# ACS Chemical Neuroscience Molecule Spotlight on Fanapt

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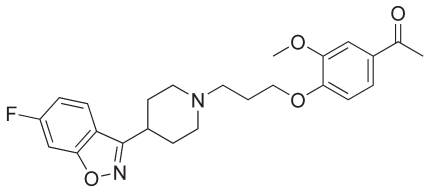
## Abstract



**Fanapt® (iloperidone)**
**Mixed dopamine $D_2$/serotonin 5-$HT_{2A}$ antagonist**

The new mixed dopamaine $D_2$/serotonin 5-$HT_{2A}$ antagonist, Fanapt (iloperidone), was approved by the FDA on May 6th, 2009 for the treatment of schizophrenia in adults.

Fanapt (iloperidone) is a recently approved atypical antipsychotic from Vanda Pharmaceuticals. Fanapt, a mixed dopamine $D_2$/serotonin 5-$HT_{2A}$ antagonist gained FDA approval on May 6, 2009 and is being manufactured by Vanda Pharmaceuticals, Inc. (*1*, *2*). Schizophrenia is a chronic, severe, and debilitating mental disorder that affects approximately 2.4 million Americans, around 1.1% of the population. The net cost of this disorder is staggering as estimates from 2002 reveal this disorder to cost $62.7 billion. A major issue with the treatment of schizophrenia is that patients show varying levels of response and tolerance to available therapies. Although the symptoms of the disease are very severe, estimates show that approximately 3 out of 4 patients discontinue medication prior to completing 18 months of treatment, many times due to the severe side effects of the approved medications.

Fanapt (iloperidone) is a monoamine and acts by antagonizing dopamine and serotonin receptor subtypes, noradrenaline ($\alpha_{2C}$), dopamine ($D_2$ and $D_3$), and serotonin (5-$HT_{1A}$ and 5-$HT_6$). The efficacy of Fanapt was demonstrated in two placebo-controlled short-term (4- and 6-week) trials. These trials were performed on patients that met the DSM-III/IV criteria for schizophrenia, and Fanapt was shown to be superior to the placebo in these trials. Unlike most other atypical antipsychotics, Fanapt displayed a superior side effect profile with the most common adverse reactions being dizziness, somnolence, and hypotension; further studies indicated that coadministration with food decreased the severity of these reactions (*3*).

Fanapt has traveled a circuitous route to approval. Originally, it was disclosed by Hoechst Marion Roussel in 1995 as a novel atypical antipsychotic agent (*2*), and soon after, HMR sold the research rights to Titan Pharmaceuticals. After obtaining the rights the previous year, Titan Pharmaceuticals then handed over the worldwide rights to Novartis Pharmaceuticals in 1998, which in turn turned over the phase III development rights to Vanda Pharmaceuticals in 2004. Unfortunately, the much traveled drug did not have a smooth route to approval. In fact, in 2008, the FDA issued a "not approvable letter" to Vanda Pharmaceuticals (*4*) for iloperidone even though the company demonstrated effectiveness in a 3101 study (*4*) that was published in December 2006 and demonstrated that iloperidone was superior to placebo in a prior study. In the letter, the FDA indicated that it would require an additional clinical trial comparing iloperidone to placebo and an additional comparator, plus additional safety data for the 20 and 24 mg/kg doses. Not even a year after the company received the "not approvable letter", the FDA approved Fanapt (tablets) to treat adults with schizophrenia. After nearly 15 years of research, rights transfers, and clinical trials, Novartis recently announced that Fanapt tablets are now available across the U.S. as a twice-daily, oral antipsychotic (*5*).

## References

1. Vanda Pharmaceuticals Press Release, May 6, 2009.

2. FDA Press Release, May 6, 2009.

3. Sainati, S. M.; Hubbard, J. W.; Chi, E.; Grasing, K.; Brecher, M. B. (1995) Safety, tolerability, and effect of food on the pharmacokinetics of iloperidone (HP 873), a potential atypical antipsychotic. *J. Clin. Pharm. 35*, 713−720.

4. Titan Pharmaceuticals Press Release, July 28, 2008.

5. Novartis Press Release, January 11, 2010. www.novartis.com/newsroom/media-releases/en/2010/1371914.shtml.

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