Health Technology Briefing
March 2022

Dexmedetomidine film for agitation in schizophrenia

Company/Developer	BioXcel Therapeutics Inc.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29609	NICE ID: 10726	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Schizophrenia is a severe long-term mental condition which can affect a person's perception and interpretation of the world around them. Symptoms include hallucinations (hearing and seeing things), delusions (beliefs not based on reality) and agitation. It is not known what causes schizophrenia, but it is likely a combination of genetic and environmental factors. It affects both men and women equally, and symptoms most commonly develop during young adulthood. Agitation is a disruptive, and related complication of many chronic mental illnesses, including schizophrenia. Agitation is associated with poor clinical outcomes for patients with schizophrenia. Dexmedetomidine oral film (sublingual) is in development for the treatment of agitation in schizophrenia for adults.

Dexmedetomidine sublingual film, administered sublingually (under the tongue) or buccally (between the gums and cheek), is a dissolving form of dexmedetomidine. Dexmedetomidine is a selective agonist against alpha 2-adrenergic receptors, which are receptors involved in modulating the activity of neurons releasing noradrenaline. The administration route has been designed to be easy to administer and provides an alternative treatment option to antipsychotic oral tablet/solutions and intramuscular (in muscle) injections that are currently used for schizophrenia-associated agitation. If licenced, dexmedetomidine sublingual film would offer a treatment option with a novel route of administration, which may provide benefits to the patient group in regards to reducing symptoms and also, ease of administration during periods of agitation.

Proposed Indication

Acute treatment of agitation in adult patients with schizophrenia.[1,2]

Technology

Description

Dexmedetomidine (BXCL501) is a selective alpha-2 receptor agonist.[1,2] Dexmedetomidine has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings which may act to reduce agitation as it has been suggested increases in noradrenaline act as a mechanism in agitation.[3,4] Dexmedetomidine attenuates central nervous system (CNS) arousal and diminishes hyper-arousal.[3]

In the phase III clinical trial (NCT04268303, SERENITY I) dexmedetomidine was given to adult patients with acute agitation associated with schizophrenia. It was administered by sublingual film at 120mcg or 180mcg doses.[2]

Key Innovation

Dexmedetomidine is licensed in the UK as an intravenous (IV) infusion. This technology utilises sublingual or buccal route of administration of dexmedetomidine. It has been designed to be easy to administer and provide a rapid onset of action. If approved, dexmedetomidine sublingual film would offer a treatment option with a novel route of administration, which may provide benefits to the patient group.[5]

Regulatory & Development Status

Dexmedetomidine, as an IV administration, is licensed in the EU and UK for the sedation of adult Intensive Care Unit patients requiring a sedation level not deeper than arousal in response to verbal stimulation, and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation.[3,6]

Dexmedetomidine sublingual film received US FDA Fast Track Designation in 2018.[7]

Dexmedetomidine sublingual film is in phase II and III clinical development for indications including dementia, delirium and opioid withdrawal.[8]

Patient Group

Disease Area and Clinical Need

Schizophrenia is a severe long-term mental health condition related to psychosis, which can alter a person's perception and interpretation.[9] Symptoms include hallucinations (hearing and seeing things), delusions (beliefs not based on reality), agitation, distress, loss of interest in everyday activities, disinterest in personal hygiene, and avoidance of people (including friends).[9,10] The exact cause of schizophrenia is unknown, but could be related to a combination of genetic and environmental factors.[9] It is estimated that around 1 in 100 (1%) of people will have schizophrenia in their lifetime.[11] It affects men and women equally, and usually develops between the ages of 15 to 35 years old.[11] People with schizophrenia have significantly lower quality of life (QoL) compared to healthy controls.[12] Agitation is a disruptive, and comorbid complication of many chronic mental illnesses, including schizophrenia.[13] Comorbid agitation is associated with poor clinical outcomes for patients with schizophrenia.[14]

In England, 2020-21, there were 18,228 finished consultant episodes (FCE) for schizophrenia, schizotypal disorders and schizoaffective disorders (ICD codes F20, F21 and F25), resulting in 43 day cases and 1,009,817 FCE bed days.[15] Based on 2008 data, the total social and economic cost for schizophrenia in England was estimated to be £3.9 billion a year.[16] However, it is unknown what proportion, if any, of these are caused by agitation nor is there UK data showing the prevalence/incidence for agitation associated with bipolar disorder.

Recommended Treatment Options

The following antipsychotic medications are recommended for the control of agitation related to schizophrenia:[17-22]

- Aripiprazole
- Chlorpromazine hydrochloride
- Haloperidol
- Loxapine
- Olanzapine

Currently, the standard of care for the acute treatment of agitation is either verbal de-escalation or pharmacological tranquilization with antipsychotics (typical or atypical) and/or benzodiazepines. These drugs are available in a variety of forms, including oral tablets, orally disintegrating tablets, oral inhalation, oral liquids, and intramuscular injections. Although these agents are effective, a serious limitation is that they overly sedate the patient and do not permit verbal interaction and proper clinical evaluation with the hospital staff to continue.[23-25]

Clinical Trial Information

Trial	**SERENITY I**, NCT04268303; A Phase III Multicenter, Randomized, Double-Blind, Placebo-Controlled Study To Determine Efficacy and Safety of BXCL501 In Agitation Associated With Schizophrenia **Phase III –** Completed **Location(s):** US **Study completion date**: May 2020
Trial Design	Randomised, quadruple masked (double-blind, placebo-controlled), parallel assignment.
Population	N=381 (actual); male and female; aged 18 to 75 years; diagnosis of schizophrenia, schizoaffective or schizophreniform disorder.
Intervention(s)	120mcg or 180mcg of sublingual film dexmedetomidine. If persistent agitation (defined as a PANSS Excited Component (PEC) change from baseline <40%), 2 additional ½ doses (60 mcg or 90 mg) were administered at least 2 hours apart.[a]
Comparator(s)	Matched placebo
Outcome(s)	Primary end point [Time frame: 120 minutes] Absolute change from baseline in the PEC total score at 2 hours. See trial record for full list of other outcomes.

[a] Information provided by BioXcel Therapeutics Inc.

Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of dexmedetomidine sublingual film is not yet know.

Relevant Guidance

NICE Guidance

- NICE guideline. Rehabilitation for adults with complex psychosis (NG181). August 2020.
- NICE guideline. Violence and aggression: short-term management in mental health, health and community settings (NG10). May 2015.
- NICE clinical guideline. Psychosis and schizophrenia in adults: prevention and management (CG178). February 2014.

NHS England (Policy/Commissioning) Guidance

- NHS England. Mental Health Implementation Plan 2019/20 - 2023/24. Publishing Approval Reference: 000830. July 2019.
- NHS England. Implementing the Five Year Forward View for Mental Health. Gateway Reference: 05574. July 2016.
- NHS England. Implementing the Early Intervention in Psychosis Access and Waiting Time Standard: Guidance. Gateway Reference: 04294. April 2016.

Other Guidance

- British Association for Psychopharmacology (BAP) and National Association of Psychiatric Intensive Care Units (NAPICU). Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. June 2018.[26]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 131: Management of schizophrenia. March 2013.[27]

Additional Information

BioXcel Therapeutics Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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