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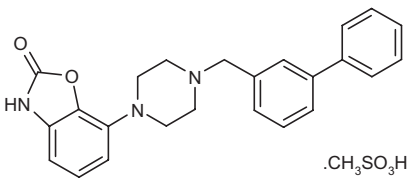
Bifeprunox Mesilate

Prop INNM

Treatment of Bipolar Disorder
Treatment of Schizophrenia
Dopamine D2 Receptor Partial Agonist
5-HT$_{1A}$ Receptor Agonist

DU-127090

7-[4-(Biphenyl-3-ylmethyl)piperazin-1-yl]benzoxazol-2(3*H*)-one methanesulfonate



$C_{25}H_{27}N_3O_5S$ Mol wt: 481.5651

CAS: 350992-13-1
CAS: 350992-10-8 (as free base)
CAS: 197954-51-1 (as hydrochloride)
EN: 308000

Abstract

Typical antipsychotics such as chlorpromazine relieve the positive symptoms of schizophrenia via antagonism of the dopamine D2 receptor, but they are associated with unwanted motor side effects and symptomatic hyperprolactinemia, and have little effect on the negative symptoms of the illness. Newer atypical antipsychotics, in contrast, have relatively low affinity for dopamine receptors, effectively relieve both positive and negative symptoms of schizophrenia, are less liable to induce extrapyramidal symptoms (EPS) and are associated with few neurological adverse events. However, these agents are linked to severe weight gain, diabetes, hypercholesterolemia, hyperprolactinemia and prolongation of the Q-T_c interval. Targeting both dopaminergic and serotonergic systems is the most recent and promising development in the area of atypical antipsychotics. Bifeprunox is a novel, full-spectrum dopamine D2 receptor partial agonist and 5-HT_{1A} receptor agonist with low intrinsic activity at the D2 receptor and high affinity and moderate to high intrinsic activity at the 5-HT_{1A} receptor. It has shown efficacy in several preclinical models, exhibiting a low liability for eliciting motor side effects. Bifeprunox was chosen for further development and is currently undergoing phase II and III development, respectively, for schizophrenia and bipolar disorder.

Synthesis

Bifeprunox is synthesized by alkylation of 7-piperazinylbenzoxazol-2(3*H*)-one (I) with 3-phenylbenzyl bromide (II) in the presence of diisopropyl ethyl amine and KI in refluxing acetonitrile (1, 2). Scheme 1.

Intermediate (I) can be prepared as follows: Reduction of one of the nitro groups of 2,6-dinitrophenol (III) with sodium sulfide by means of $NaHCO_3$ in MeOH/water gives the aniline (IV), which is condensed with carbonyldiimidazole (CDI) in dry THF to yield 7-nitro-1,3-benzoxazolidin-2-one (V). Reduction of compound (V) with Raney-Ni in acetone provides the aniline (VI), which is condensed with bis(2-choroethyl)amine (VII) in refluxing chlorobenzene to afford the desired intermediate (I) (3, 4). Scheme 2.

Introduction

Schizophrenia is a common and severe chronic psychiatric illness which, according to the World Health Organization (WHO), affects approximately 24 million individuals worldwide. The illness is characterized by lifelong patterns of acute extreme disturbances of cognition affecting language, perception and sense of self, and chronic poor psychosocial adjustment. Schizophrenia is characterized by marked heterogeneity of symptoms among patients. It can involve positive symptoms (*i.e.*, auditory hallucinations, disorganized or bizarre thoughts, delusions, irrational fears) which reflect an excess or distortion of normal function, and negative symptoms (*i.e.*, social withdrawal, poor motivation, poverty of speech, apathy, lack of energy) which are due to an attenuation or loss of normal functions. All patients experience positive symptoms, although not continuously, while negative symptoms are experienced by most but not all subjects. Patients may also develop depression, anxiety and/or cognitive dysfunction ranging from impaired attention to abnormal executive functions (5-9).

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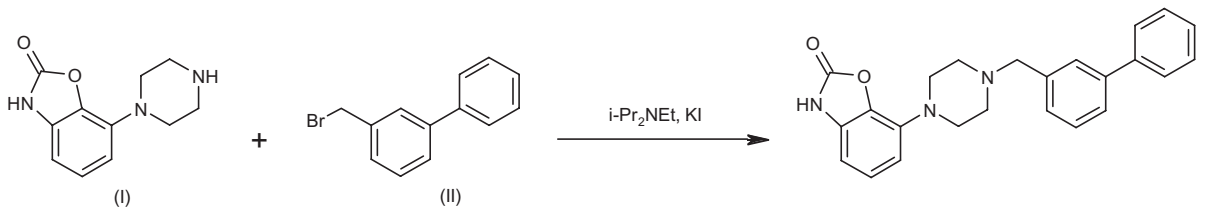
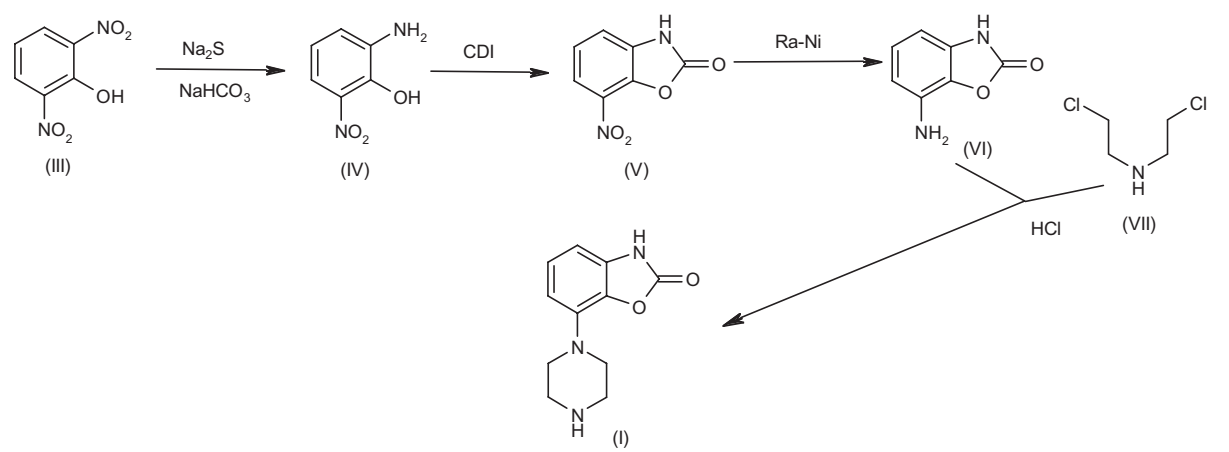
Scheme 1: Synthesis of Bifeprunox Mesilate



Scheme 2: Synthesis of Intermediate (I)



There are 5 recognized subtypes of schizophrenia. The paranoid type is the least severe form of the disorder and involves marked delusions and auditory hallucinations with preserved cognitive function. The disorganized type is the most severe form of the disorder and is characterized by disorganized speech and behavior and inappropriate or flat affect which severely interferes with simple daily living. The catatonic type is characterized by a disturbance of motor skills and can manifest as immobility, mutism or excessive motor activity. The undifferentiated type is diagnosed when an individual exhibits symptoms of schizophrenia but does not meet the criteria for the above subtypes, and the fifth subtype is known as residual and is diagnosed when an individual does not experience psychotic symptoms at the time of diagnosis but has experienced at least 1 prior episode (5-9).

Although schizophrenia was first described over 100 years ago, its etiology is unknown. Genetic and non-genetic factors (viral/retroviral infection, severe maternal malnutrition, obstetric complications, advanced paternal age, seasonal and socioeconomic variables) are both thought to be involved. Human chromosome 22q11 has been strongly linked to schizophrenia with deletions described in 25-30% of the patients. The genes encoding catechol *O*-methyltransferase (COMT), a dopamine-degrading enzyme, the serotonin 5-HT_{2A} receptor and the DISC1 (Disrupted in Schizophrenia) protein have all been implicated as possible candidate genes. Abnormal brain architecture has been described in schizophrenic patients, although the changes are subtle and generally not consistent among patients. These changes include slight reductions in brain weight, small increases in ventricular volume, increases in the volume of the thalamus and temporal lobe structures, and variations in the size or orientation (but not number) of neurons in several brain regions. The neurotransmitters dopamine, serotonin and glutamate have been implicated in the neurodevelopmental defects leading to schizophrenia (5-11).

The treatment of schizophrenia involves drug therapy to relieve symptoms and prevent relapses, education and psychosocial intervention, and rehabilitation to facilitate reintegration. There is no cure and ongoing maintenance therapy is required to prevent relapses. In most patients, positive symptoms can be controlled by pharmacotherapy, although negative symptoms are less responsive. Over the past 40 years, antipsychotic drug development has been based on the hyperdopaminergic hypothesis of schizophrenia implicating the involvement of excessive

dopamine production (presynaptic dopamine overactivity) and/or an increase in dopamine D2 receptor density or increased postsynaptic dopamine overactivity. Typical antipsychotics such as chlorpromazine relieve the positive symptoms of schizophrenia via antagonism of the D2 receptor. The majority of the typical antipsychotics antagonize the D2 receptor to some degree but are associated with extrapyramidal symptoms (EPS), tardive dyskinesia and symptomatic hyperprolactinemia, and they only relieve the positive symptoms of schizophrenia. More recent investigations have identified D1, D3 and D4 receptors as potential targets. In contrast to typical antipsychotics, atypical antipsychotic have relatively low affinity for dopamine receptors, effectively relieve both positive and negative symptoms of schizophrenia and are less liable to induce EPS. Agents targeting the serotonergic receptor have been introduced and shown to improve both the positive and negative symptoms. *Post mortem* studies have reported an upregulation of the serotonin 5-HT_{1A} receptor in the frontal cortex and other brain regions of schizophrenics. This upregulation may be in response to insufficient activation of this site in the serotonergic system, and agents acting as agonists at the 5-HT_{1A} receptor appear to be particularly effective in relieving symptoms of schizophrenia. Moreover, 5-HT_{1A} agonists possess anticataleptic properties, suggesting that these agents could attenuate EPS induced by D2 receptor blockade. The new atypical antipsychotics that have been introduced are associated with fewer neurological adverse events. However, these agents are not optimal and are linked to severe weight gain, diabetes, hypercholesterolemia, hyperprolactinemia and prolongation of the Q-T_c interval. (5, 6, 12-20).

The search for more effective, safer antipsychotics for the treatment of schizophrenia continues. It is generally agreed that an effective agent must retain some D2-antagonist function. Partial dopamine receptor agonists such as preclamol are thought to improve symptoms via stabilization of dysregulated cortical and subcortical dopamine systems, without generating EPS and metabolic side effects. Targeting of both dopaminergic and serotonergic systems is the most recent development in the area of atypical antipsychotics. Risperidone, one of the first atypical antipsychotics, combines D2 antagonism with 5-HT_{2A} antagonism and has a low liability for EPS. In addition, other novel agents that are combined dopamine receptor partial agonists and 5-HT_{1A} receptor agonists (e.g., SLV-313 and SSR-181507, both in phase I) are currently being actively developed as possible safe and effective treatments for schizophrenia (5, 12-20).

However, one particularly exciting new agent is the full-spectrum D2 partial agonist and 5-HT_{1A} agonist bifeprunox (DU-127090), identified from a series of 1-aryl-4-(biarylmethylene)piperazine compounds. Bifeprunox has low intrinsic activity for the D2 receptor and high affinity and moderate to high intrinsic activity at the 5-HT_{1A} receptor. Bifeprunox exhibited a profile similar to existing antipsychotic agents (*i.e.*, antagonism of dopamine agonist-induced behaviors) in several animal models predictive of modulation of dopamine-mediated behavior *in vivo*. However, the agent was unique in that it stimulated dopaminergic receptors under conditions where dopaminergic tone was low or where dopamine receptors were upregulated. Bifeprunox has also shown a low liability for eliciting motor and metabolic side effects and was chosen for further development as a treatment for schizophrenia (1).

Pharmacological Actions

Experiments performed *in vitro* using [^{3}H]-spiperone and [^{3}H]-8-OH-DPAT as radioligands for dopamine D2 and serotonin 5-HT_{1A} receptors, respectively, reported K_i values for bifeprunox of 2.2 and 9.3 nM, respectively. In functional assays assessing the effect on adenylate cyclase activity in CHO cells expressing cloned human D2 or 5-HT_{1A} receptors, bifeprunox exhibited potent but incomplete antagonism of the dopamine agonist quinpirole (pA_2 = 10.1), weak D2 receptor-agonist effects (28% intrinsic activity at 1 μM compared to quinpirole) and potent 5-HT_{1A} receptor-agonist effects (pEC_{50} = 9.95; 73% efficacy). Bifeprunox also showed high affinity for the human D2, D3 and D4 receptors (pK_i = 8.5, 9.2 and 8.8, respectively) and the 5-HT_{1A} receptor (pK_i = 8.0), but relatively little or no affinity for 5-HT_{2A}, 5-HT_{2C}, α_1- and α_2-adrenoceptors, muscarinic and histaminergic receptors. In experiments in rat striatal slices, bifeprunox acted as a highly potent antagonist at presynaptic dopamine D2 receptors (pA_2 = 9.4), and it inhibited dopamine D2 receptor-sensitive adenylate cyclase activity with a pD_2 of 7.9. Further analysis of *in vitro* results showed that when endogenous dopamine levels were low, such as was the case in adenylate cyclase activity assays in CHO cells and superfused striatal slices, the agent induced partial agonist effects. In contrast, when endogenous dopamine levels were high, as was the case in the [^{3}H]-dopamine release assay in which depolarizing potassium concentrations increased dopamine levels, bifeprunox acted as a potent antagonist. From these results, it was speculated that in brain regions where dopaminergic activity is suspected to be high in psychotic patients, bifeprunox would act as an antagonist, attenuating dopamine activity. However, in the prefrontal cortex where activity of the dopaminergic system is low, the agent may restore dopaminergic transmission (1, 21-23). This unique profile was confirmed *in vivo* in microdialysis studies in rats (24).

Other studies compared the binding affinities and efficacy of several antipsychotics in a series of *in vitro* 5-HT_{1A} signal transduction assays including G-protein activation at native rat hippocampal 5-HT_{1A} receptors and recombinant human 5-HT_{1A} receptors expressed in HeLa cells. In addition, agonist efficacy as conferred by induction of adenylyl cyclase activity was compared using recombinant human 5-HT_{1A} receptors stably expressed in HeLa cells. The K_i ratios at native rat cortical 5-HT_{1A} receptors and striatal D2 receptors were also determined in competition binding experiments. Results showed that risperidone and haloperidol were ineffective at the 5-HT_{1A}

receptor and aripiprazole exhibited modest affinity for 5-HT_{1A} with low efficacy, whereas bifeprunox displayed low affinity for the receptor but high efficacy. Binding affinities (pK_i) for bifeprunox, sarizotan, aripiprazole, clozapine, haloperidol and risperidone were 7.19 ± 0.14, 8.65 ± 0.02, 7.42 ± 0.13, 6.31 ± 0.06, 5.77 ± 0.04 and 6.03 ± 0.09, respectively, at rat cortical 5-HT_{1A} receptors and 7.69 ± 0.07, 8.86 ± 0.09, 6.99 ± 0.01, 7.33 ± 0.03, 6.99 ± 0.01, 5.97 ± 0.20 and 6.56 ± 0.03, respectively, at human 5-HT1A receptors expressed in HeLa cells. E_{max} values obtained (relative to 100% for 10 μM 5-HT) for G-protein activation for bifeprunox, sarizotan, aripiprazole, clozapine, haloperidol and risperidone were 35.9 ± 2.0%, 66.5 ± 1.9%, 15.0 ± 0.6%, 7.52 ± 2.3%, –11.6 ± 2.2% and –16.1 ± 4.1%, respectively, at rat hippocampal 5-HT_{1A} receptors and 60.8 ± 1.8%, 135.1 ± 11.4%, 48.8 ± 3.3%, 51.6 ± 7.3%, –6.6 ± 3.5% and –4.2 ± 1.3%, respectively, at recombinant human 5-HT_{1A} receptors expressed in HeLa cells. The K_i ratios (5-HT_{1A}/D2) for bifeprunox, sarizotan, aripiprazole, clozapine, haloperidol and risperidone at native rat receptors were 44, 0.3, 15, 3.3, 1738 and 468, respectively. From the results obtained, it was concluded that the contribution of 5-HT_{1A} receptor activation to the action of antipsychotics appears to be dependent on relative 5-HT_{1A}/D2 affinities and 5-HT1A agonist efficacy (25).

In studies using several animal models of antipsychotic-like effects, bifeprunox exhibited a profile similar to existing antipsychotic agents in that it successfully antagonized behaviors induced by dopamine agonists. Bifeprunox effectively suppressed conditioned avoidance in rats with a potency similar to that of the D2 receptor antagonist haloperidol (ED_{50} = 0.8 and 0.5 mg/kg p.o., respectively; minimum effective dose [MED] = 0.31 and 0.080 mg/kg s.c., respectively). In addition, both bifeprunox and haloperidol potently antagonized apomorphine-induced climbing in mice (ED_{50} = 0.1 and 0.2 mg/kg p.o., respectively) (1, 26, 27). Treatment with the agent antagonized phencyclidine (PCP)-induced hyperactivity in mice (ED_{50} = 0.00096 mg/kg s.c.); inhibitory effects on baseline activity were only observed at higher doses (ED_{50} = 0.083 mg/kg s.c.). Bifeprunox also antagonized *d*-amphetamine (0.5 and 2 mg/kg)-induced hyperactivity in rats (ED_{50} = 0.005 and 0.02 mg/kg s.c. for the respective amphetamine doses *vs.* 0.036 mg/kg s.c. for inhibition of baseline activity) (26-28).

Results from microdialysis studies in freely moving rats showed that treatment with bifeprunox (0.01-1 mg/kg i.p.) dose-dependently decreased extracellular dopamine and 5-HT levels in the nucleus accumbens to 80% of controls. These reductions were suggested to be due to activation of presynaptic D2 receptors and 5-HT_{1A} receptors. Preclamol and quinpirole produced similar decreases and haloperidol (ED_{150} = 0.14 mg/kg) increased dopamine levels without affecting 5-HT (24, 29). The effects of bifeprunox on dopamine and 5-HT synthesis rates were also examined. Bifeprunox (0.1-3 mg/kg p.o.) dose-dependently increased the accumulation of the dopamine precursor L-DOPA in the striatum of rats subjected to aromatic decarboxylase inhibition. The maximum effect was an increase of 150% over controls; haloperidol increased striatal L-DOPA levels to 380% of controls (ED_{200} = 0.7 mg/kg p.o.). Moreover, treatment with bifeprunox, also dose-dependently reduced 5-HTP accumulation (ED_{75} = 13.5 mg/kg p.o.). Bifeprunox was less potent but equally effective compared to the 5-HT_{1A} agonist 8-OH-DPAT (ED_{75} = 0.22 mg/kg i.p.). These results supported its profile of a partial dopamine D2 receptor/full but weak 5-HT_{1A} receptor agonist (29).

In contrast to most antipsychotics, bifeprunox also possesses antidepressant, anxiolytic and antiparkinsonian actions. In a rat model of differential reinforcement of low rates of responding, the agent dose-dependently decreased the response rate (lowest effective dose [LED] = 0.03 mg/kg i.p.) and increased the reinforcement rate (LED = 0.1 mg/kg i.p.) in a manner similar to antidepressant agents. In another rat model for anxiolytic/antidepressant activity, treatment with bifeprunox suppressed ultrasonic vocalizations in rats subjected to a threatening environment (LED = 0.01 mg/kg i.p.); haloperidol was ineffective in this model (LED > 2 mg/kg i.p.). No cataleptic effect was seen in rats (ED_{50} > 16 mg/kg s.c. and 25 mg/kg p.o.), in contrast to haloperidol (ED_{50} = 0.15 mg/kg s.c. and 6.7 mg/kg p.o.) (26, 27). The antiparkinsonian effects of bifeprunox were demonstrated in a study using a primate model of Parkinson's disease (*i.e.*, MPTP-treated marmosets treated with domperidone). Treatment with bifeprunox reversed MPTP-induced hypomotility and disability in a dose-related manner, such that administration of the maximum effective dose (MED) of 1 mg/kg i.p. produced a 410% increase in spontaneous locomotor activity and a 63% decrease in disability. Significant effects on hypoactivity (392% increase) and disability (52% decrease) were also observed following oral administration of the agent (30).

An *in vivo* study in rats compared the cataleptogenic potential of bifeprunox and other antipsychotics (0.1, 1, 10 and 100 mg/kg i.p.) in the crossed-leg position (CLP) and bar catalepsy tests. In contrast to ziprasidone which produced significant and dose-dependent catalepsy in both tests when administered alone, bifeprunox dose-dependently increased catalepsy in the bar test to a much lesser degree and had no effect in the CLP test; similar effects were observed with sarizotan and SLV-313. However, when animals were pretreated with the 5-HT_{1A} receptor blocker WAY-100635 (0.63 mg/kg s.c.), treatment with bifeprunox or sarizotan produced marked catalepsy in both tests. In this same experiment, catalepsy was enhanced in ziprasidone-treated animals, while aripiprazole and SSR-181507 induced only modest cataleptic effects in animals pretreated with a higher WAY-100635 dose (2.5 mg/kg s.c.). Bifeprunox and SSR-181507 were also shown to potently reverse haloperidol (2.5 mg/kg s.c.)-induced catalepsy in both tests. In comparison, ziprasidone and aripiprazole did not significantly reduce haloperidol-induced catalepsy and SLV-313 and sarizotan only attenuated catalepsy in the CLP test. These results suggest that 5-HT_{1A} agonism reduces the

cataleptogenic potential of agents, although other mechanisms such as partial D2 agonism may also be involved (31).

The behavioral effects of single doses of bifeprunox (0.125-50 mg/kg p.o.) were examined in a study in Cebus monkeys, with results showing a unique profile compared to other antipsychotic agents tested in this model. The agent produced mild sedation, dystonia and parkinsonian symptoms, and locomotor activity was decreased. The EPS produced by the agent peaked at a low dose and moderate reductions in EPS were seen with higher doses. Moreover, bifeprunox increased reactivity and alertness to environmental stimuli. It was concluded that bifeprunox has a favorable benefit/risk ratio in terms of EPS and may have beneficial effects on negative and cognitive symptoms (32).

Clinical Studies

An open-label, dose-escalating pilot study using positron emission tomography with [^{11}C]-raclopride was conducted in 6 healthy male volunteers (18-45 years) to determine the D2 receptor occupancy at 2 and 24 h and changes in plasma prolactin following oral administration of bifeprunox (0.25, 2, 10 and 20 mg). No clinically significant changes in laboratory or ECG parameters or vital signs were observed and adverse events were similar to those previously reported for the agent. Following treatment with bifeprunox, dose-dependent D2 receptor occupancy was seen, with [^{11}C]-raclopride displacement rates at 2 h postdosing of 13%, 46%, 90% and 90%, respectively. D2 receptor occupancy plateaued at a dose of 10 mg and remained at about 79% at 24 h postdosing although the plasma elimination half-life of bifeprunox was 9 h. Bifeprunox treatment also markedly decreased prolactin levels to 43%, 12%, 2.5% and 5.5% of baseline levels, respectively. From these results, a once-daily dosing regimen was suggested for further studies (33).

A placebo-controlled, dose-finding phase II study assessed the efficacy and tolerability of bifeprunox in the treatment of patients with schizophrenia. The agent was well tolerated with no indication of weight gain, cardiovascular side effects or EPS. Bifeprunox is presently undergoing phase II/III development as a treatment for schizophrenia and bipolar disorder. Patients with schizophrenia or schizoaffective disorder are currently being recruited for a 2-month, randomized, double-blind phase II study to examine the safety and tolerability of a 5-day titration schedule (with b.i..d. dosing for the first 3 days) to achieve a dose of 40 mg/day. Another 2-month, randomized, double-blind, placebo-controlled phase II trial in patients with schizophrenia or bipolar disorder has initiated patient recruitment to examine the tolerability of bifeprunox with the progressive elimination of titration steps to achieve the shortest tolerated titration dosing to 40 mg/day; this study also includes an optional open-label 26-week extension study. Patient recruitment has been initiated for another randomized, double-blind, placebo-controlled phase II pharmacokinetic study to examine the safety, tolerability and pharmacokinetic interaction of concurrent valproate and bifeprunox treatment in subjects with bipolar I disorder. A 7-10-week, randomized, double-blind, placebo-controlled phase II study is also recruiting patients to examine the safety and tolerability of different treatment interruption intervals on reinitiation of bifeprunox in patients with schizophrenia or schizoaffective disorder. A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study was initiated in June of this year in approximately 380 depressed patients and is examining the efficacy of bifeprunox (20-40 mg/day for 8 weeks) in bipolar disorder. Submissions for bifeprunox are planned in a number of markets in 2006, with an expected launch in 2007 (34-39).

Sources

Discovered by Solvay Pharmaceuticals, B.V. (NL) and codeveloped by H. Lundbeck A/S (DK); licensed to Wyeth Pharmaceuticals (US).

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