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Caplyta® (lumateperone): A Unique, New Therapy Option for the Treatment of Schizophrenia.

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Schizophrenia is a debilitating psychotic disorder that affects around 1.1% of the population, affecting males more than females, with the usual onset of the condition presenting between the ages of 18 to 25 years old.[1,2] Symptoms of this condition can lead to severe social, occupational, and educational impairment. Schizophrenia is characterized by "positive symptoms" defined as a distortion or exaggeration of normal cognitive functions. Positive symptoms include delusions, hallucinations, as well as disorganized thoughts, speech, and behaviors.[3] Schizophrenia is also characterized by "negative symptoms", defined as diminution or loss of normal function that attribute to poor functional outcomes. Symptoms such as flattened affect (poor eye contact, reduced body language, facial immobility), alogia, avolution, and anhedonia are classified as negative symptoms.[3] The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for diagnosis of schizophrenia include the persistence of two or more of the following symptoms with each lasting a significant portion of at least a one-month period: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms (one symptom being delusions, hallucinations, and/or disorganized speech).[4] The pathophysiology of schizophrenia is not fully elucidates but many theories revolve around either an excess or deficiency of neurotransmitters such as dopamine, serotonin, and glutamate.[5] While current antipsychotic therapy has been effective at improving positive symptoms associated with schizophrenia, efficacy of improving negative symptoms and cognitive impairment have been limited.[6] Additionally, current antipsychotic therapy has been associated with various adverse effects such as QTc prolongation, abnormal prolactin levels, weight gain, and extrapyramidal symptoms (EPS).[7] As of now, antipsychotic medications still remain the cornerstone for treatment of schizophrenia such as first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA).[8] SGAs have been associated with fewer extrapyramidal side effects than FGAs, however, SGAs tend to have adverse metabolic side effects such as hyperlipidemia and diabetes mellitus that could lead to an increased risk of cardiovascular mortality.[9]

A new antipsychotic medication acting on the serotonergic, dopaminergic, and glutamatergic systems, improving positive symptoms of schizophrenia, while able to benefit the social and cognitive functioning of patients without producing EPS would be of exceptional benefit to schizophrenic patients.[10] In December 2019, lumateperone (CAPLYTA®; ITI-007), a mechanistically novel investigational antipsychotic agent, was approved by the FDA for the treatment of schizophrenia in adults. The purpose of this article is to assess the efficacy and safety of lumateperone for the treatment of schizophrenia in adults.

Clinical Pharmacology

Mechanism of Action

The mechanism of action of lumateperone, is not fully understood, however, its efficacy could potentially be mediated through a dual action as a serotonin 5-HT2A receptor antagonist and a dopamine and glutamate modulator.[1,11] This is unique to lumateperone versus other antipsychotics.[1] Specifically, lumateperone is perhaps a potent serotonin 5-HT2A receptor antagonist, a dopamine D2 receptor presynaptic partial agonist and postsynaptic antagonist, a D1 receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor.[12] Additionally, lumateperone has negligible binding to receptors such as H1-histaminergic, 5-HT2C, and muscarinic receptors that are associated with metabolic and cognitive adverse effects of FGAs and SGAs.[10] Due to these unique mechanisms, lumateperone classified as a second-generation serotonin-dopamine antagonist (SDA) antipsychotic.

Pharmacokinetics

During clinical trial evaluation, large variability was observed in maximum concentration (Cmax) and exposure (AUC) changing at rates of 68% to 97% at steady-state.[11] Ingestion of a high-fat meal lowers the mean Cmax by about 33% and increases the mean AUC by 9%.[11] The median time to maximum concentration (Tmax) is one hour in a fasted state to two hours in the presence of food.[11] Lumateperone is extensively metabolized with more

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than twenty metabolites identified in vivo. The remainder of pharmacokinetic information for lumateperone is available in **Table 1**.

Pharmacodynamics

Lumateperone has high binding affinity for serotonin 5-HT2A receptors (Ki = 0.54 nM) and moderate binding affinity for dopamine D2 (Ki = 32 nM) receptors. Additionally, lumateperone has moderate binding affinity for serotonin transporters (Ki = 33 nM) and moderate binding affinity for dopamine D1 (41 nM) and D4 and adrenergic alpha1A and alpha1B receptors (Ki projected at < 100 nM). Nonetheless, lumateperone has low binding affinity (less than 50% inhibition at 100 nM) for muscarinic and histaminergic receptors.[11] Cardiac Electrophysiology QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled, four-arm crossover study utilizing concentration-QTc effect modeling in 33 patients with schizophrenia.[11] The placebo corrected change from baseline QTcF (90% two-sided upper confidence interval) values of 4.9 (8.9) and 15.8 (19.8) ms for the 42 mg and the supratherapeutic dose of 126 mg (three times the recommended daily dosage) lumateperone, respectively, administered orally once daily for 5 days.[11]

Table 1 | Select Lumateperone Pharmacokinetics[12]

Absorption	
Tmax[a]	1-2 hours
F[b]	4.4% (oral administration)
C_{ss}[c]	~ 5 days
Distribution	
Vd[d]	4.1 L/kg (IV administration)
Protein Binding	97.4%
Metabolism	
UGT1A1, UGT1A4. UGT2B15 AKR1C1, AKR1B10, AKR1C4 CYP3A4, CYP2C8, CYP1A2	
Elimination	
Cl[e]	27.9 L/hr
T1/2[f]	18 hours
Fecal Excretion	29%
Renal Excretion	58%

[a]Time to maximum concentration; [b]Bioavailability; [c]Steady-state concentration; [d]Volume of distribution; [e]Clearance; [f]Half-life

CLINICAL TRIALS

Lieberman et al.

Lieberman et al. conducted a randomized, double-blind, placebo-controlled, multi-center study in patients diagnosed with schizophrenia and an acute exacerbation of psychosis.[13] The purpose of this study was to evaluate whether lumateperone is effective in reducing symptoms associated with schizophrenia in patients who are having an acute worsening of their psychosis. Patients were randomly assigned to receive lumateperone (ITI-007) 60 mg or 120 mg once daily, placebo, or risperidone 4 mg once daily for 28 days. The primary goal was to assess the effects of lumateperone on psychosis and also the safety of lumateperone. Upon completion of the inpatient 28-day study treatment period, patients were then started on standard antipsychotic medication (quetiapine, risperidone, aripiprazole, olanzapine, haloperidol, or paliperidone) and stabilized over a 5-day period before discharge from the study clinic. Patients were seen for a final outpatient safety evaluation at the End-of-Study visit approximately two weeks after discharge.

The primary outcome of this study was the total score of the Positive and Negative Syndrome Scale (PANSS; considered the "gold standard" for the assessment of antipsychotic treatment efficacy) with the timeframe being the change from baseline to day 28 (day of last dose of lumateperone). The secondary outcome was the total score of the PANSS with the timeframe being the change from baseline to day 8, 15, and 22, with no outcomes taken 2 weeks after the last dose of lumateperone. Patients aged 18-55 years old, current diagnosis of schizophrenia and experiencing an acute exacerbation of psychosis, a history of at least three months exposure to one or more antipsychotic therapy(ies) and a prior response to antipsychotic therapy within the previous five years were included in the study. They were excluded with the following: any female patient who is pregnant or breast-feeding, any patient presenting with concurrent dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, history of significant brain trauma, schizoaffective disorder, bipolar disorder, acute mania, major depression with psychotic features, hematological/renal/hepatic/endocrinological/neurological/cardiovascular disease or substance abuse as defined by protocol, any patient considered to be an imminent danger to themselves or others and/or judged by the investigator to be inappropriate for the study.

The results showed lumateperone 60 mg ($p = .017$) and risperidone ($p = .013$) demonstrated antipsychotic efficacy superiority over placebo on the primary end point (total PANSS change from baseline to day 28). The mean change for lumateperone 60 mg and risperidone 4 mg were -13.2 ± 1.69 and -13.4 ± 1.72 respectively, indicating no significant difference between lumateperone and risperidone. Lumateperone 120 mg did not separate from placebo in the primary outcome. Furthermore, lumateperone (both 60 mg and 120 mg) had low discontinuation rates (60 mg = 20%; 120 mg = 17%) when compared to placebo (22%). Lastly, the adverse event rates did not differ in the lumateperone 60mg group when compared to placebo (lumateperone 60 mg RR = 1.14; 95% CI: 0.89-1.46; $p = 0.346$). A summary of the results for Lieberman et al. is provided in **Table 2**.

Correll et al.

Correll et al. conducted a randomized, double-blind, placebo-controlled, phase 3 clinical trial from 12 clinical sites in the United States from November 13, 2014, to July 20, 2015, on patients with schizophrenia who were aged 18 to 60 years and were experiencing an acute exacerbation of psychosis.[6] The purpose of this trial was to examine the efficacy and safety of lumateperone for the short-term treatment of schizophrenia. Patients were randomized 1:1:1 (150 patients in each arm) to receive lumateperone tosylate, 40 mg; lumateperone tosylate, 60 mg (equivalent to 28 or 42 mg, respectively, of the active moiety lumateperone); or placebo once daily for 4 weeks. The prespecified primary efficacy endpoint was mean change from baseline to day 28 in the Positive and Negative Syndrome Scale (PANSS) total score vs placebo. The key secondary efficacy measure was the Clinical Global Impression–Severity of Illness (CGI-S) score (a well-established re-

Table 2 | Primary Endpoints from Lumateperone Trials[6,13]

Trial	Primary Outcome	Intervention	Results	Difference From Placebo
Lieberman et al[13]	Mean change from baseline to day 28 in the PANSS[a] total score	Placebo	-7.4 ± 1.68	-
		Lumateperone 60 mg	-13.2 ± 1.69	-5.8 (p = 0.017)
		Lumateperone 120 mg	-8.3 ± 1.68	-0.9 (p = 0.708)
		Risperidone 4 mg	-13.4 ± 1.72	-6.0 (p = 0.013)
Correll et al[6]	Mean change from baseline to day 28 in the PANSS total score	Placebo	-10.3	-
		Lumateperone tosylate[†] 40 mg	-12.9	-2.6 (95% CI: -6.6 to 1.1)
		Lumateperone tosylate 60 mg	-14.5	-4.2 (95% CI: -7.8 to -0.6)

[a]Positive and negative syndrome scale
[†]Lumateperone tosylate 40 mg and 60 mg is equivalent to lumateperone 28 mg and 42 mg respectively.

search rating tool applicable psychotic disorders).[14] Those included in the study were male or female subjects of any race, ages 18-60 inclusive, with a clinical diagnosis of schizophrenia experiencing an acute exacerbation of psychosis. Subjects were excluded if they were unable to provide informed consent, any female subject who is pregnant or breast-feeding, and any subject judged to be medically inappropriate for study participation.

The study comprised 450 patients with a mean [SD] baseline PANSS score, 89.8 [10.3]and a mean [SD] baseline CGI-S score, 4.8 [0.6]). In the prespecified modified intent-to-treat efficacy analysis (n = 435), lumateperone tosylate 60 mg of met the primary and key secondary efficacy objectives, demonstrating a statistically significant improvement vs placebo from baseline to day 28 on the PANSS total score (least-squares mean difference [LSMD], -4.2; 95% CI, -7.8 to -0.6; P = .02; effect size [ES], -0.3) and the CGI-S (LSMD, -0.3; 95% CI, -0.5 to -0.1; P = .003; ES, -0.4). Lumateperone tosylate 40 mg did not reach statistical significance with the LSMD from baseline to day 28 was -2.6 (95% CI, -6.2 to 1.1; P = .16; ES, -0.2) on the PANSS total score and -0.2 (95% CI, -0.5 to 0.0; P = .02; ES, -0.3) on the CGI-S. Both lumateperone tosylate doses were well tolerated without clinically significant treatment-emergent motor adverse effects or changes in cardiometabolic or endocrine factors vs placebo. A summary of the results for Correll et al. is provided in Table 2.

Adverse Effects and Precautions

During short-term clinical trial evaluation of lumateperone there were several adverse effects reported which can be seen in Table 3.

Available data from case reports on lumateperone use in pregnant women are insufficient to establish any drug associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes.[11] There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including lumateperone, during pregnancy. Additionally, there is no available data on the presence of lumateperone or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Based on findings of toxicity in animal studies and the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment with lumateperone.[11] Safety and effectiveness of lumateperone have not been established in pediatric patients.[11] Controlled clinical studies of lumateperone did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients. Use of lumateperone is not recommended for patients with moderate (Child-Pugh class B) to severe hepatic impairment (Child-Pugh class C). Patients with moderate and severe hepatic impairment experienced higher exposure to lumateperone. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).[11]

Dosing and Administration

Caplyta®(lumateperone) capsules are available as a 42 mg strength (equivalent to 60 mg lumateperone tosylate) with the normal indicated dosing of 42 mg by mouth once daily for treatment of schizophrenia. The capsule has a blue cap and opaque white body imprinted with "ITI-007 42 mg."[11] Lumateperone interacts with moderate to strong CYP3A4 inhibitors and UGT inhibitors, which increases lumateperone's exposure that could lead to more adverse reactions. This leads to the assumption that concomitant use of lumateperone and moderate to strong CYP3A4 inhibitor and/or UGT inhibitors should be avoided. Additionally, CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, St. John's wort, and pioglitazone can decrease the exposure of lumateperone when used concomitantly. Likewise, concomitant use of CYP3A4 inducers and lumateperone should also be avoided.

Cost and Availability

According to GoodRX.com, the cost of a 30-day supply (30 capsules) of CAPLYTA® (lumateperone) 42 mg is around $1300.

Table 3 | Adverse Effects of Lumateperone[6,13]

Adverse Reaction	Incidence
Headache	16-19.3%
Somnolence	11.3-32.5%
Sedation	9.3-32.5%
Nausea	4.7-10.7%
Dry Mouth	4.8-8.4%
Dizziness	4.7-8.4%
Constipation	4-6.7%
Fatigue	4.7-5.3%

This means that the average annual cost of lumateperone would be around $15,600 for a schizophrenic patient. At this time, there is a lack of information about co-pay card or insurance companies covering this medication; likely because of how new it is.

Clinical Implications

Lieberman et al. showed the mechanistically novel investigational drug lumateperone was effective for the treatment of acute exacerbations of positive and negative symptoms of schizophrenia and comparable with placebo on safety measures. Secondary analyses indicated that lumateperone improved negative and depression symptoms, which is atypical of current therapies.[13] These results from the clinical trials have shown lumateperone to have the potential to be as efficacious as other SGAs, such as risperidone, as a first-line treatment for schizophrenia in adults for short term use. However, only Lieberman et al used an active comparator (risperidone), which could limit generalizability of lumateperone's efficacy as compared to the myriad other antipsychotics that are available. Clinical significance of differences between similar medications will need to be established in further trials as well in addition to statistical significance on trial endpoints. This leads to the need for further evidence and comparisons before a true place in therapy will likely be established for lumateperone.

There are no currently-known adverse reactions severe enough to limit the usage of lumateperone in the schizophrenic population. However, potential widespread market use could lead to newfound adverse reactions. Both doses of lumateperone were well tolerated in this patient population, as evidenced by low discontinuation and adverse event rates, and were associated with a benign metabolic profile as evidenced by significantly lower levels of prolactin, fasting glucose, total cholesterol, and triglycerides than risperidone. This drug has not been well studied in special populations

Despite the positive outcomes in both efficacy and safety, the price of lumateperone will be a limiting factor for most patients that do not have insurance and for those that would have to pay out of pocket. Patient assistance programs are not yet established, the lack of which could further hinder use of the medication.

Conclusion

The unique pharmacologic mechanisms of lumateperone seem to confer antipsychotic efficacy with favorable safety and tolerability. More trials will need to be conducted to further establish lumateperone's efficacy compared to other agents for schizophrenia. The limited evidence so far on efficacy and safety of lumateperone offer hope for another potential agent to combat schizophrenia.

References

1. Pankhuri Vyas, Brian Jaeho Hwang & James Robert Brašić (2020) An evaluation of lumateperone tosylate for the treatment of schizophrenia, Expert Opinion on Pharmacotherapy, 21:2, 139-145, DOI: 10.1080/14656566.2019.1695778
2. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2 (5):e141. doi:10.1371/journal.pmed.0020141
3. Stępnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. Molecules. 2018;23(8):2087. Published 2018 Aug 20. doi:10.3390/molecules23082087
4. American Psychiatric Association . Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013. Schizophrenia and other psychotic disorders; pp. 89–122.
5. Lavretsky H. History of Schizophrenia as a Psychiatric Disorder. In: Mueser KT, Jeste DV, editors. Clinical Handbook of Schizophrenia. New York, New York: Guilford Press; 2008. pp. 3–12.
6. Correll CU, Davis RE, Weingart M, et al. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. Published online January 08, 2020. doi:10.1001/jamapsychiatry.2019.4379
7. Leucht S,Cipriani A,Spineli L, et al.Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3
8. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. P T. 2014;39(9):638–645.
9. Raedler TJ. Cardiovascular aspects of antipsychotics: Curr Opin Psychiatry. 2010;23(6):574–581.
10. Snyder, G.L., Vanover, K.E., Zhu, H. et al. Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. Psychopharmacology 232, 605–621 (2015). https://doi.org/10.1007/s00213-014-3704-1
11. Davis RE,Correll CU. ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes. Expert Rev Neurother. 2016;16(6):601-614. doi:10.1080/14737175.2016.1174577 12
12. Intra-Cellular Therapies, Inc. CAPLYTA (lumateperone) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209500s000lbl.pdf. Revised December 2019.
13. Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, Mates S, Vanover KE. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. Biol Psychiatry. 2016 Jun 15;79 (12):952-61. doi: 10.1016/j.biopsych.2015.08.026. Epub 2015 Aug 31
14. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28–37

Editor's Corner

NDMA Impurities Continue

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On May 28, 2020, the US Food and Drug Administration (FDA) announced findings of N-Nitrosodimethylamine (NDMA) above the acceptable intake limit in multiple lots of metformin extended-release products.[1] According to the press release, five individual firms have been notified and recommended to voluntarily recall their supplies. Two companies have so far complied and issued voluntary nationwide recalls: Amneal Pharmaceuticals LLC and Apotex Corp.[2] At this time, the FDA has also noted that while there are additional manufacturers supplying substantial amounts to the US drug market, the recalls do not extend to all companies making the medication.

The drug impurity, notated as NDMA, can occur in drinking water through chemical degradation, as a by-product during disinfection process and multiple other industrial processes.[3] It is known to be a potent carcinogen in animals, and is classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic in humans.

Over the past year, there have been two other major incidents of NDMA impurities in common medications. Multiple drugs in the Angiotensin II Receptor Blocker (ARB) class – valsartan, losartan and irbesartan – had recalls issued due to high levels of NDMA.[4] More recently, the over-the-counter product ranitidine, brand name Zantac®, was also removed from shelves due to the same contamination issues.[5] A common cause of NDMA contamination has not yet been identified in the manufacturing process across multiple manufacturers and different drug entities.

At this time, only a handful of companies have been found to have polluted lots of metformin extended-release products, and no blanket warning has yet been issued. Per the FDA, patients should continue to take their metformin until directed otherwise by their healthcare professional.[1] There have not been any reports of contamination with immediate-release metformin, allowing treatment with a metformin product to continue if the extended-release formulation recalls expand.[6]

1. FDA Alerts Patients and Health Care Professionals to Nitrosamine Impurity Findings in Certain Metformin Extended -Release Products [Internet]. Silver Spring: US Food and Drug Administration; c2020 [updated 2020 May 28, cited 2020 May 29]. Available from: https://www.fda.gov/news-events/press-announcements/fda-alerts-patients-and-health-care-professionals-nitrosamine-impurity-findings-certain-metformin
2. Recalls, Market Withdrawals, & Safety Alerts [Internet]. Silver Spring: US Food and Drug Administration; c2020 [updated 2020 May 28, cited 2020 May 29]. Available from: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts
3. N-Nitrosodimethylamine (NDMA) [Internet]. Geneva: World Health Organization; c2020 [published 2008, cited 2020 May 29]. Available from: https://www.who.int/water_sanitation_health/dwq/chemicals/ndmasummary_2ndadd.pdf?ua=1
4. FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan) [Internet]. Silver Spring: US Food and Drug Administration; c2020 [updated 2019 Nov 11, cited 2020 May 29]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
5. Questions and Answers: NDMA impurities in ranitidine (commonly known as Zantac) [Internet]. Silver Spring: US Food and Drug Administration; c2020 [updated 2020 April 1, cited 2020 May 29]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/questions-and-answers-ndma-impurities-ranitidine-commonly-known-zantac#:~:text=FDA%20has%20found%20N%2Dnitrosodimethylamine,ranitidine%20they%20may%20currently%20have.
6. Laboratory Tests | Metformin [Internet]. Silver Spring: US Food and Drug Administration; c2020 [updated 2020 Feb 3, cited 2020 May 29]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-metformin

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