Health Technology Briefing
March 2022

Dexmedetomidine film for agitation associated with bipolar disorder

Company/Developer	BioXcel Therapeutics Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29613	NICE ID: 10725	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Dexmedetomidine sublingual film is in clinical development for the treatment of agitation associated with bipolar disorder. Bipolar disorder is mental health condition characterised by periods of mania and severe depression. Agitation is a disruptive, and comorbid complication of many chronic mental illnesses, including bipolar disorders. Agitation is described as excessive motor activity associated with a feeling of inner tension. Activity which characterises an episode of agitation is usually non-productive and repetitious. Although in clinical practice pharmacological treatments are used, there are currently no NICE recommended treatment options for agitation associated with bipolar disorder.

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 alpha2-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 has demonstrated a rapid onset of action in clinical studies. 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 regard to reducing symptoms and also, ease of administration during periods of agitation.

Proposed Indication

Acute treatment of agitation associated with bipolar disorders in adults aged 18 to 75 years.[1]

Technology

Description

Dexmedetomidine sublingual film (BXCL501) is a film formulation of dexmedetomidine which is a selective alpha-2a receptor agonist.[2] Dexmedetomidine (Dexdor) 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 sublingual film targets a causal agitation mechanism involving alpha-2a.[5]

In a phase III clinical trial (NCT04276883), 120 or 180µg dexmedetomidine sublingual film was administered.[1] If persistent agitation occurs (defined as a PANSS Excited Component (PEC) change from baseline <40%), 2 additional ½ doses (60 µg or 90 µg) were administered at least 2 hours apart.[a]

Key Innovation

Dexmedetomidine is currently licensed in the UK as an intravenous (IV) infusion.[3] This form of dexmedetomidine uses an alternative sublingual or buccal route of administration. It has been designed to be easy to administer and has demonstrated a rapid onset of action in clinical studies.[2] If approved, dexmedetomidine sublingual film would offer a treatment option with a novel route of administration, which may provide benefits to the patient group.

If licensed, dexmedetomidine sublingual film will offer a treatment option for adults aged 18 to 75 years who are suffering from agitation associated with bipolar disorder.

Regulatory & Development Status

Dexmedetomidine has Marketing Authorisation in the EU/UK for the following indications: for sedation of adult Intensive Care Unit patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.[3]

Dexmedetomidine film is in phase III/II clinical development for the treatment of schizophrenia, opioid withdrawal and dementia.[6]

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

Patient Group

Disease Area and Clinical Need

Bipolar is a severe mental health condition characterised by significant mood swings including manic highs and depressive lows. The majority of individuals with bipolar experience alternating episodes of mania and depression.[8] Agitation is described as excessive motor activity associated with a feeling of inner tension. Acutely agitated patients often have an underlying major psychiatric disorder. Severe agitation occurs most often in psychotic illnesses, such schizophrenia and the manic phase of bipolar disorder. Activity which

[a] Information provided by BioXcel Therapeutics

characterises an episode of agitation is usually non-productive and repetitious. Agitation may escalate over time, and the behaviour of some patients may be perceived as being threatening. People with lesser degrees of agitation can be treated with psychological methods to ease anxiety and tension. When agitation becomes more severe, pharmacological treatment may be required. Such treatment may be adjunctive to that used to treat the underlying psychiatric disorders.[9]

Around 1.3 million people in the UK have bipolar disorder.[8] In the UK, using hospital episode statistics for 2020-2021, there were 1,221 admissions for bipolar affective disorder, current episode manic with psychotic symptoms (F31.2), 2,035 finished consultant episodes (FCE) and 65,051 FCE bed days.[10] 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

There are currently no NICE recommended treatment options for acute agitation in bipolar disorder. Current UK clinical practice includes the use of antipsychotics (such as haloperidol, olanzapine, risperidone and aripiprazole) and benzodiazepines (such as lorazepam), given either alone or in combination, for the treatment of acute agitation.[9]

Clinical Trial Information

Trial	**SERENITY II,** NCT04276883; A Phase III Multicentre, Randomized, Double-Blind, Placebo-Controlled Study to Determine Efficacy and Safety of BXCL501 In Agitation Associated With Bipolar Disorder **Phase III –** Completed **Location(s):** USA **Study Completion Date:** May 2020
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=378; aged 18-75 years old; patients who have met DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) criteria for bipolar I or II disorder; patients who are judged to be clinically agitated at screening and baseline
Intervention(s)	120 or 180µg sublingual film containing dexmedetomidine
Comparator(s)	Matched placebo
Outcome(s)	Primary End Point [Time frame: 120 minutes]: Absolute change from baseline in the PEC score at 2 hours See trial record for full list of other outcomes
Results (efficacy)	• Mean 2-hour changes from baseline in PEC score were −10.4 for BXCL501 180µg, −9.0 for BXCL501 120µg, and −4.9 for placebo (both doses P<.0001 vs placebo) • Significant improvement from baseline in the PEC began at 20 minutes post dose and continued through 2 hours post dose • Both BXCL501 treatment groups maintained significant improvements in PEC score at 4, 6, and 8 hours post dose (P<.0001 vs placebo) • Mean PEC response rates in both BXCL treatment groups were greater than placebo from 30 minutes through 2 hours post dose, resulting in a

	number needed to treat versus placebo of 3 (95% CI 2 - 3) for BXCL501 180µg and 4 (95% CI 3 - 6) for BXCL501 120µg • On the Clinical Global Impressions-Improvement (CGI-I) and Agitation-Calmness Evaluation Scale (ACES) subjects in both BXCL treatment groups were improved versus baseline at 2 hours post dose (P<.0001).[11]
Results (safety)	• The incidence of adverse events (AEs) was 35.7% with BXCL501 180 µg, 34.9% with 120µg, and 17.5% with placebo • The most common AEs with BXCL501 were somnolence, dry mouth, hypotension, and dizziness • Of 53 patients reporting somnolence with BXCL501, the event was mild in 64% and moderate in 36%, as judged by the investigator • No severe adverse events AEs were reported.[11]

Estimated Cost

The cost of dexmedetomidine film is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Bipolar disorder: assessment and management. (CG185). Last updated: February 2020.
- NICE quality standard. Bipolar disorder in adults (QS95). July 2015.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- Shah N, Grover S, Rao GP. Clinical Practice Guidelines for Management of Bipolar Disorder. January 2017.[12]
- British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations. March 2016.[13]

Additional Information

BioXcel Therapeutics 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.

References

1 ClinicalTrials.gov. *Dexmedetomidine in the Treatment of Agitation Associated With Bipolar Disorder (SERENITY II). Trial ID: NCT04276883*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT04276883 [Accessed 07 February 2022].

2 BioXcel Therapeutics. *Our Pipeline: BXCL501.* Available from: https://www.bioxceltherapeutics.com/our-pipeline/ [Accessed 09 February 2022].

3 Electronic Medicines Compendium. *Dexdor 100 micrograms/ml concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/4783/smpc#PHARMACOLOGICAL_PROPS [Accessed 09 February 2022].

4 Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry*. 2000;61:5-10. Available from: https://www.psychiatrist.com/read-pdf/13935/.

5 BioXcel Therapeutics. *BioXcel Therapeutics Announces FDA Acceptance for Filing of NDA for BXCL501 for the Acute Treatment of Agitation Associated with Schizophrenia and Bipolar Disorders I and II.* 2021. Available from: https://ir.bioxceltherapeutics.com/news-releases/news-release-details/bioxcel-therapeutics-announces-fda-acceptance-filing-nda-bxcl501 [Accessed 09 February 2022].

6 ClinicalTrials.gov. *5 Studies found for: BXCL501 | Phase 2, 3.* Available from: https://clinicaltrials.gov/ct2/results?term=BXCL501&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 09 February 2022].

7 BioXcel Therapeutics. *BioXcel Therapeutics Receives FDA Fast Track Designation for BXCL501 for Acute Treatment of Agitation.* 2018. Available from: https://ir.bioxceltherapeutics.com/news-releases/news-release-details/bioxcel-therapeutics-receives-fda-fast-track-designation-bxcl501 [Accessed 09 February 2022].

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9 National Institute for Health and Care Excellence. *Loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar disorder.* 2012. Available from: https://www.nice.org.uk/guidance/ta286/documents/schizophrenia-or-bipolar-disorder-loxapine-appendix-b-final-scope2 [Accessed 09 February 2022].

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11 Zeller S, Citrome L, Goldberg J, Finman J, De Vivo M, Yocca F, et al. Safety and Patient Acceptability of BXCL501 for Treating Acute Agitation in Patients with Bipolar Disorder. *23rd Annual Conference of the International Society for Bipolar Disorders*. 2021. Available from: https://ir.bioxceltherapeutics.com/static-files/1355e588-b3bc-437a-b1b2-b1f74782ee9d.

12 Shah N, Grover S, Rao GP. Clinical Practice Guidelines for Management of Bipolar Disorder. *Indian J Psychiatry*. 2017;59:S51-s66. Available from: https://doi.org/10.4103/0019-5545.196974.

13 Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes TRH, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*. 2016;30(6):495-553. Available from: https://doi.org/10.1177/0269881116636545.

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