Dexmedatomidine (Igalmi®)
FDA approved April 2022 (BioXcel Therapeutics)

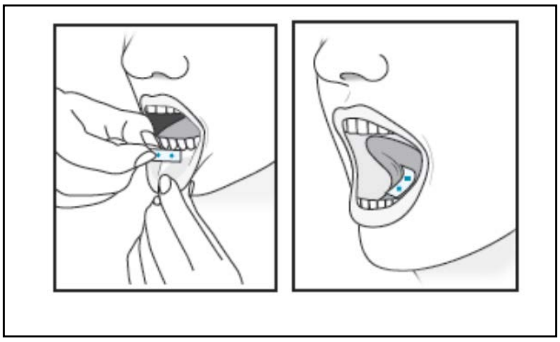
Indication: Dexmedatomidine Sublingual (SL) film is indicated for the acute treatment of agitation associated with schizophrenia and bipolar I or II disorder in adults

- Limitations of Use: Safety and effectiveness has not been established beyond 24 hours from the first dose

Mechanism of action: Dexmedetomidine is an α-2 adrenergic receptor agonist. The mechanism of action in the acute treatment of agitation is thought to be due to activation of presynaptic alpha-2 adrenergic receptors.

Dosage & administration

Patient Population	Agitation Severity	Initial Dose*
Adults	Mild or Moderate	120 mcg
	Severe	180 mcg
Mild or Moderate Hepatic Impairment	Mild or Moderate	90 mcg
	Severe	120 mcg
Severe Hepatic Impairment	Mild or Moderate	60 mcg
	Severe	90 mcg
Geriatric Patients (≥ 65 years old)	Mild, Moderate, or Severe	120 mcg



Additional doses	- If agitation persists, up to 2 additional doses (at least 2 hours apart) may be given depending upon the patient & agitation severity - Assess vital signs including orthostatic measurements before giving additional doses
Administration	- Administer sublingually or buccally (do not chew/swallow). Close mouth & let the film dissolve - Should be administered under the supervision of a healthcare provider to monitor vital signs and alertness post administration to prevent falls & syncope - Do not eat or drink for at least ‣15 minutes after SL administration or ‣60 minutes after buccal administration
How Supplied	120 mcg & 180 mcg sublingual film (may be cut in half to provide 60 mcg & 90 mcg strengths)

Adverse Reactions

Common (≥5% and at least twice the rate of placebo)	Somnolence (22 - 23%), paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, & orthostatic hypotension
Serious	• CV: Bradyarrhythmia (2%), hypotension (5%), orthostatic hypotension (3 to 5%), Prolonged QT interval • Neurologic: Somnolence • Other: Drug tolerance, tachyphylaxis, withdrawal symptom

Table 2: Adverse Reactions Reported in ≥2% of IGALMI-Treated Patients and Greater than Placebo in Two Placebo-Controlled Studies of Agitated Adult Patients with Schizophrenia or Bipolar I or II Disorder (Studies 1 and 2)

Adverse Reaction	IGALMI 180 mcg N=252 %	IGALMI 120 mcg N=255 %	Placebo N=252 %
Somnolence[1]	23	22	6
Paresthesia or hypoesthesia oral	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]	2	0	1

[1]Somnolence includes the terms fatigue and sluggishness
[2]Abdominal discomfort includes dyspepsia, gastroesophageal reflux disease

Warnings and Precautions

Precautions	• Hypotension, orthostatic hypotension, & bradycardia - avoid use in clts with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. - Ensure that clts are alert/not experiencing hypotension before resuming ambulation • QT interval prolongation - Dexmedetomidine SL increases QT interval; avoid use in clts at risk of QT prolongation • Somnolence - clts should not perform activities requiring mental alertness, for at least 8 hours after taking dexmedetomidine SL film • Risk of Withdrawal Reactions • Tolerance and Tachyphylaxis

Drug Interactions

- QT interval prolonging drugs: Avoid use
- Anesthetics, Sedatives, Hypnotics, Opioids: Concomitant use may cause additive CNS depressant effects. Dosage reduction may be required

Pharmacokinetics

Bioavailability	72 % (SL), 82 % (buccal)
T_{max}	2 hours
Half-life	2.8 hours
Metabolism	Liver: Major via glucuronidation & hydroxylation N-methylation: Major
Excretion	Primarily renal (95%); feces (4%)

Clinical Efficacy

- "The efficacy of Igalmi for the treatment of agitation associated with schizophrenia or bipolar I or II disorder was evaluated in two randomized, double-blind, placebo-controlled, fixed-

dose studies in 758 patients who met the DSM-5 criteria for schizophrenia, schizoaffective or schizophreniform disorder. Patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment.

- The primary efficacy endpoint was the change from baseline in the Positive and Negative Syndrome Scale-Excited Component (PEC) score assessed two hours following the initial score.
- In Study 1, Igalmi 180 mcg and Igalmi 120 mcg demonstrated statistically significant superiority in the PEC Score at two hours in agitated patients when compared to placebo [Least-squares (LS) mean difference (95% Confidence Interval) = -5.5 (-6.5 to -4.4) for Igalmi 180 mcg; LS mean difference (95% Confidence Interval) = -3.7 (-4.8 to -2.7) for Igalmi 120 mcg].
- In Study 2, Igalmi 180 mcg and Igalmi 120 mcg demonstrated statistically significant superiority in the PEC Score at two hours in agitated patients when compared to placebo [LS mean difference (95% Confidence Interval) = -5.4 (-6.5 to -4.3) for Igalmi 180 mcg; LS mean difference (95% Confidence Interval) = -4.1 (-5.1 to -3.0) for Igalmi 120 mcg].
- Study considerations:
    - The PEC score is a validated score that is commonly used to detect changes in agitated patients."

Comments/Role in Therapy

- Dexmedetomidine SL film is the first orally dissolving self-administered medication designed to rapidly dissolve and absorb, bypassing first-pass hepatic metabolism
    - new dosage form of dexmedetomidine originally approved in 1999 for procedural sedation and sedation of intubated/mechanically ventilated ICU patients
- offers another non-controlled treatment option with a different mechanism of action (selective α-2A-adrenergic receptor agonist) for the acute treatment of agitation associated with schizophrenia and bipolar disorder
- Dexmedetomidine SL film may offer an advantage for clts who prefer non-invasive treatment option that avoids the need for injections, elderly clts (no black box warning for dementia-related psychosis), and clts for whom antipsychotics or benzos are not preferred
- Initial dose is based on agitation severity, hepatic function, and age with a lower dose recommended for clts with hepatic impairment and geriatric patients
- Other FDA approved pharmacological treatments for agitation associated with schizophrenia or bipolar disorder include olanzapine & ziprasidone IM injections and loxapine (Adasuve) oral inhaler
    - Olanzapine and loxapine are approved for the acute treatment of agitation associated with schizophrenia or bipolar I disorder
    - ziprasidone is approved for the acute treatment of agitation associated with schizophrenia
    - Olanzapine, loxapine, & ziprasidone have black box warnings for increased mortality in elderly patients with dementia-related psychosis
    - Loxapine is only available through a REMS program due to risk of bronchospasm
    - Dexmedetomidine SL is the only FDA-approved drug for the treatment of agitation associated with schizophrenia, bipolar I or bipolar II disorder and there are no black box warnings or REMS
- The 2020 American Psychiatric Association Guidelines for the Treatment of Patients of Schizophrenia recommend olanzapine, ziprasidone, and loxapine as treatment options for agitation
- Other pharmacologic options include antipsychotics, benzodiazepines, and combinations such as haloperidol and promethazine

- There is potential for off-label use of dexmedetomidine SL formulation for long term treatment of agitation
  - Dexmedetomidine SL formulation's safety and effectiveness has not been established beyond 24 hours from the first dose
- The manufacturer is evaluating dexmedetomidine SL formulation (BXCL501) use for other indications including the treatment of agitation in patients with Alzheimer's disease
- Further research is needed to identify candidates for whom dexmedetomidine SL film would be beneficial and to better understand the clinical importance of the observed effect size
  - no published comparative studies with IM olanzapine or ziprasidone
  - more clinical experience needed to assess role in therapy

Pricing and Formulary Considerations:

Brand (generic)	Dosing Regimen	Cost per Dose (WAC)	Formulary Status BHRS	Formulary Status CareAdvantage	Formulary Status DHCS
Igalmi (dexmedetomidine)	60 mcg to **180 mcg** sublingually or buccally as an initial dose. Maximum dose of 360 mcg daily.	Brand: $105			PA required
Zyprexa (olanzapine)	**10 mg** IM, 5 mg or 7.5 mg may be used when clinically warranted. Maximum of 3 doses two to four hours apart	Brand: $48 Generic: $23	PA required Documentation to indicate patient is unable to tolerate or noncompliant with oral formulations	Formulary	PA required
Geodon (ziprasidone)	10 mg to **20 mg** IM up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours.	Brand: $57 Generic: $47	PA required Documentation to indicate patient is unable to tolerate or noncompliant with oral formulations	PA required Documentation to indicate that the patient tried and failed on an oral antipsychotic therapy.	PA required
Adasuve (loxapine)	**10 mg** inhaled as single-dose	Brand: $180.00	PA required Documentation required to indicate enrollment into Adasuve REMS Program	NonFormulary	PA required

Wholesale Acquisition Cost (WAC) pricing from RxNova on 6/1/2022

Recommend:
PA requirement for BHRS and CMC formularies PA
Approval criteria:

- **Adults with acute agitation associated with schizophrenia or bipolar I or II**
- **Administered under the supervision of a healthcare provider who will monitor vital signs and alertness to prevent falls or syncope** (most likely PES, hospital, IMD)
- **Tried and failed IM Olanzapine or have intolerance/contraindication olanzapine**

References

- BioXcel Therapeutics announces FDA approval of IGALMI™ (dexmedetomidine) sublingual film for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. BioXcel. News release. April 6, 2022. https://ir.bioxceltherapeutics.com/news-releases/news-release-details/bioxcel-therapeutics-announces-fda-approval-igalmitm
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- Preskorn SH, Zeller S, Citrome L, et al. Effect of sublingual dexmedetomidine vs placebo on acute agitation associated with bipolar disorder: A randomized clinical trial. *JAMA* 2022;327:727-736.