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Dear Healthcare Provider,

Thank you for your inquiry regarding IGALMI™ (dexmedetomidine) sublingual film and bradycardia/sinus bradycardia.

IGALMI is an alpha-2 adrenergic receptor agonist indicated in adults for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder.

IGALMI is an orally dissolving film formulation for sublingual or buccal use under the supervision of a health care provider.

Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

The approved IGALMI package insert/prescribing information provides the following information:

- IGALMI causes dose-dependent bradycardia.

- In IGALMI phase 3 clinical trials, a total of 5 participants experienced **bradycardia**: 3 (1.2%) subjects in the 180 mcg group and 2 (0.8%) subjects in the 120 mcg group. Of the 5 cases, 4 were rated mild in severity and 1 (120 mcg group) was rated as moderate in severity. Of the 3 cases of bradycardia in the 180 mcg group, 2 were considered to be not clinically meaningful, and the 2 cases of bradycardia in the 120 mcg group were considered to be clinically meaningful.

- Five subjects experienced **sinus bradycardia**: 2 (0.8%) subjects in the 180 mcg group and 3 (1.2%) subjects in the 120 mcg group. All cases were rated mild in severity. Of the 2 cases of sinus bradycardia in the 180 mcg group, 1 was not clinically meaningful. Of the 3 cases of sinus bradycardia in the 120 mcg group, 1 was not clinically meaningful.

- In addition to investigator reported AEs of bradycardia, additional cases were identified by prespecified heart rate criteria. In phase 3 clinical trials, 7%, 6%, and 1% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced HR ≤ 50 beats per minute within 2 hours of dosing. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP <70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension.

- Because clinical trials are conducted under conditions that differ in important ways from real world clinical practice, adverse reactions observed in clinical trials cannot be compared across different drugs and may differ from what is observed in clinical practice.

- Because IGALMI decreases sympathetic nervous system activity, bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients.

- No placebo-treated subject experienced bradycardia or sinus bradycardia.

Additional published information may be available for intravenous (IV) and intrathecal dexmedetomidine. Please refer to the bibliography below. This bibliography is not comprehensive but may provide additional information relevant to your query. These references were identified from the National Library of Medicine (PubMed) on 201June 2023 using search terms [dexmedetomidine] and [bradycardia] and may include information outside the FDA approved indication for IGALMI. They are included as a professional courtesy and are not intended to recommend use of IGALMI outside the FDA approved indication.

Important Information
BioXcel Therapeutics does not recommend the use of IGALMI outside of the FDA approved prescribing information. Please refer to the IGALMI FDA approved package insert for important safety information and full prescribing information at https://www.igalmihcp.com/igalmi-pi.pdf

If you have any additional questions and would like to speak with our Medical Affairs team, please contact medicalaffairs@bioxceltherapeutics.com.

References:

1. IGALMI [Prescribing Information]. New Haven, CT: BioXcel Therapeutics, Inc; 2022

2. A Phase III Multicenter, Randomized, Double Blind, Placebo- Controlled Study to Determine Efficacy and Safety of BXCL501 in Agitation Associated with Schizophrenia (Serenity I). ClinicalTrials.gov identifier: NCT04268303. Updated: August 19, 2020. Accessed: November 15, 2022, https://clinicaltrials.gov/ct2/show/NCT04268303?term=bxcl501&draw=2&rank=8

3. A Phase III Multicenter, Randomized, Double Blind, Placebo- Controlled Study to Determine Efficacy and Safety of BXCL501 in Agitation Associated with Bipolar Disorder (Serenity II). ClinicalTrials.gov identifier: NCT04276883. Updated: August 19, 2020. Accessed November 15, 2022, https://clinicaltrials.gov/ct2/show/NCT04276883?term=bxcl501&draw=2&rank=7

Selected Dexmedetomidine Bibliography

1. Ingebrigtson M, Miller JT. Adverse Hemodynamic Effects of Dexmedetomidine in Critically Ill Elderly Adults. Journal of pharmacy practice. 2022:8971900221110159.

2. Kim HJ, Ahn E. Risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia: A retrospective study. *Medicine (Baltimore)*. 2022;101(43):e31306. doi:10.1097/MD.0000000000031306

3. Lee S. Dexmedetomidine: present and future directions. *Korean J Anesthesiol*. 2019;72(4):323-330. doi:10.4097/kja.19259

4. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet*. 2017;56(8):893-913. doi:10.1007/s40262-017-0507-7

5. Wujtewicz M, Twardowski P, Jasiński T, Michalska-Małecka K, Owczuk R. Evaluation of the Relationship between Baseline Autonomic Tone and Haemodynamic Effects of Dexmedetomidine. *Pharmaceuticals (Basel)*. 2023;16(3):354. Published 2023 Feb 25. doi:10.3390/ph16030354

6. Yang H, Fu Y, Deng F, Shao Y, Lu YG, Song JC. Median Effective Dose of Dexmedetomidine Inducing Bradycardia in Elderly Patients Determined by Up-and-Down Sequential Allocation Method. *Int J Med Sci*. 2022;19(6):1065-1071. Published 2022 Jun 13. doi:10.7150/ijms.71380

For U.S. Healthcare Professionals Use Only

This information is provided as a professional courtesy in response to your unsolicited request for information and may contain information that is not part of the FDA-approved labeling. This information is intended to provide pertinent data that may assist you in forming your own conclusions and making your own decisions. It is not intended to recommend any use of IGALMI other than recommended in the FDA-approved prescribing information.

The information contained in this letter is for the sole use of the intended recipient(s). It is for informational purposes only and not intended for publication or distribution.

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch