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ACS Chemical Neuroscience Molecule Spotlight on Dimebon

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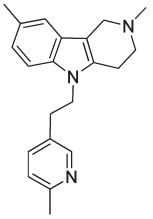
Abstract



Dimebon® (latrepirdine)

Dimebon (latrepirdine) is an antihistamine drug that has been used clinically in Russia since the early 1980s and is being studied jointly by Pfizer and Medivation for patients with Alzheimer's disease. The results from a pivotal Phase 3 clinical trial (CONNECTION) showed that Dimebon (latrepirdine) failed to meet its coprimary or secondary efficacy end points.

Keywords: Neurodegeneration, Alzheimer's Disease, AD, clinical trials, Dimebon

Dimebon (latrepirdine), a nonselective antihistamine drug once used in Russia is currently under development by Pfizer and Medivation for the treatment of patients with Alzheimer's disease. Alzheimer's disease (AD) is the most common neurodegenerative disease and is a progressive brain disorder that destroys a person's memory, including the ability to learn, make judgments, and carry out daily activities (*1*). It is the most common cause of dementia. It is estimated that as many as 5.3 million Americans are living with AD, and it is a disease that is ultimately fatal. AD is the seventh-leading cause of death, and the economic impact of AD is estimated to be (both direct and indirect costs) ~$150 billion/year (*1*). AD has no cure, and the current medications available only treat the symptoms. A hallmark of AD is the formation of abnormal structures in the brain, plaques and tangles, which are suspected of damaging and killing nerve cells. However, despite the considerable progress that has been made in understanding the underlying causes of AD, its effect on the brain, and why it kills brain cells, the disease still remains elusive for the pharmaceutical community in finding a cure or even an effective therapy. This despite a significant amount of resources put forth in both the area of small molecule therapies as well as biological agents.

In a 2000 published result, Dimebon was shown to improve learning in animals with experimental AD (*2*). On the basis of these results, Medivation was formed in 2003, and Dimebon was in-licensed. Medivation had seen encouraging results in a phase II/III clinical trial in which Dimebon demonstrated statistically significant improvements over placebo on all five efficacy end points (memory, thinking, activities of daily living, behavior, and overall clinical function) at both the 6- and 12-month time periods. This trial was conducted with 183 patients with mild-to-moderate Alzheimer's disease (*3*). After the results of this pivotal study, Pfizer announced that it was paying $225 million in cash up front and up to $500 million in development expenses (plus assuming 60% of the development costs and commercialization expenses) for a 60% share of profits for Dimebon (*4*). On the basis of these promising results, another phase III trial was approved by the FDA (CONNECTION) and was initiated by Medivation (and Pfizer) in mid-2009. The CONNECTION study was looking at the effects of Dimebon in about 600 patients with mild-to-moderate AD in North America, Europe, and South America. The patients were randomly assigned either Dimebon or placebo for six months, and during that time their cognitive function was scored. Unfortunately, Medivation and Pfizer announced on March 3, 2010 that Dimebon did not meet their coprimary or secondary efficacy end points compared to those of placebo (coprimary end points being cognition and global function) (*5*). The results of the CONNECTION study are being evaluated by Medivation and Pfizer; however, the path forward for Dimebon for AD treatment is bleak at best. The drug, however, is not totally dead as it is currently being investigated in a phase III trial (HORIZON) for a potential treatment for Huntington's disease (*6*).

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