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Lumateperone for acute exacerbations of psychosis in schizophrenia

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LAY SUMMARY

Schizophrenia is a chronic mental health disorder causing changes in people's thoughts and behaviour. Common symptoms include hallucinations (experiencing things that aren't there), delusions (strong and unusual beliefs), confusion and disorganised thoughts. Schizophrenic symptoms usually come and go in 'episodes', where for a period of time symptoms may become more severe. Schizophrenia is usually treated with different types of psychological therapies and antipsychotic drugs which alter the levels of chemicals such as dopamine and serotonin in the brain. However, antipsychotic drugs can cause side effects including drowsiness, weight gain, blurred vision, constipation, lack of libido and dry mouth.

Lumateperone is a new, orally administered antipsychotic drug which alters levels of several chemicals in the brain including dopamine, serotonin and glutamate. Studies on lumateperone in people with schizophrenia experiencing an episode of severe symptoms suggest it may reduce symptoms with less side effects than current antipsychotic medication.

If licensed lumateperone may provide an alternative treatment option for people with schizophrenia which may cause fewer side effects.

TARGET GROUP

Schizophrenia: patients having an acute exacerbation of psychosis.

TECHNOLOGY

DESCRIPTION

Lumateperone (ITI 007; ITI 722) is a novel combination serotonin (5HT2A) receptor antagonist, serotonin reuptake inhibitor, dopamine receptor phosphoprotein modulator (DPPM) and glutamate receptor modulator intended for use in a range of psychiatric disorders. At high doses, lumateperone acts as a dual serotonin receptor antagonist and DPPM, by blocking overactive dopamine responsive phosphoprotein pathways without stimulating compensatory dopamine synthesis. It has been reported to be a partial agonist of the dopamine D2 receptor. At lower doses, lumateperone acts primarily as a serotonin (5HT2A) receptor antagonist.[1, 2]

In the phase III clinical trial for schizophrenia and psychosis, lumateperone is administered orally at 40mg or 60mg once daily in the morning for 28 days.[3]

INNOVATION and/or ADVANTAGES

If licensed, lumateperone will offer a novel alternative treatment option for patients with acute exacerbations of psychosis in schizophrenia, with the potential to cause fewer side effects, e.g. cardiovascular events, sedation and weight gain, compared to currently available antipsychotics. One US key opinion leader highlights the unmet need for antipsychotics with better tolerability profiles:

"[T]here's still the issue of metabolic abnormalities and weight gain with some of the second-generation antipsychotics, so if there's a way to reduce or eliminate them, that would be very useful. Some of the second-generation antipsychotic[s] that are associated with very poor tolerability are some of our best medicines in terms of efficacy. So clozapine and olanzapine are two examples of excellent drugs in terms of efficacy, but very poor in terms of tolerability." *(US Key Opinion leader – Global Data)*[4]

DEVELOPER

Intra-Cellular Therapies Inc.

AVAILABILITY, LAUNCH or MARKETING

The company anticipate submitting an NDA (New Drug Application) to the FDA for Lumateperone for Schizophrenia in Q2/Q3 2018.[5] Lumateperone does not currently have Marketing Authorisation in the EU for any indication. Lumateperone is currently in phase III clinical trials for acute exacerbations of psychosis in schizophrenia.[3]

PATIENT GROUP

BACKGROUND

Schizophrenia is a chronic and severe mental disorder affecting approximately 21 million people worldwide. It is characterised by disruptions in thinking which may affect perception and behaviour and usually develops between the ages of 16 and 30.[6, 7] Symptoms fall into three categories: positive, negative and cognitive symptoms. Positive symptoms are psychotic behaviours not experienced by healthy people, including: hallucinations, delusions, thought disorders (dysfunctional ways of thinking) and movement disorders (agitated body movements). Negative symptoms cause disruptions to normal emotions and behaviours and include: 'flat effect' (reduced expression of emotions), reduced pleasure in everyday life, difficulty beginning and sustaining activities and reduced speaking. Finally, cognitive symptoms are those which affect memory and thinking and include: poor executive functioning (ability to understand information and use it to make decisions), problems focusing and paying attention and impaired working memory (ability to use information immediately after learning it).[7] Schizophrenic symptoms usually come in 'episodes' during which symptoms become exacerbated and severe (acute schizophrenia). These are usually followed by periods of few or no symptoms. During these episodes, exacerbations of psychotic behaviours can occur, including increases in hallucinations (where people experience things that aren't there, e.g. hearing voices) and delusions (where people have strong and unusual beliefs, e.g. believing that there is a conspiracy to harm them).[8, 9]

The causes of schizophrenia are likely complicated and there are many factors which contribute to risk of developing schizophrenia. These include genetics (likely to be many genes and not a single gene), imbalances of neurotransmitters (dopamine and glutamate), brain damage (caused by problems during birth causing blood flow restrictions to the baby's brain or viral infections in early pregnancy), drug use (e.g. amphetamines and cannabis) and psychosocial factors (e.g. stress, family problems and childhood trauma).[6, 10]

Schizophrenia can have negative impacts on sufferers beyond symptoms. People with schizophrenia are more likely to suffer from various physical (e.g. diabetes and obesity) and psychiatric (e.g. anxiety, depression and substance abuse) comorbidities which may negatively impact quality of life. People with schizophrenia are also more likely to commit suicide, at a lifetime risk of 5%.[11-13]

CLINICAL NEED and BURDEN OF DISEASE

In the UK the prevalence of schizophrenia was 223,045 in 2016, equating to 0.41% of the UK population. It affects 21 million people worldwide of which approximately 12 million are male and nine million are female.

In 2015, there were 15,632 admissions for schizophrenia (ICD10 F20) in England, resulting in 1,785,106 bed days and 23,367 finished consultant episodes.[14]

Schizophrenia is associated with significant disability mainly by affecting educational and occupational performance. People with schizophrenia may also experience stigma, discrimination (limiting access to general healthcare, education, housing and employment) and violation of human rights, inside mental health institutions and within communities.[15]

Morbidity is high with various physical and psychological comorbidities associated with schizophrenia (as discussed above). People with schizophrenia are also 2 to 2.5 times more likely to die earlier than the general population, usually as a result of associated comorbidities.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Structural neuroimaging in first-episode psychosis (TA136). February 2008.
- NICE clinical guideline. Psychosis and schizophrenia in adults: prevention and management (CG178). March 2014.
- NICE clinical guideline. Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings (CG120). March 2011.
- NICE clinical guideline. Guidance on the use of electroconvulsive therapy (TA59). October 2009.
- NICE quality standard. Psychosis and schizophrenia in adults (QS80). February 2015.
- NICE guideline. Coexisting severe mental illness and substance misuse: community health and social care services (NG58). November 2016.
- NICE guideline. Violence and aggression: short-term management in mental health, health and community settings (NG10). November 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for medium and low secure mental health services. C03/S/a.
- NHS England. 2014/15 NHS Standard Contract for high secure mental health services (adults). C02/S/a.
- NHS England. Guidance to support the introduction of access and waiting time standards for mental health services in 2015/16. February 2015.
- NHS England. Improving access to psychological therapies (IAPT) waiting times: Guidance and FAQs. February 2015. Manual for Prescribed Specialist Services 2016/17. May 2016.
- NHS England. The National Collaborating Centre for Mental Health and National Institute for Health and Care Excellence. Implementing the early intervention in psychosis access and waiting time standard: Guidance (V1). April 2016.
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- NHS England. The National Collaborating Centre for Mental Health and National Institute for Health and Care Excellence. Achieving better access to 24/7 urgent and emergency mental health care – Part 2; Implementing the evidence based treatment pathway for urgent and emergency liaison mental health services for adults and older adults: Appendices and Helpful Resources (V1). November 2016.

OTHER GUIDANCE

- Mental Health Taskforce: NHS England. The five year forward view for mental health. February 2016.

- Scottish Intercollegiate Guidelines Network. Management of Schizophrenia (SIGN131). March 2013.

CURRENT TREATMENT OPTIONS

Treatment for schizophrenia is tailored to the individual and usually consists of a combination of therapy and medication. Most people are treated by community mental health teams (consisting of social workers, mental health nurses, social and support workers) who provide daily support and treatment when required.[16]

When acute psychotic episodes are encountered in schizophrenia more intensive care is provided. This can mean treatment with antipsychotic medication, referral to a crisis resolution team (providing support at home or in specialised day centres) or, if a particularly serious episode (e.g. if the individual is a danger to themselves or others), individuals can be detained in hospital (on a voluntary or compulsory basis) for treatment. Individuals with schizophrenia may prepare an 'advanced statement' in which they can detail what they would like to happen in the case of an acute episode.[16]

NICE guidelines[17] on the treatment of psychosis and schizophrenia in adults suggest the following treatments:

First line treatments:

- Improving physical health, e.g. stopping smoking, healthy eating and physical activity are recommended.
- Discouraging use of illicit drugs.
- Self-management and support, e.g. provision of information about schizophrenia and psychosis, managing symptoms, support services available, coping with stress and problems, what to do in a crisis (acute episode) and preventing relapse and planning recovery goals.
- Antipsychotic medication – the exact antipsychotic medication prescribed will depend on physical health. Medication is titrated from the initial dose to find the lowest possible effective dose with the fewest/least severe side effects:
    - Typical (first generation) antipsychotics: act by blocking the action of dopamine[18]
        - Chlorpromazine: 75 to 300mg (maximum daily dose 1000 mg)
        - Haloperidol: 3 to 15mg (maximum daily dose 30mg)
        - Pimozide: 4 to 20mg (maximum daily dose 20mg)
        - Trifluoperazine: 5 to 20mg
        - Sulpiride: 200-800mg (maximum daily dose 2400mg)
    - Atypical antipsychotics: act by affecting both dopamine and serotonin[18]
        - Amisulpride: 50 to 800mg (maximum daily dose 1200mg)
        - Aripiprazole: 10 to 30mg (maximum daily dose 30mg)
        - Clozapine: 200 to 450mg (maximum daily dose 900mg)* The most prescribed antipsychotic as it has better efficacy than any other antipsychotic and reduces suicidal feelings.
        - Olanzapine: 10 to 20mg (maximum daily dose 20mg)
        - Quetiapine: 300 to 450mg (maximum daily dose 750mg)
        - Risperidone: 4 to 6mg (maximum daily dose 16mg)
- Psychological interventions:

- Cognitive Behavioural Therapy (CBT) – covering re-evaluation of thoughts, feelings and beliefs; monitoring and coping with symptoms; reducing distress and improving functioning.
- Art therapies (particularly for those in an acute episode or to relieve negative symptoms).
- Family intervention – covering problem solving and crisis management.

Second line treatments:

- Tranquilisers/sedatives – patients who are violent or aggressive and pose harm to themselves or others may need to be rapidly tranquilised.
- Review dosage and adherence to antipsychotic medication
  - If patient is non-responsive to clozapine, consider adding second antipsychotic drug
  - If patient is non-adherent to medication, consider offering depot/long lasting injectable antipsychotic
- Review engagement with psychological treatments
- Review possibility of substance misuse (illicit drugs and alcohol) and impact of other prescribed medications or physical illnesses

Electroconvulsive therapy may also be used but is not recommended by NICE.

It is important to note that antipsychotic medications have side effects, most commonly: drowsiness, weight gain, blurred vision, constipation, lack of libido and dry mouth. Typical antipsychotics can also cause shaking, trembling, muscle twitches and spasms. If side effects are too severe then an alternative antipsychotic or additional medications addressing the side effects may be prescribed.[16]

EFFICACY and SAFETY		
Trial	Lumateperone, NCT02469155; ITI-007-302; GDC40003062; GDCT0228770, adults 18-60 years with acute exacerbation of psychosis in schizophrenia, lumateperone 20mg vs lumateperone 60mg vs placebo vs risperidone 4mg, phase III trial.	Lumateperone, NCT02282761, ITI-007-301, adults 18-60 years with acute exacerbation of psychosis in schizophrenia, lumateperone 40mg vs lumateperone 60mg vs placebo, phase III trial.
Sponsor	Intra-Cellular Therapies Inc.	Intra-Cellular Therapies Inc.
Status	Complete and published in abstract	Complete and published in abstract
Source of Information	trial registry[19]	abstract[20], trial registry[3]
Location	USA	USA
Design	Randomised, placebo and active controlled, double blinded trial.	Randomised, placebo controlled, double blinded trial.
Participants	N=696; aged 18 to 60 years; schizophrenia; acute exacerbation of psychosis	N=450; aged 18 to 60 years; schizophrenia; acute exacerbation of psychosis
Schedule	Participants were screened for 1 week then randomised to one of 4 treatment groups:	Randomised to one of 3 treatment groups: e) Lumateperone 40mg oral capsules once daily (morning) for 28 days

	a) Lumateperone 20mg oral capsules once daily for 6 weeks b) Lumateperone 60mg oral capsules once daily for 6 weeks c) Placebo oral capsules once daily for 6 weeks d) Risperidone (active comparator) 4mg oral capsules once daily for 6 weeks	f) Lumateperone 60mg oral capsules once daily (morning) for 28 days g) Placebo capsules once daily (morning) for 28 days
Follow-up	Active treatment for six weeks followed by a five day stabilisation period (where participants were switched to standard antipsychotic treatment) and two week follow up visit.	Active treatment for 28 days
Primary Outcomes	Change from baseline to Day 42 on the Positive and Negative Syndrome Scale (PANSS) total score.	Positive and Negative Syndrome Scale (PANSS) Total Score at 28 days.
Secondary Outcomes	Positive and Negative Syndrome Scale Subscales at six weeks, safety and tolerability of ITI-007, adverse events, 12-lead electrocardiograms (ECGs), 3-positional vital sign assessments, clinical laboratory assessments (haematology, serum chemistry and urinalysis), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Rating Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Columbia - Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression of Disease Severity (CGI - S), Personal and Social Performance Scale (PSP).	Safety and tolerability of lumateperone, adverse events, 12-lead electrocardiograms (ECGs), 3-positional vital sign assessments, clinical laboratory assessments (haematology, serum chemistry and urinalysis), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Rating Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Columbia - Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression Scale for Severity of Illness (CGI-S). No quality of life measurement.
Key Results	Improvements in the primary outcome measure (PANSS) were seen in the lumateperone 60mg intervention but were not significantly different from placebo at week six. The company stated this may be due to an 'unusually high placebo response at certain sites which disproportionately affected the trial results'. Treatment with risperidone (active comparator) did result in significant difference in primary outcome measurement compared to placebo at week six.[21]	Significant differences in the primary outcome (PANSS) measure was seen between 60mg lumateperone (-14.5 points) (ES= 0.3) and placebo (-10.3 points) (p=0.022) at week 4. Lumateperone 60mg showed significant antipsychotic effect as early as week 1 of treatment which was maintained throughout the intervention period. Lumateperone 60mg also showed statistically significant improvement in Clinical Global Impression Scale for Severity of Illness (p=0.003).[22]
Adverse effects (AEs)	There was no significant difference between lumateperone and placebo	Mild somnolence (10.7% in 40mg and 17.3% in 60mg lumateperone vs 4% in

	in safety measurements. Most frequent AEs with lumateperone were mild sedation and somnolence. There were significant advantages in safety measures (prolactin, glucose and lipid measures) with lumateperone compared to risperidone.[23]	placebo), mild sedation (9.3% in 40mg and 12.0% in 60mg lumateperone vs 5.4% in placebo) and mild fatigue (4% in 40mg and 5.3% in 60mg lumateperone vs 1.3 in placebo).[22]
Expected reporting date	-	-

ESTIMATED COST and IMPACT

COST

The cost of lumateperone is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: wider societal benefits (e.g. earlier return to normal activities, including employment)

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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