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Viewpoint

ACS Chemical Neuroscience Molecule Spotlight on Latuda (Lurasidone; SM-13,496)

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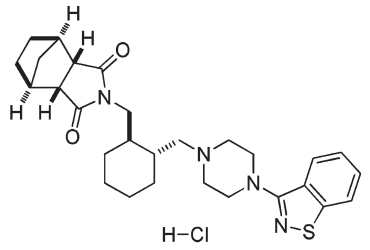

Latuda® (Lurasidone, SM-13,496)
D_2 and α_{2C} adrenergic receptor antagonists, 5-HT_{1A} receptor agonist

Schizophrenia is a chronic and extremely severe disorder of the mind and brain that affects approximately 1% of the population; more than 2 million Americans suffer from the disease a year. The overall cost of this devastating disease is exceptionally high, with estimates from the year 2002 being $62.7 billion (U.S. alone) with greater than $20 billion direct health care cost (in/outpatient, medication, long-term care) (*1*). Schizophrenia is a disorder that is found all over the world and affects both men and women with equal frequency (although the disease usually presents itself at an earlier age in men (late teens/early twenties) than in women (twenties/early thirties)). Individuals with schizophrenia often suffer from symptoms ranging from delusions, hallucinations, and having false beliefs and paranoid thoughts which leave them fearful and withdrawn from society. These symptoms are classified as positive symptoms (hallucinations, delusions, etc.), negative symptoms (social withdrawal, apathy, etc.), and cognitive dysfunction (executive function and memory deficiencies). Most of the so-called first-generation antipsychotics (e.g., haloperidol, D_2 antagonists) are generally effective against the positive symptoms. Unfortunately, these compounds are less beneficial toward the negative and cognitive symptoms, and they also suffer from significant extrapyramidal side effects (EPS), such as dysonia, akathisia, and parkinsonism. The second-generation antipsychotics, combined 5-HT_{2A} and D_2 antagonists, offer significant improvements for negative symptoms and are generally better tolerated with less EPS. However, side effects with these compounds (e.g., clozapine) include significant weight gain and metabolic disorders, as well as other side effects associated with other off-target activities (α1, muscarinic, and H_1 antagonism). Both first- and second-generation antipsychotics have limited efficacy for the cognitive symptoms. Due to these issues, there still exists a significant need for more beneficial medications to treat this devastating disease, since most schizophrenics continue to suffer from some of the symptoms throughout their lives, with as few as 20% of the individuals being able to recover fully.

Latuda (lurasidone HCl) is a newly approved atypical antipsychotic from Dainippon Sumitomo Pharma (approved October 29, 2010) which should be made available in early 2011. Lurasidone HCl acts as a dopamine D_2 (K_i = 1.7 nM) and serotonin 5-HT_{2A} (2.0 nM) receptor antagonist, and it has high binding affinities for serotonin 5-HT_{1A} (6.8 nM) and 5-HT_7 (0.5 nM) as well as the α_{2C} adrenoceptor (10.8 nM) (*2*, *3*). Although lurasidone possesses potent D_2 antagonist activity in vivo, it has shown limited EPS. It has been postulated that the lurasidone may be beneficial for treating the cognitive and memory deficiencies in schizophrenia based on several factors: (1) lurasidone does not possess any activity against muscarinic acetylcholine or histamine H_1 receptors, two receptors that potentially disrupt memory and learning; (2) lurasidone has high affinity for a number of receptors that have been reported to improve cognitive function (5-HT_{1A}, 5-HT_{2A}, 5-HT_7, and α_{2C}); and (3) due to its low potential for generating EPS, lurasidone should be a stand-alone treatment (not requiring coadministration with anticholinergic drugs) (*2*, *3*).

The FDA approval of Latuda (lurasidone) was based on more than 40 clinical trials involving more than 2500 adult subjects. The key studies were four 6-week placebo-controlled double blind clinical trials. These studies showed that lurasidone was effective for both positive and negative symptoms of schizophrenia (compared to placebo) and there were no clinically significant differences between lurasidone and placebo in measures of EPS (*4*, *5*). The most common reported adverse events (AEs) were drowsiness, akathisia, nausea, and movement abnormalities (*6*). With the approval of Latuda, physicians have another drug in their "toolbox" for the effective treatment of adults with schizophrenia.

References

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Received Date: December 20, 2010
Accepted Date: December 20, 2010
Published on Web Date: February 16, 2011

DOI: 10.1021/cn1001123 | *ACS Chem. Neurosci.* (2011), *2*, 58–59

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DOI: 10.1021/cn1001123 | *ACS Chem. Neurosci.* (2011), *2*, 58–59