International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 7 Issue 4, July-August 2023 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Efficacy of ITI-007 Related with Mood Regulation and Mental Disorder

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ABSTRACT

Schizophrenia imposes a heavy burden on both the individual and society. A wide range of symptoms, including as psychosis, hallucinations, delusions, and associated positive feelings, as well as difficulties in social functioning, cognitive problems, and, frequently, debilitating mood disorders like chronic depression, are used to describe the disease. Often, lifelong medication is necessary for the disease's management. A novel antipsychotic drug called lumateperone (ITI-007, CAPLYTATM) was discovered and created by Intra-Cellular Therapies, Inc. (ITCI) and was authorized for the treatment of schizophrenia in adults in December 2019. Serotonin, dopamine, and glutamate neurotransmission, three important neurotransmitters linked to schizophrenia, are simultaneously modulated by lumateperone. The US Food and Drug Administration has authorized its use.

Patients with treatment-resistant schizophrenia and those who are at risk of developing metabolic dysfunction should take into account using lumateperone abnormalities of movement. Lumateperone should not be used, however, in the following situations: (a) women who are pregnant or nursing; (b) children, adolescents, and elderly patients with dementia-related psychosis; (c) patients who are at risk for cerebrovascular diseases; (d) patients who use alcohol or other sedative drugs; and (e) patients who use inducers and moderate or strong inhibitors of the cytochrome P450-3A4 (CYP3A4) isozyme. Future research will lay the groundwork for identifying the proof for thorough analyses of the function of lumateperone in the treatment of those with schizophrenia and other illnesses.

How to cite this paper: Ms. Bhusare Kalpana Marutirao | Mr. Salvi Ajay Sanjay "Efficacy of ITI-007 Related with Mood Regulation and Mental Disorder" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-4, August 2023, pp.243-249, URL: www.ijtsrd.com/papers/ijtsrd59645.pdf

IJTSRD59645

KEYWORDS: *Antipsychotic, Lumateperone, Depression, Anhedonia, Pharmacodynamic, Pharmacokinetic*

INTRODUCTION

Schizophrenia

Schizophrenia is a severe mental illness that has an impact on how a person perceives reality, communicates emotions, thinks, and behaves.

Characterized by a wide range of cognitive, emotional, and behavioral symptoms that begin in adolescence or early adulthood. Hallucinations (auditory, visual, gustatory, olfactory, and tactile), delusions (persecutory, referential, somatic, erotomanic, grandiose, and religious), muddled ideas, disorganized speech, difficulty concentrating, catatonic behavior, and movement problems are examples of positive symptoms. Anhedonia, apathy, asociality, alogia, flattening of affect, disengagement, emotional blunting, and inattention are examples of negative symptoms.

Schizophrenia is the sixth most common cause of disability among adults aged 15 to 44 worldwide. Every year, there are 1.5 new instances per 10,000 people. In those who are susceptible, both genetic and environmental factors may hasten the onset of schizophrenia.

Objectives:

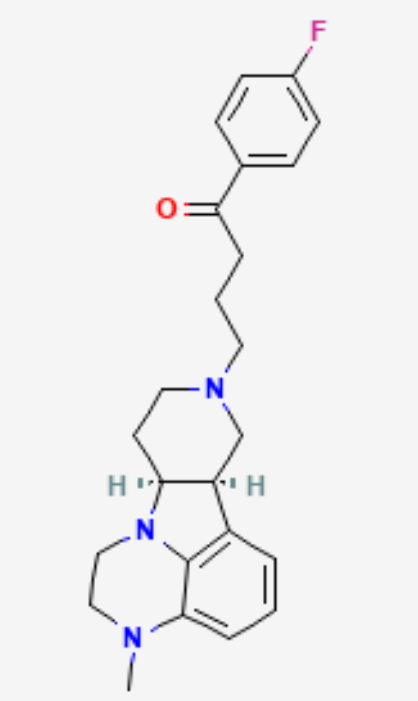
1. Give an explanation of how lumateperone works to treat schizophrenia.
2. Write a summary of the most recent research on lumateperone, a brand-new drug used to treat a number of neuropsychiatric illnesses.
3. Review the key clinical aspects of lumateperone usage in the management of neuropsychiatric diseases.

4. Give examples of how better interprofessional team care coordination might help patients with schizophrenia have better results.

Drug Profile

General profile of Lumateperone

Structure



Category- Antipsychotic

ChemicalName-1-(4-fluorophenyl)-4-[(10*R*,15*S*)-4-methyl-1,4,12-triazatetracyclo [7.6.1.0.0]hexadeca-5,7,9(16)-trien-12-yl]butan-1-one

Molecular formula - $C_{24}H_{28}FN_3O$

Molecular Weight- 393.5 g/mol

pKa Value - 8.47

Route of Administration

The suggested dose is 42mg taken orally with food once daily. In addition, a 26-year-old man with treatment-resistant paranoid schizophrenia required increasing the dose of lumateperone to 84 mg/day in order to experience improvement in auditory and visual hallucinations without experiencing any negative side effects after 6 months of sustained therapy. Lumateperone has a moderate half-life of 13 to 21 hours and exhibits rapid absorption after oral administration. In 3 to 4 hours, T-max happens. The full excretion of lumateperone and its metabolites occurs in the feces.

Mechanism of Action

Lumateperone functions as a dopamine receptor phosphoprotein modulator, a postsynaptic antagonist at dopamine D2 receptors, a presynaptic partial agonist at serotonin 5-HT2A receptors, and a serotonin transport inhibitor.5,22,28,45–49 It also indirectly modulates glutamatergic -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid52 and N-methyl-D-aspartate (NMDA) GluN2B receptors in a dopamine D1 receptor-dependent manner.

Pharmacological Action

Dopaminergic, serotonergic, and glutamatergic neurotransmission are all simultaneously modulated by lumateperone as part of its mode of action. The indications, mode of action, and administration of lumateperone as an effective schizophrenia treatment are covered in this activity.

Pharmacodynamics

Serotonin 5-HT2A receptors are highly affine for the drug lumateperone, whereas dopamine D1 receptors, dopamine D2 receptors, and serotonin transporters are moderately affine. Additionally, it exhibits a modest affinity for muscarinic and histaminergic receptors and a high affinity for dopamine D4, adrenergic receptors -1A and -1B.

D2 dopamine receptor

Lumateperone exclusively binds to mesolimbic and mesocortical dopamine D2 receptors with a high affinity (Ki=32 nM). The medication affects dopamine D2 receptors as both a presynaptic partial agonist and postsynaptic antagonist. The lumateperone dose and D2 receptor occupancy have a good correlation. Lumateperone quickly entered the brains of healthy volunteers (n=16) and occupied striatal dopamine D2 receptors for an extended period of time in a dose- and plasma concentration-dependent manner. In contrast to a dose of 40 mg of lumateperone, which showed peak occupancy of up to 39% of striatal dopamine D2 receptors, a dose of 10 mg of lumateperone showed low occupancy (12%) of striatal dopamine D2 receptors. Patients with schizophrenia who took 60 mg of lumateperone once day displayed peak dorsal striatal dopamine D2 receptor activity in a phase II positron emission tomography (PET) trial (NCT02288845).

Dopamine D1 receptor and glutamate GluN2B receptor Lumateperone phosphorylates the GluN2B (NR2B) subunit of the NMDA receptor via acting on dopamine D1 receptors with dose-dependent high affinity (Ki=52nM).

Transporter of dopamine

A unique quality of lumateperone is its ability to inhibit the dopamine transporter, which may have positive effects on schizophrenia 1 hour after administration.

Serotonin 5-HT2A receptor

Lumateperone functions as a potent antagonist of the serotonin 5-HT2A receptor (Ki = 0.54 nM).5 In a study of 16 healthy men with a mean age of 30.7 years and an average baseline metabolic index of 24.6

and a standard deviation of (3.0), oral dosages of lumateperone as low as 10mg completely saturated (5-HT2A receptors) (>80%).21 40 mg of lumateperone showed occupancy of striatal serotonin transporters up to 33%.

Transporter of serotonin

Lumateperone functions as a strong serotonin transporter inhibitor at mild dosages (Ki=62nM).

Serotonin transporter inhibition and 5-HT2A receptor antagonism work together synergistically to increase the effectiveness of antidepressants.

Pharmacokinetics

The body's absorption of lumateperone, where it is distributed throughout the body, how it is conjugated in the liver, and how it is eliminated from the body are all important components of lumateperone's pharmacokinetics.

Absorption

3–4 hours after lumateperone was given orally. At 8 hours after oral delivery, plasma concentrations of lumateperone and its metabolites ranged from 0.05 to 50 ng/ml.

Bioavailability

The plasma concentration of lumateperone reaches its peak in 1 to 2 hours.43 In around 5 days, steady-state concentrations are reached. Lumateperone's steady-state exposure rises with repeated doses between 21 and 56 mg in a roughly dose-proportional manner. Individual differences exist in the pharmacokinetics of lumateperone, with a range of 68% to 97% for the area under the curve (AUC) and Cmax at steady state. The absolute bioavailability of this medication is 4.4%. When lumateperone is administered along with a high-fat meal, C_{max} increases by 33%, AUC increases by 9%, and the median time to C_{max} is delayed by around 1 hour (moving from 1 hour in the fasting state to 2 hours in the presence of food).

Distribution

Lumateperone has a volume of distribution of 4.1L/kg after intravenous injection.24 At 5M (70 times higher than therapeutic concentrations), it binds to 97.4% of plasma proteins.

Metabolism

Lumateperone generates over 20 metabolites after being metabolized by various enzymes.

UDP glycosyltransferase (UGT)1A1, UGT1A4, UGT2B15, Aldo-keto reductase (AKR)1C1, AKR1B10, AKR1C4, CYP3A4, CYP2C8, and CYP1A2 are among them.

Excretion

Lumateperone and glucuronidated metabolites account for 2.8% and 51% of total plasma radioactivity after a single dosage of radiolabeled lumateperone, respectively. Around 58% of the radioactivity is eliminated in the urine, 1% of the medication in unchanged form is excreted in the urine, and 29% is excreted in the feces. The terminal half-life after intravenous administration is 18 hours, and the clearance is 17.9L/h.

Adverse Effects

The administration of lumateperone is associated with mild to moderate side effects. The most frequent adverse effects at the 42mg/day FDA-approved dosage include somnolence, drowsiness, weariness, and constipation.

In a 148-person Phase III clinical trial, 17.6% of participants reported somnolence, 12.7% reported drowsiness, and 5.3% reported weariness after receiving the current FDA-approved dosage of 42 mg. 64.7% of the cohort as a whole reported negative outcome. In neither of the lumateperone groups (n=294) did extrapyramidal symptoms occur in more than 5% of subjects. In addition, the median weight did not differ statistically significantly from the placebo. The absence of affinity for the metabolic endpoints, such as increases in triglycerides, blood sugar, and prolactin levels, prevented them from differing significantly from placebo. In another clinical research, 302 individuals received either lumateperone or a standard-of-care antipsychotic for six weeks. The metrics measuring LDL-cholesterol, triglycerides, and prolactin levels improved statistically significantly in those who converted from their existing antipsychotics to lumateperone. Evidence suggests that lumateperone has a lower risk of side effects than are typically associated with second-generation antipsychotics, despite the fact that there have only been a small number of clinical trials thus far. Long-term studies are being conducted to ascertain the long-term safety and efficacy of lumateperone.

Contraindications

Lumateperone undergoes cytochrome P450-3A4 isozyme metabolism and interacts with drugs that activate or inhibit this isozyme. Therefore, it is advised that patients taking CYP3A4 inducers or moderate to potent CYP3A4 inhibitors avoid using lumateperone. Additionally, because lumateperone causes sleepiness, especially at lower concentrations, it is likely to interact with alcohol and other sedatives.

Clinical Trials

Several clinical trials undertaken by the pharmaceutical business that markets lumateperone have revealed favorable results with no safety concerns. Table 1 summarizes clinical trials for lumateperone in schizophrenia.

Sr. No.	Name	Sponsors &collaborators	Indication	Phase	Stage of development
1	Lumateperone-oral administration	Intracellular Therapies	Pediatric patients with schizophrenia	1	Not Yet Recruiting
2	Lumateperone	Intracellular Therapies	patients with schizophrenia	1	Recruiting
3	Lumateperone	Intracellular Therapies	schizophrenia	2	completed
4	Lumateperone	Intracellular Therapies	patients with stable schizophrenia	2	completed
5	Lumateperone	Intracellular Therapies	schizophrenia	2	completed
6	Lumateperone	Intracellular Therapies	patients with schizophrenia having an acute exacerbation of psychosis	3	completed
7	Lumateperone	Intracellular Therapies	patients with schizophrenia	3	completed

Phase II

Persistent schizophrenia

To ascertain the connection, a phase II, open-label PET trial (NCT02288845) was carried out. In patients with stable schizophrenia between lumateperone dosage, plasma levels, and brain receptor occupancy. The trial included a total of 14 participants with stable schizophrenia; 10 patients, aged 26 to 57, who received lumateperone 60 mg and finished the study. Nine patients (90%) were Black or African American, while one (10%) was Asian. Just one of these patients (10%) was a woman. At baseline, the patients' mean Clinical Global Impressions Severity (CGI-S) score was 3.8 with a standard deviation of (+/0.63), and their mean Positive and Negative Syndrome Scale (PANSS) total score was 72.7 with a range of (+/7.39). All of the patients took at least one antipsychotic prior to the washout period. The two most commonly used drugs were quetiapine (used by eight patients, or 80% of patients) and risperidone (used by three patients, or 30% of patients). Other drugs used included haloperidol, olanzapine, lurasidone, and paliperidone. No other antipsychotics were used during the trial and washout periods. The only psychotic medicine that was administered concurrently was lorazepam (nine individuals; 90%). In schizophrenia patients (n=10), a dose of 60 mg lumateperone was given orally once daily for two weeks, open-label in the morning and at least after a washout period of two weeks. Using PET, the radiotracer [11C] raclopride was utilized to measure the occupancy of the dopamine D2 receptor. Peak dorsal striatal dopamine D2 receptor occupancy (mean 39%) was seen in patients who received 60 mg of lumateperone once daily at 1 hour after the dose. This study demonstrated that lumateperone is well tolerated and has a good safety profile.

Acute worsening of schizophrenia-related psychosis

Another phase II (NCT01499563) randomized clinical study was carried out in patients with schizophrenia who were experiencing an acute exacerbation of psychosis in a double-blind, placebo-controlled, multicenter setting. The purpose of the study was to compare two dose levels of lumateperone against a placebo in order to evaluate the effectiveness and safety of each. The positive control used was risperidone.

Patients between the ages of 18 and 55 were randomly assigned to receive lumateperone 42 mg, lumateperone 84 mg, risperidone 4 mg, or placebo once day for four weeks. On day 28, the least squares (LS) mean change from baseline in the PANSS total score (primary endpoint) was 13.22, 8.3, 13.4, and 7.4, respectively. Patients were started on normal antipsychotic medication after 28 days of inpatient therapy and stabilized for 5 days before being discharged from the study clinic. Patients were evaluated for final outpatient safety at the end of the study visit two weeks following discharge. While there was no statistical significance between lumateperone 84mg once daily and placebo (p=0.017), there was statistical significance between lumateperone 42mg once daily and placebo (p=0.013). When compared to placebo, risperidone plus lumateperone 42mg once day significantly (p=0.05) improved positive symptoms and general psychopathology on the PANSS subscales. Lumateperone 42mg once daily alleviated depressed and psychotic symptoms in a subset of critically sick individuals with concomitant depression.

Phase III

Acute psychotic exacerbation

A multi-center, phase III (NCT02282761) randomized, double-blind, parallel-group, placebo-controlled investigation in patients with schizophrenia was done. The study's purpose was to investigate lumateperone's efficacy and safety for the short-term treatment of schizophrenia. The trial involved 450 participants between the ages of 18 and 60 from 12 clinical sites in the United States. In each group, 150

patients were randomly assigned to receive lumateperone tosylate 60mg or 40mg (equivalent to 42 mg or 28mg of the active moiety) or placebo once day for four weeks. The key outcome was the change in PANSS score from baseline to day 28 versus placebo. In the prespecified modified intention-to-treat analysis (n=435), the LS mean change from baseline in the PANSS total score at day 28 was 14.5 in the lumateperone 42mg once daily group compared to 10.3 in the placebo group (LS mean difference 4.2; p=0.02). Lumateperone 28mg once daily versus placebo had no statistically significant therapeutic effect (LS mean difference 2.6). At day 28, there were significant improvements (p0.05) with lumateperone 42mg versus placebo on the PANSS positive symptom and general psychopathology subscales, as well as in psychosocial function, as measured by the PANSS derived prosocial factor score and personal and social performance (PSP) scale. Both lumateperone dosages were well tolerated, with no changes in cardio metabolic or endocrine variables or substantial treatment-emergent motor side effects when compared to placebo. The medicine had a favorable safety profile as well as efficacy in alleviating schizophrenia symptoms.

Acute psychotic exacerbation in schizophrenia

A phase III (NCT02469155) clinical trial was done to assess the antipsychotic efficacy of lumateperone in a randomized, double-blind, parallel-group, placebo- and active-controlled, and multi-center research in patients with schizophrenia experiencing an acute psychotic exacerbation. For 6 weeks, 696 patients were randomly assigned to receive lumateperone 42mg, lumateperone 14mg, risperidone 4mg, or placebo. There was no significant difference between doses in terms of change in PANSS baseline score. A significant placebo response was observed.

Stable Schizophrenia

A 12-month open label safety study of lumateperone (NCT03817528) was done in patients with stable schizophrenia symptoms. In the first part of this trial, 303 patients with schizophrenia were moved from standard of care (SOC) antipsychotic medication to 42mg lumateperone once daily for 6 weeks. The patients were subsequently transferred back to SOC for two weeks. Part one of the study found that lumateperone was related with improvements in the PANSS negative factor scale scores, positive symptom and general psychopathology subscale scores, and the PSP scale from baseline. Patients with concomitant depression and strong negative symptoms at baseline showed more recovery. In the second stage of this study, 602 schizophrenia patients were switched from SOC to 42mg lumateperone once daily for up to a year. At day 368, the mean change in the Calgary Depression Scale for Schizophrenia score from the baseline was 0.6 (p=0.01), while the mean change in the PANSS total score from the SOC baseline was 4.0 (p0.001). Improvements were more obvious at baseline in patients with moderate to severe depression.

Phase II and phase III pooled trials

A pooled analysis (n=520) found that 42mg of lumateperone taken once daily lowered the PANSS total score (LS mean difference versus placebo 4.76; p0.001) and was equivalent to risperidone (LS mean difference versus placebo 4.97; p=0.014).Significant gains on PANSS subscales and the CGI-S64 scale were associated with 70 Lumateperone, as were significantly higher PANSS response rates. When all three investigations were combined, the capacity of lumateperone 42mg once daily to demonstrate statistical supremacy over placebo was unaffected by the unfavorable results of one.

Discussion

Lumateperone's involvement in the treatment of persons with schizophrenia can be inferred using limited evidence and indirect comparisons with other current medications. Antipsychotic efficacy and side-effect profiles should be considered when personalizing prescriptions. The newest antipsychotics have an excellent overall safety profile. Lumateperone has the advantage of having relatively minimal risks of common antipsychotic side effects such as weight gain, Parkinsonism, and akathisia.

Because newer antipsychotics are not necessarily the most effective, they should be compared to older ones. Older medications may be more effective, while newer ones are more essential in terms of adverse effects. The use of pooled studies and statistical reasoning to explain the unfavorable results of some clinical trials limits the available research. Furthermore, the current evaluation of some clinical trials is confined to abstracts and posters because the data have not been published as original research articles.

Limitations

The risk of bias, inconsistency, indirectness, or publication bias reduces the credibility of the current evidence for lumateperone.

The results of studies conducted by a pharmaceutical business with a financial interest in marketing lumateperone confirm the possibility of bias, inconsistency, indirectness, or publication bias in the existing literature. The present lumateperone literature is hampered by a lack of data from authors who are not financed by the pharmaceutical business that markets lumateperone.

The capacity to assess the value of lumateperone and other antipsychotics in comprehensive reviews is limited due to low to extremely low confidence in published articles.

Conclusion

Lumateperone, a first-in-class selective and simultaneous modulator of dopamine, serotonin, and glutamate, earned its first global approval for the treatment of schizophrenia in adults on December 20, 2019. Lumateperone has shown efficacy against both positive and negative symptoms of schizophrenia, as well as a favorable tolerance and safety profile. In clinical trials for bipolar depression, dementia, and sleep maintenance insomnia, lumateperone has proven to be a promising medication. It is now used in clinical trials all around the world. While lumateperone is licensed for the treatment of schizophrenia in adults, additional research is needed to determine its efficacy in the treatment of bipolar depression, dementia, and sleep maintenance insomnia. To use precision medicine to produce the optimum treatment plan for individuals with schizophrenia, clinicians must balance the positive results of trials supported by the lumateperone sponsor with a candid appraisal of limited data. To demonstrate its usefulness under the aforementioned conditions, a full examination of its efficacy in long-term human research will be required.

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