Drugs of the Future 2008, 33(4): 316-322

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.04.1191052

Lurasidone Hydrochloride

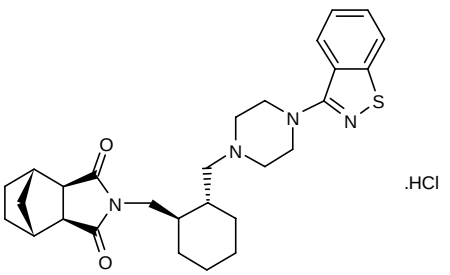
Dopamine D2/5-HT$_{2A}$ Antagonist
Treatment of Schizophrenia

Rec INNM; USAN

MK-3756 (former code name)
SM-13496
SMP-13496

(3a*R*,4*S*,7*R*,7a*S*)-2-[(1*R*,2*R*)-2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl]hexahydro-1*H*-4,7-methanoisoindole-1,3-dione hydrochloride

InChI=1/C28H36N4O2S.ClH/c33-27-24-18-9-10-19(15-18)25(24)28(34)32(27)17-21-6-2-1-5-20(21)16-30-11-13-31(14-12-30)26-22-7-3-4-8-23(22)35-29-26;/h3-4,7-8,18-21,24-25H,1-2,5-6,9-17H2;1H/t18-,19+,20-,21-,24+,25-;/m0./s1



$C_{28}H_{37}ClN_4O_2S$
Mol wt: 529.1378

CAS: 367514-88-3

CAS: 367514-87-2 (free base)

EN: 371997

Abstract

Despite important innovations in the pharmacotherapy of schizophrenia in the last few decades, most notably the introduction of a number of dual-acting dopamine D2/5-HT$_{2A}$ antagonists, there remains a need for more effective treatments. Efforts to discover new molecules with a balance of effects on dopamine and 5-HT receptors resulting in an improved therapeutic profile have therefore continued. One of the agents furthest along in development is lurasidone hydrochloride, a dual dopamine D2/5-HT$_{2A}$ antagonist currently undergoing phase III investigation. Lurasidone has a receptor binding profile distinct from other agents and preclinical data point to potentially beneficial effects on negative symptoms, cognitive function and mood, as well as a reduced potential for EPS. Clinical studies reported to date have indeed shown significant effects on positive and negative symptoms in schizophrenia patients in the absence of an effect on weight.

Synthesis

Lurasidone hydrochloride can be synthesized as follows. The condensation of 1-(1,2-benzoisothiazol-3-yl)piperazine (I) with (*R,R*)-1,2-bis(methanesulfonyloxymethyl)cyclohexane (II) in the presence of potassium carbonate and tetrabutylammonium bisulfate in boiling toluene gives the spiropiperazinium salt (III) (1-3), which is further reacted with bicyclo[2.2.1]heptane-2,3-dicarboximide (IV) by means of potassium carbonate in hot xylene or toluene to yield lurasidone (1-4). Lurasidone base is finally converted to the corresponding hydrochloride salt by treatment with HCl in acetone (5). Scheme 1.

Background

Schizophrenia is a chronic disorder with a prevalence worldwide of approximately 1%, with as many as 24 million people affected (6, 7). Its effects on an individual can be devastating, leading to loss of independence. Most patients have recurring problems over a period of years, as well as problems with drug and alcohol use and an increased risk of suicide (7-10). Schizophrenia patients are also at increased risk for obesity, hypertension, diabetes, sexually transmitted diseases, smoking and cardiovascular disorders, resulting in a mortality rate significantly higher than the general population (9, 11).

Although schizophrenia therapy has advanced greatly in recent years and the number of treatment options has swelled, as many as 30% of schizophrenia patients continue to have severe, persistent symptoms despite treatment with doses normally considered to be effective, and 60% of responders will relapse within 2 years of maintenance therapy due to breakthrough symptoms or noncompliance (12). Nevertheless, positive symptoms

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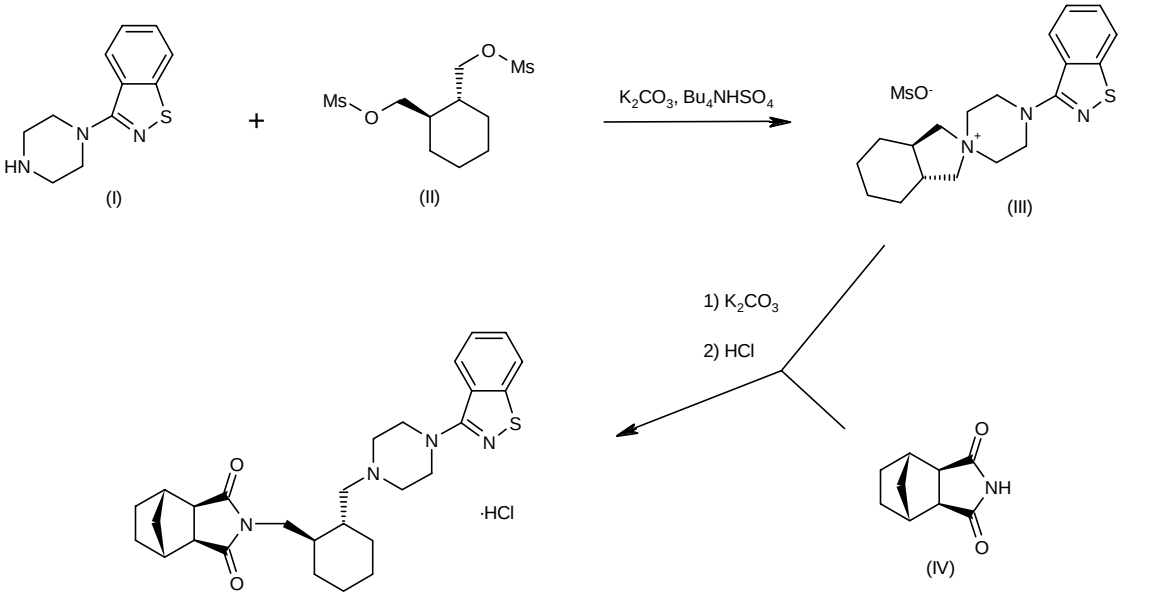
Scheme 1: Synthesis of Lurasidone Hydrochloride



(auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears) can be controlled by medication in most patients, while negative symptoms (social withdrawal, loss of will or drive, poverty of speech, apathy and lack of energy) are less responsive to pharmacotherapy (8, 13).

Antipsychotic drug development has long been based on the “hyperdopaminergic hypothesis” of schizophrenia, pointing to excessive production of dopamine (presynaptic dopamine overactivity) and/or increased D2 receptor density or increased postreceptor action (postsynaptic dopamine overactivity). All of the marketed antipsychotic drugs that are capable of reducing the symptoms of schizophrenia act at least in part by decreasing dopaminergic neurotransmission (6, 14).

The discovery that clozapine improves negative as well as positive symptoms was a landmark in schizophrenia treatment. This agent is a dual-acting dopamine D2 and 5-HT_{2A} antagonist and its success led to the exploration of serotonergic pathways and the development of a new generation of atypical antipsychotic agents, including olanzapine, risperidone and quetiapine. These drugs cause fewer extrapyramidal symptoms (EPS) than classical neuroleptics and can treat a wider range of schizophrenia symptoms (7, 9, 15, 16).

There are safety differences among atypical antipsychotics; while EPS are reduced with these agents compared to conventional drugs, some have a better EPS profile than others, depending on their precise mechanism of action. Some atypical antipsychotics are also associated with increased prolactin levels, which can result in galactorrhea, gynecomastia, sexual dysfunction, infertility and amenorrhea. Weight gain is an important adverse event seen with atypical agents and can affect compliance and have important health consequences. Some atypical antipsychotics appear to carry a greater risk of hyperglycemia and the development of type 2 diabetes compared to typical antipsychotics, and the same appears to be true of dyslipidemia. Both typical and atypical antipsychotics can cause dose-related prolongation of the Q-T interval, although again the potential for this effect varies among drugs. Atypical antipsychotics have also been linked to manic/hypomanic symptoms and sedation (17).

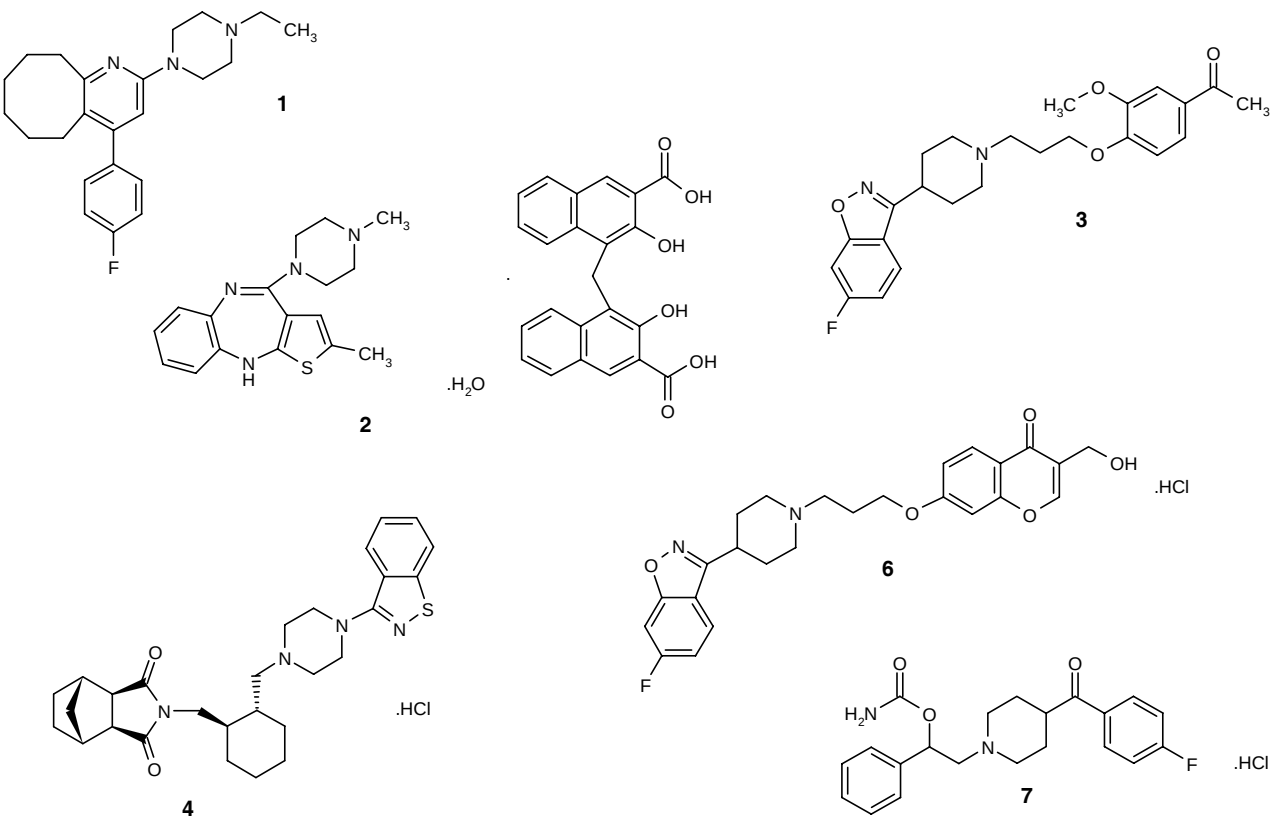
The atypical antipsychotics also have differential effects on negative symptoms, cognitive function, depressive symptoms and anxiety. An atypical agent may be advantageous in terms of some aspects of efficacy but may also be associated with increased risks of certain adverse effects. A low D2 occupancy with higher 5-HT_2 activity – the 5-HT_2:D2 ratio – appears to be a key element for improving negative symptoms and reducing EPS. Olanzapine has a high 5-HT_{2A}:D2 ratio and has some of the strongest effects on negative symptoms among the atypical agents; it is also associated with minimal EPS and does not elevate prolactin. It is associated, however, with a higher risk of weight gain, diabetes and hyperlipidemia. Other mechanistic actions can also have the desired effects, such as the lack of EPS with amisulpride, a dual D2/D3 receptor antagonist with little affinity for 5-HT_{2A} receptors, or a similar lack of EPS with a greater effect on negative symptoms with aripiprazole, a partial D2 and 5-HT_1 agonist and 5-HT_2 antagonist (6, 17).

As it stands, second-generation antipsychotics are typically given as first-line therapy, with first-generation agents tried in patients not responding to second-generation drugs. In the meantime, the search is on for drugs with the enhanced antipsychotic efficacy initially seen with clozapine, but without metabolic side effects (6, 18). Finding the right balance and interplay between dopamine and 5-HT receptor antagonism and agonism, with effects on relevant receptor subtypes, and between efficacy and safety, is one of the primary aims of antipsychotic drug development. Naturally, the proper balance of these factors most likely varies by patient, and the achievement of effective therapy for schizophrenia in general will rely on the existence of a variety of treatment options.

Lurasidone (SM-13496, SPM-13496) is one of several dopamine D2 and 5-HT_{2A} antagonists under development, and it has reached phase III (Table I). It has demonstrated high binding affinity for both receptors in preclinical studies, with a binding profile different from both typical antipsychotics and other atypical antipsychotics. Preclinical evidence also points to the potential for effects on negative symptoms and cognitive function, and anxiolytic and mood-stabilizing activity. The EPS-inducing potential of lurasidone appeared to be low in animal experiments, and a safety study in schizophrenia patients found no increase in prolactin levels and no adverse effects on lipid profiles, glucose regulation or weight gain with the drug. Significant clinical efficacy has also been seen in studies in patients, several of which are ongoing or have been completed. These and further evaluations, including head-to-head comparisons, will help reveal the place of lurasidone in the landscape of atypical antipsychotic medications and in the overall panorama of schizophrenia treatment.

Table I: Dual-acting dopamine D2/5-HT_{2A} antagonists under active development for schizophrenia.

Drug	Source	Phase
1. Blonanserin	Dainippon Sumitomo Pharma/Almirall	R-2007
2. Olanzapine pamoate	Lilly	Prereg.
3. Iloperidone	Vanda Pharmaceuticals	Prereg.
4. Lurasidone hydrochloride	Dainippon Sumitomo Pharma	III
5. TGOF02N*	Fabre-Kramer	II
6. Abaperidone hydrochloride	Ferrer	I
7. YKP-1358	SK Bio-Pharmaceuticals	I



*Structure not available.

Preclinical Pharmacology

In receptor binding studies, lurasidone demonstrated high affinity for dopamine D2 (K_i = 1.68 nM), 5-HT_7 (K_i = 0.495 nM), 5-HT_{2A} (K_i = 2.03 nM) and 5-HT_{1A} receptors (K_i = 6.75 nM) and α_{2C}-adrenoceptors (K_i = 10.8 nM). In contrast to other antipsychotics, much lower or no affinity has been noted for α_1-adrenoceptors (K_i = 47.9 nM), histamine H_1 receptors (IC_{50} > 1000 nM) and 5-HT_{2C} receptors (19-22). The binding affinity for the D2 receptor was similar to that of haloperidol and risperidone and greater than that of chlorpromazine, olanzapine and clozapine, while binding affinity for the 5-HT_{2A} receptor was lower than for risperidone but greater than for olanzapine, clozapine, chlorpromazine and haloperidol. The rank order of affinity for 5-HT_{1A} receptors was lurasidone > clozapine > risperidone > haloperidol = chlorpromazine, and that for 5-HT_7 receptors was lurasidone > risperidone > clozapine > chlorpromazine > haloperidol = olanzapine. For α_{2C}-adrenoceptors the order was lurasidone = risperidone > clozapine > chlorpromazine > haloperidol, for α_1-adrenoceptors the order was risperidone > chlorpromazine > clozapine = haloperidol > lurasidone, and for histamine H_1 receptors the order was clozapine > risperidone > chlorpromazine > haloperidol > lurasidone (20).

Lurasidone antagonized dopamine-induced inhibition of cAMP accumulation in Chinese hamster ovary (CHO) cells expressing human D2L receptors, with a potency similar to haloperidol (EC_{50} = 3.0 nM *vs.* 3.4 nM), while it was much less potent than haloperidol in reversing quinpirole-induced inhibition of [^{3}H]-acetylcholine release in striatal slices (EC_{50} = 280 nM *vs.* 8.3 nM). In experiments in rats, lurasidone (1-30 mg/kg p.o.) increased levels of the dopamine metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) in the frontal cortex, striatum, thalamus, hypothalamus and hippocampus. The increase in dopamine turnover seen with lurasidone in the frontal cortex was slightly higher than in the striatum and appeared to involve 5-HT_{1A} receptors. Lurasidone was similar to clozapine in this respect but different from haloperidol, which markedly increased striatal turnover. Also like clozapine, lurasidone significantly increased Fos-like immunoreactivity in the nucleus accumbens, but it only weakly increased immunoreactivity in the striatum (21-24).

The effects of lurasidone on cognitive performance were evaluated in a rat passive avoidance test, in which the drug and other antipsychotics were administered 1 h before footshock training and the test was conducted the next day. Neither haloperidol (0.3, 1 mg/kg p.o.) nor lurasidone (1-30 mg/kg p.o.) affected step-through latency in the training or the test. Co-treatment with lurasidone and scopolamine dose-dependently recovered the test response impaired by scopolamine alone. The atypical antipsychotics clozapine (10, 30 mg/kg p.o.), olanzapine (3, 10 mg/kg p.o.), quetiapine (30 mg/kg p.o.), aripiprazole (10 mg/kg p.o.) and risperidone (3 mg/kg p.o.) significantly shorted the latency in the test, unlike lurasidone. Binding to muscarinic M_1 or histamine H_1 receptors appeared to be involved in the impairment of passive avoidance response by clozapine, olanzapine and risperidone (25, 26). In related studies, the effects of lurasidone and other antipsychotics on memory impairment induced by MK-801 were investigated in rats. Animals given MK-801 0.05 mg/kg s.c. before passive avoidance training and before the test on day 2 displayed decreased step-through latency in the test. The MK-801-induced memory impairment was dose-dependently and almost completely reversed by pretraining administration of lurasidone (1, 3 mg/kg p.o.), while it was partially reversed by quetiapine (10 mg/kg p.o.), clozapine (0.3, 1 mg/kg p.o.) and risperidone (1 mg/kg p.o.). Memory impairment was not affected by haloperidol (0.3, 1 mg/kg p.o.), olanzapine (0.3-1 mg/kg p.o.) or aripiprazole (0.3-1 mg/kg p.o.). Furthermore, when lurasidone (0.1, 0.3 mg/kg i.v.) was administered 10 min after animals received footshock training, dose-dependent reversal of the effect of MK-801 on step-through latency was seen. This indicates that lurasidone restored the memory consolidation process impaired by MK-801 (26-29).

Acute administration of MK-801 (0.15 or 0.2 mg/kg i.p.) also caused cognitive impairment in rats in the Morris water maze and radial-arm maze tests. Lurasidone (1, 3 mg/kg p.o.) reversed the impairment of learning and memory in both tests, while haloperidol (0.3, 1 mg/kg p.o.) had no effect and aripiprazole, clozapine and risperidone had only marginal effects (30).

In studies of the behavioral effects of lurasidone, oral administration of the drug inhibited methamphetamine-induced hyperactivity in rats and apomorphine-induced climbing behavior in mice, with ED_{50} values of 0.9 and 4.9 mg/kg, respectively. Conditioned avoidance responses in rats were also suppressed by lurasidone, with an ED_{50} of 4.7 mg/kg, while little effect was seen on the escape response. 5-HT_2 receptor-mediated behaviors such as tryptamine-induced clonic seizures and *p*-chloroamphetamine-induced hyperthermia in rats were inhibited with ED_{50} values of 3.0-5.6 mg/kg (31, 32).

To evaluate the potential of lurasidone in treating mood disturbances, its effects on conditioned fear stress-induced freezing behavior in rats were assessed. Freezing was reduced by the anxiolytic diazepam and the antidepressants desipramine and imipramine. The behavior was also dose-dependently and significantly inhibited by lurasidone 0.3-6 mg/kg p.o. Freezing behavior was reduced by clozapine and risperidone, although to a lesser extent than with lurasidone. Induction of freezing behavior was also diminished by ritanserin and ketanserin, but haloperidol, chlorpromazine, thioridazine, mosapramine or tiapride had no effect. Given the mechanism of action of the agents studied and their effects in this model, the results indicate that the 5-HT_2-blocking activity of lurasidone may be involved in its mood-stabilizing potential (33). Lurasidone also demonstrated anxiolytic and mood-stabilizing potential by significantly increasing punished water licking in the Vogel conflict test (34).

Pharmacokinetics and Metabolism

Analysis of the *in vivo* metabolism of [^{14}C]-labeled lurasidone in rats led to the identification of 14 metabolites. Four metabolic reactions were deduced: hydroxylation of the norbornane ring, cleavage of the C-N bond between cyclohexylmethyl and piperazine, oxidation of sulfur in the benzoisothiazole ring and cleavage of the N-S bond of the benzoisothiazole ring and subsequent methylation. [^{14}C]-Lurasidone was extensively metabolized following oral administration. Unchanged compound was the most abundant in serum, followed by hydroxylated analogues, cleaved analogues and sulfoxidated analogues. Cleaved analogues were most common in urine, where parent drug was not detected. When [^{14}C]-lurasidone was incubated with mouse, rat, rabbit, dog, monkey and human liver microsomes in the presence of NADPH, the extent of metabolism varied among species but the metabolic profiles were similar (35).

Safety

The EPS liability of the drug was evaluated using catalepsy and paw tests in rats. No cataleptogenic activity was seen at oral doses up to 1000 mg/kg. The rank order of conventional and atypical antipsychotics showed lurasidone to have the lowest potency for inducing catalepsy: lurasidone (ED_{50} > 1000 mg/kg) < thioridazine (ED_{50} = 890 mg/kg) < sertindole (ED_{50} < 300 mg/kg) = clozapine (ED_{50} > 300 mg/kg) < olanzapine (ED_{50} = 28 mg/kg) < chlorpromazine (ED_{50} = 25 mg/kg) = risperidone (ED_{50} = 20 mg/kg) < haloperidol (ED_{50} = 12 mg/kg). The paw test evaluated latencies for withdrawal of rat forelimbs (FRT) and hindlimbs (HRT) from holes in the test apparatus. Lurasidone was more potent in increasing HRT than in increasing FRT, with minimal effective doses (MEDs) of 300 and > 1000 mg/kg, respectively. The ratio of the MED resulting in increases in FRT to that for increases in HRT was calculated for various agents, and the rank order was: lurasidone (> 3.3) > clozapine (3) > thioridazine (> 1) > risperidone (1) = chlorpromazine (1) = haloperidol (1). In other experiments, ED_{50} values for potentiation of hexobarbital anesthesia, bradykinesia in the mouse pole test, muscle relaxation in the traction test and inhibition or potentiation of electrically induced convulsions were all above 1000 mg/kg. Performance on the rotarod test was only weakly inhibited by lurasidone (ED_{50} = 252 mg/kg) (31, 32, 36).

The safety and tolerability of lurasidone were also evaluated in a randomized, double-blind, placebo-controlled phase II study in 180 patients with schizophrenia experiencing an acute exacerbation who were treated with lurasidone 80 mg or placebo for up to 6 weeks. While a higher rate of discontinuation due to adverse events was seen in the lurasidone group (6.7% *vs.* 1.1%), no clear pattern of adverse events leading to discontinuation was identified in either group. Nausea was significantly more common in the lurasidone group (16.7% *vs.* 3.3%), but all of the cases in the lurasidone group were mild to moderate and only 1 discontinuation was attributed to nausea. There was no between-group difference in prolactin levels in males completing 6 weeks of treatment, and lurasidone did not affect lipid profiles, glucose regulation or weight gain (≥ 7 kg increase: 6.7% and 7.8% with lurasidone and placebo, respectively) (37).

Clinical Studies

The dopamine D2 receptor occupancy of lurasidone was investigated in healthy adult males, 20 of whom underwent positron emission tomography (PET) for 90 min after i.v. administration of [^{11}C]-raclopride before and 90 min following lurasidone administration as single oral doses of 10-80 mg. The percentage of D2 receptor occupancy in the putamen, caudate nucleus and ventral striatum increased with doses up to 60 mg. Dose-dependent increases in mean D2 receptor occupancies were seen, as were dose-dependent increases in serum lurasidone concentrations, peaking at 60 mg. Serum concentrations were related to D2 receptor occupancy for the parent drug and its major metabolite: the 10-mg dose was associated with a mean concentration of 3.36 ng/ml and occupancy rates of approximately 40%, the 60-mg dose was associated with maximal receptor occupancies of 75-85% and the 80-mg dose was associated with occupancies of 70-80% (38, 39).

Lurasidone has been evaluated in two phase II studies in which patients with schizophrenia experiencing an acute exacerbation of symptoms as diagnosed by DSM-IV criteria were treated for 6 weeks. The randomized, double-blind studies evaluated daily doses of lurasidone of 40, 80 and 120 mg. In Study 196, 180 patients were treated at 22 centers in the United States. Lurasidone 80 mg once daily was significantly superior to placebo in terms of improvement in Positive and Negative Syndrome Scale (PANSS) total scores and Clinical Global Impression-Severity (CGI-S) score. Significant effects were evident 3 days into treatment and were maintained throughout the study. Lurasidone was associated with significant differences compared to placebo in mean changes from baseline in the PANSS Total, PANSS Positive, PANSS Negative, PANSS Cognitive Component, PANSS Depression, Brief Psychiatric Rating Scale (BPRS) Total, Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-S scores. In Study 006 (n=132), lurasidone 40 and 120 mg once daily was significantly superior to placebo in terms of the change from baseline to day 42 on the BPRS. The drug was also superior on secondary endpoints in this study. The treatment was reported to be safe and well tolerated (40-42).

A number of other clinical studies of lurasidone are ongoing or have been completed. A recently completed double-blind, randomized, placebo-controlled, crossover phase I study assessed the possible interaction between lurasidone and an oral contraceptive (Ortho Tri-Cyclen®) in 24 healthy female volunteers (43), and a 12-month, multicenter, open-label trial (44) examined the safety and tolerability of lurasidone for the treatment of schizophre-

nia in 100 patients. Ongoing studies include a phase II trial comparing lurasidone to haloperidol and placebo in patients with schizophrenia with acute exacerbations of symptoms (45), a multicenter, randomized open-label study evaluating the safety and tolerance of different doses of lurasidone for 6 months in patients with schizophrenia (46), and two phase III trials of lurasidone in acutely psychotic patients with schizophrenia (47, 48). The results from these studies are eagerly awaited.

Source

Dainippon Sumitomo Pharma Co., Ltd. (JP).

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