

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215390Orig1s000

Trade Name: IGALMI

Generic or Proper Name: dexmedetomidine

Sponsor: BioXcel Therapeutics, Inc.

Approval Date: April 5, 2022

Indication: For the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults.

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NDA 215390

NDA APPROVAL

BioXcel Therapeutics, Inc.
Attention: Margaret Foley
Executive Director, Regulatory Affairs
555 Long Wharf Drive, 12th Floor
New Haven, CT 06511

Dear Ms. Foley:

Please refer to your new drug application (NDA) dated and received March 5, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Igalmi (dexmedetomidine) sublingual film.

We also refer your October 28, 2021, and November 16, 2021, submissions, which together constituted a major amendment to this application and extended the goal date by 3 months.

This NDA provides for the use of Igalmi (dexmedetomidine) sublingual film for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.¹ Content of labeling must be identical to the enclosed labeling text for the Prescribing Information as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on April 5, 2022 and January 24, 2022, respectfully, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 215390.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Igalmi (dexmedetomidine) sublingual film shall be 24 months from the date of manufacture when stored at controlled room temperature 20° to 25°C (68° to 77° F).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for 0 to 12 years of age in schizophrenia because necessary studies are impossible or highly impracticable. This is because of the very low incidence of schizophrenia in this age range. We are waiving the pediatric study requirement for 0 to 9 years of age in bipolar I or II disorder because necessary studies are impossible or highly impracticable. This is because it is extremely difficult to make a diagnosis of bipolar I or II disorder in children younger than 10 years of age.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We are deferring submission of your pediatric studies in schizophrenia (13 to 17 years of age) and in bipolar I or II disorder (10 to 17 years of age) for this application until additional safety and effectiveness data are collected.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

- 4254-1 Conduct a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dexmedetomidine films for the acute treatment of agitation in pediatric patients with schizophrenia (13 to 17 years of age) or bipolar I or II disorder (10 to 17 years of age).

Final Protocol Submission:	09/2021
Study Completion:	06/2024
Final Report Submission:	12/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 140184, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of tolerance, tachyphylaxis, or withdrawal when available data indicate the potential for serious risks.

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 4254-2 Conduct a study to determine whether tolerance, tachyphylaxis, or withdrawal occur following repeat dosing of dexmedetomidine oral films.

Final Protocol Submission: 10/2022

Study Completion: 05/2023

Final Report Submission: 10/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁴

Submit clinical protocol(s) to your **IND 140184** with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

⁴ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Submit clinical protocols to your IND for this product (IND 140184). Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁵

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

⁵ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

POSTMARKETING SAFETY REPORTS

We request that for a period of 2 years from the U.S. approval date, you submit all U.S. cases of medication errors associated with Igalmi (dexmedetomidine) as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of medication errors reported post-marketing in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report (PADER) described under 21 CFR 314.80(c)(2)). These analyses should provide the type of medication error (e.g., wrong dose, missed dose, unintentional exposure), contributing factors for the error, and actions recommended or taken to mitigate the risk of the medication error. Your periodic safety report should also include an analysis of medication errors received during the current reporting interval and an analysis of cumulative medication errors received from the date of approval through the end of the current reporting interval.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER) format in lieu of the PADER format, you must submit a formal waiver request as described under 21 CFR 314.90 to CDER's Office of Surveillance and Epidemiology. You should ensure that your proposal does not result in any gaps in reporting.

If you have any questions, please contact the regulatory project manager, CAPT Kofi Ansah, PharmD, at Kofi.Ansah@fda.hhs.gov or 301-796-4158.

Sincerely,

{See appended electronic signature page}

Bernard Fischer, MD
Deputy Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
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