Lumateperone for acute exacerbations of psychosis in schizophrenia

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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.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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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.\(^5\)
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

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


#### NHS ENGLAND and POLICY GUIDANCE

- 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


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 guidelines17 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 dopamine18
    - 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 serotonin18
    - 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 tranquillised.
- 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

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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
5. Intra-cellular therapies. Intra-Cellular Therapies Provides Corporate Update On Schizophrenia Program. 01/05/2017.

Intra-cellular Therapies. Intra-Cellular Therapies Announces Positive Top-Line Results From the First Phase 3 Trial of ITI-007 in Patients With Schizophrenia and Confirms the Unique Pharmacology of ITI-007 in a Separate Positron Emission Tomography Study.  2015.