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Dear Healthcare Provider,

Thank you for your inquiry regarding IGALMI™ (dexmedetomidine) sublingual film and hepatic impairment.

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 has not been established beyond 24 hours from the first dose.

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

- Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). Thus, a dosage reduction of IGALMI is recommended in patients with hepatic impairment compared to patients with normal hepatic function
- In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for intravenous dexmedetomidine were lower than in subjects with normal hepatic function. After an intravenous infusion of 0.6 mcg/kg of this dexmedetomidine product over 10 minutes the mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in subjects with normal hepatic function, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in subjects with normal hepatic function, respectively
- Recommended dosage

Patient Population	Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Adults	Mild or Moderate	120mcg	60 mcg	240 mcg
	Severe	180 mcg	90 mcg	360 mcg
Patients with Mild or Moderate Hepatic Impairment**	Mild or Moderate	90 mcg	60 mcg	210 mcg
	Severe	120 mcg	60 mcg	240 mcg
Patients with Severe Hepatic Impairment**	Mild or Moderate	60 mcg	60 mcg	180 mcg
	Severe	90 mcg	60 mcg	210 mcg
Geriatric Patients (≥ 65 years old)	Mild, Moderate, or Severe	120mcg	60 mcg	240 mcg

*IGALMI 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively
** Hepatic impairment: Mild (Child-Pugh Class A); Moderate (Child-Pugh Class B); Severe (Child-Pugh Class C)

Additional published information may be available for intravenous (IV) or 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 13 June 2023 using search terms [dexmedetomidine] and [hepatic impairment] 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 medcalaffairs@bioxceltherapeutics.com

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

Selected Dexmedetomidine Bibliography:

1. 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

2. Rolle A, Paredes S, Cortínez LI, et al. Dexmedetomidine metabolic clearance is not affected by fat mass in obese patients. *Br J Anaesth*. 2018;120(5):969-977. doi:10.1016/j.bja.2018.01.040

3. De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg*. 2001;93(5):1205-1209. doi:10.1097/00000539-200111000-00031

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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