to overcome this difficulty by designing small molecules that cross the blood-brain barrier and mimic the effects of nerve growth factors when they are taken by mouth or injected. The active ingredient in leteprinim is one such small molecule that successfully crosses the blood-brain barrier, where it activates genes that produce nerve growth factors.

What drugs are available now to treat symptoms of Alzheimer’s?
The FDA currently approves five drugs specifically to treat symptoms of Alzheimer’s disease. Tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Razadyne®, formerly Reminyl®) are cholinesterase inhibitors that work by increasing the brain’s supply of acetylcholine, a specialized chemical messenger produced and secreted by nerve cells that are deficient in people with Alzheimer’s disease.

Memantine (Namenda®) is classified as an uncompetitive low-to-moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist. It appears to work by regulating the activity of glutamate, one of the brain’s specialized messenger chemicals involved in information processing, storage and retrieval.

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The Alzheimer’s Association, the world leader in Alzheimer research, care and support, is dedicated to finding prevention methods, treatments and an eventual cure for Alzheimer’s.

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