Dexmedetomidine (Igalmi®)

Classification

Alpha-2-adrenergic agonist; Sedative

Pharmacology

Selective alpha-2-adrenoceptor agonist with anesthetic and sedative properties. The sedative properties are thought to be due to activation of G-proteins by alpha-2a-adrenoceptors in the brainstem resulting in inhibition of norepinephrine release.

Indication

Acute treatment of agitation associated with schizophrenia or bipolar I or II disorder.

Pharmacokinetics

Igalmi® is a film that should be administered sublingually or buccally. The mean time for the film to dissolve in the mouth was 6-8 minutes for sublingual administration and 18 minutes for buccal administration.

Pharmacokinetic Parameter	Details

Absorption	• Absolute bioavailability is 72% (sublingual) or 82% (buccal).
	• Mean maximal plasma concentrations were reached two hours after both routes of administration. Mean Cmax of 143 ng/L (sublingual) and 144 ng/L (buccal). Mean AUC 851 hour*ng/L (sublingual) and 584 hour*ng/L (buccal).
	• Effects of water:
	  ○ When water was consumed two hours post dose, the total exposure was comparable for both administration routes.
	  ○ Sublingual: Consumption of water 15 minutes as compared to two hours post dose had minimal effect on absorption.
	  ○ Buccal: Effects of water intake before two hours post dose not evaluated.

Pharmacokinetic Parameter	Details
Distribution	• Steady state volume of distribution was approx. 118 L. • Avg protein binding was 94% in healthy subjects, similar in males and females. Fraction of protein bound was significantly lower in subjects with hepatic impairment. • Protein binding displacement was not noted for either dexmedetomidine or concomitant medications studied.
Metabolism	• Undergoes direct glucuronidation. • Undergoes cytochrome P450 metabolism via CYP2A6 (major) and CYP1A2, CYP2E1, CYP2D6, CYP2C19 (minor).
Excretion	• Elimination half-life 2.8 hours after sublingual or buccal administration. • For intravenous administration, 95% eliminated in urine and 4% in feces. No unchanged dexmedetomidine found in urine.

Dosage/Administration

Dosage: See dosing tables below.

Initial dosage depends on agitation severity.

If agitation persists, up to two additional doses at lower strengths depending on the agitation severity can be administered at least two hours apart. Prior to administration of subsequent doses, assess vital signs including orthostatic measurements. Additional doses are not recommended with blood pressures less than 90/60, heart rate less than 60, or postural decrease of 20/10 or more.

Dosage Recommendations for Igalmi® in Adults (table adapted from Igalmi® package insert)

Agitation Severity	Initial Dose	Optional Additional Doses (up to two)	Maximum Recommended Total Daily Dose
Mild or Moderate	120 mcg	60 mcg	240 mcg
Severe	180 mcg	90 mcg	360 mcg

Dose adjustment in geriatric population and hepatic impairment are recommended.

Dosage Recommendations for Igalmi® in Adults with Hepatic Impairment and Geriatric Patients (table adapted from Igalmi® package insert)

Patient Population	Agitation Severity	Initial Dose	Optional Additional Doses (up to two)	Maximum Recommended Total Daily Dose
Mild or Moderate Hepatic Impairment (Child-Pugh Class A to Class B)	Mild or moderate	90 mcg	60 mcg	210 mcg
Mild or Moderate Hepatic Impairment (Child-Pugh Class A to Class B)	Severe	120 mcg	60 mcg	240 mcg
Severe Hepatic Impairment (Child-Pugh Class C)	Mild or moderate	60 mcg	60 mcg	180 mcg
Severe Hepatic Impairment (Child-Pugh Class C)	Severe	90 mcg	60 mcg	210 mcg
Geriatric Patient (≥65 years old)	Mild, moderate, or severe	120 mcg	60 mcg	240 mcg

Preparation and Administration:

- A healthcare provider should prepare the dose by opening the pouch and then give the appropriate dose to the patient with instructions on how to self-administer. This medication should be administered under the supervision of a healthcare provider with monitoring of vital signs and alertness to prevent falls and syncope.
- Dosage preparation by healthcare provider:
  - Open the pouch with clean, dry hands.
  - This medication is available in 120 mcg and 180 mcg dosage strengths. These can be cut in half to obtain the 60 mcg and 90 mcg doses. If a half of a film is needed, remove the film with clean, dry hands and cut in half with clean, dry scissors. Place the half film for administration back into the pouch and discard the unused half.

    - Give the pouch to the patient with clean, dry hands. Instruct the patient to remove the film and place under the tongue or behind lower lip.
- This medication should be administered sublingually or buccally, it should not be chewed or swallowed.
- Eating and drinking should be avoided for 15 minutes after sublingual administration, one hour after buccal administration.
- This medication should be kept in the foil pouch, it should be immediately administered once the pouch is opened and the dose is prepared.

Use in Special Populations

- Pediatrics/Adolescents: Safety and efficacy have not been established.
- Geriatric: No observed difference in pharmacokinetics based on age, but adjusted dosing recommendations are provided for patients 65 years of age or older. See Dosing/Administration above.
- Renal: No significant difference in pharmacokinetics based on renal function difference.
- Hepatic: In patients with Child-Pugh Class A, B, C hepatic impairment, clearance was reduced and dosing adjustment is recommended. See Dosing/Administration above.
- Pregnancy and Breastfeeding: Safety and efficacy have not been established.

Contraindication

None

Precautions

The safety and effectiveness of Igalmi® have not been established beyond 24 hours from the first dose.

Hypotension, Orthostatic Hypotension, Bradycardia

- Dose dependent hypotension, orthostatic hypotension, and bradycardia can be seen. These may be more pronounced in patients with hypovolemia, diabetes, chronic hypertension or in geriatric patients.
- In clinical studies, patients were excluded if they received alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug; also excluded if they had a history of syncope, low blood pressure, HR <55, evidence of hypovolemia or orthostatic hypotension.

Blood Pressure and Heart Rate Changes (table adapted from Igalmi® package insert)

Effect	Igalmi® 180 mcg	Igalmi® 120 mcg	Placebo
Mean SBP Decrease (mmHg)	15	13	1
Mean DBP Decrease (mmHg)	8	7	<1
Mean Heart Rate Decrease (BPM)	9	7	3
Percent experiencing SBP ≤ 90 mmHg and SBP decrease ≥ 20 mmHg within 24 hrs	13%	8%	<1%
Percent experiencing DBP ≤ 60 mmHg and DBP decrease ≥ 10 mmHg within 24 hrs	19%	17%	2%
Percent with HR ≤ 50 BPM and HR decrease ≥ 20 BPM within 24 hrs	4%	3%	0%

  - Monitoring of vital signs and orthostatic vital signs occurred at regular intervals beginning at 30 min and up to 8 hours post dose. The maximum effect on BP and HR (including positional) were observed at two hours post dose.
  - 16-18% experienced orthostatic hypotension (SBP decrease ≥20 mmHg or DBP decrease ≥10 mmHg) 2 hours post dose, with higher incidence at higher doses, compared to 9% on placebo.
  - 6-7% experienced HR ≤50 within 2 hours of dosing, with higher incidence at higher doses, compared to 1% on placebo.
- Note that for intravenous dexmedetomidine, there have been serious reports of hypotension and bradycardia (some resulting in fatalities). These reports have been seen in young, healthy adult volunteers after receiving rapid intravenous or bolus administration of dexmedetomidine.

QT Interval Prolongation

Dexmedetomidine can cause concentration dependent QT prolongation. Avoid in patients at risk of torsades de pointes (known QT prolongation, history of arrhythmia, symptomatic bradycardia, hypokalemia, hypomagnesemia, receiving other drugs known to prolong QT interval).

QTcF Increase from Baseline (table adapted from Igalmi® package insert)

Dose	Mean QTcF Increase from Baseline
120 mcg single dose	6
120 mcg + 2 additional doses of 60 mcg	8
180 mcg	8
180mcg + 2 additional doses of 90 mcg	11

Somnolence

- In clinical studies, somnolence was reported in 22-23% of patients treated with Igalmi® compared to 6% of those treated with placebo.
- Patients should avoid performing activities requiring mental alertness for at least 8 hours following administration.

Risk of Withdrawal Reactions

- Symptoms of withdrawal have been seen within 24 hours of discontinuing intravenous dexmedetomidine after receiving intravenous dexmedetomidine for up to 7 days. Withdrawal reactions may include nausea, vomiting, agitation.
- Igalmi® was not studied for longer than 24 hours post dose.

Tolerance and Tachyphylaxis

- Use of intravenous dexmedetomidine for longer than 24 hours has been associated with tolerance and tachyphylaxis.
- Igalmi® was not studied for longer than 24 hours post dose.

Adverse Effects

Two placebo controlled randomized clinical studies evaluating the safety of Igalmi® included 507 hemodynamically stable adult patients with agitation related to schizophrenia or bipolar disorder who received at least one dose of Igalmi® (180mcg or 120 mcg) or placebo. Second doses were administered as recommended in the dosing recommendations above as needed.

Adverse Reactions Reported in at least 2% of Patients treated with Igalmi® (table adapted from Igalmi® package insert)

Adverse Reaction	Igalmi® 180 mcg, 120 mcg	Placebo
Somnolence	23, 22	6

Adverse Reaction	Igalmi® 180 mcg, 120 mcg	Placebo
Oral paresthesia or hypoesthesia	7, 6	1
Dizziness	6, 4	1
Hypotension	5, 5	0
Orthostatic hypotension	5, 3	<1
Dry Mouth	4, 7	1
Nausea	3, 2	2
Bradycardia	2, 2	0
Abdominal discomfort	2, 0	1

Monitoring

Healthcare provider should monitor vital signs and alertness after administration to prevent falls and syncope. Peak effects on vital signs seen at two hours post dose.

Interactions

- Avoid concomitant use with drugs that prolong the QT interval due to potential additive effects increasing the risk of arrhythmia
- Concomitant use with medications that cause CNS depression (ie anesthetics, sedatives, hypnotics, opioids) due to potential additive effects. If using Igalmi® with an anesthetic, sedative, hypnotic, or opioid, consider reduction in dosage of Igalmi®.

Efficacy

The effectiveness of Igalmi® in the treatment of acute agitation associated with schizophrenia or bipolar I/II disorder in adults was established in two randomized, double-blind, placebo-controlled fixed studies. Study 1 included 380 patients diagnosed with schizophrenia, schizoaffective, or schizophreniform disorder aged 18 to 71 years of age (mean 46). 37% female, 63% male; 78% black, 20% white, 1% multiracial, 1% Asian. Study 2 included 378 patients diagnosed with bipolar I or bipolar II disorder aged 18 to 70 years (mean 47). 55% female, 45% male; 56% black, 41% white, 1% Asian, 1% multiracial, 1% other. Patients were

admitted to a clinical research unit or hospital and observed for at least 24 hours after dosage administration.

The Positive and Negative Syndrome Scale-Excited Component (PEC) was used. This is an investigator-rated instrument containing 5 items (poor impulse control, tension, hostility, uncooperativeness, excitement) scaled from 1 to 7 (1=absent, 7=extremely severe) with higher total score indicating greater overall severity of symptoms. The patients enrolled had to have a PEC score of 14 or greater and at least one individual item score of at least 4. Mean baseline PEC scores were similar in all treatment groups. Patients were randomized to receive a single sublingual dose of Igalmi® 180 mcg, 120mcg, or placebo with the primary endpoint being the change from baseline in PEC score (two hours after initial dose). The secondary endpoint was the time to effect onset (PEC measured at 10, 20, 30, 45, 60, 90 min after initial dose).

The mean change from baseline in the PEC total score at two hours after the first dose in patients treated with both doses of Igalmi® was statistically greater than patients who received placebo. In Study 1 (Schizophrenia), the decrease in PEC from baseline was statistically significant when compared to placebo at 20 minutes after the 180 mcg dose and at 30 minute after the 120 mcg dose. In Study 2 (Bipolar), the decrease in PEC from baseline was statistically significant when compared to placebo at 20 minutes for both doses.

Dosage Forms/Cost (AWP)

Igalmi® is available in 120 mcg and 180 mcg films.

Igalmi® is sold in packages of 10 at AWP $1,260 ($126 per film). It is available through MMCAP wholesalers, as a drop-ship item in some cases.

Summary/Conclusion

Currently on formulary, oral agents for acute agitation for schizophrenia or bipolar disorder include aripiprazole, olanzapine, ziprasidone, haloperidol (not FDA indicated), and lorazepam (not FDA indicated). There are cases where a patient is not a candidate for or does not respond to one of these agents. Igalmi® has a different mechanism of action compared to the above agents, is not a controlled substance, and the statistically significant decrease in an objective measure of agitation at 20 minutes post dose is faster than many of our current options. Igalmi® is an alpha-2 adrenergic receptor agonist, in the same class as formulary agents clonidine and guanfacine. Dexmedetomidine has a much higher potency and agonist efficacy at alpha-2 receptors at much lower doses. It is important to consider that Igalmi® is self-administered so the patient willingness and ability to

understand administration instructions should be considered. It would be beneficial to have an alternative option to treat acute agitation.

Recommendation

Igalmi® should be added to the formulary.

References

1. Igalmi®. Prescribing information. BioXcel Therapuetics, Inc; July 2022. Accessed April 14, 2023.
2. Igalmi® Dosage and Administration Guide. BioXcel Therapeutics, Inc; July 2022. Accessed April 14, 2023.
3. Preskorn SH, Zeller S, Citrome L, Finman J, Goldberg JF, Fava M, Kakar R, De Vivo M, Yocca FD, Risinger R. Effect of Sublingual Dexmedetomidine vs Placebo on Acute Agitation Associated With Bipolar Disorder: A Randomized Clinical Trial. JAMA. 2022 Feb 22;327(8):727-736. doi: 10.1001/jama.2022.0799. PMID: 35191924; PMCID: PMC8864508.
4. Citrome L, Preskorn SH, Lauriello J, Krystal JH, Kakar R, Finman J, De Vivo M, Yocca FD, Risinger R, Rajachandran L. Sublingual Dexmedetomidine for the Treatment of Acute Agitation in Adults With Schizophrenia or Schizoaffective Disorder: A Randomized Placebo-Controlled Trial. J Clin Psychiatry. 2022 Oct 3;83(6):22m14447. doi: 10.4088/JCP.22m14447. PMID: 36198061.

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