**Dexmedatomidine (Iгалмі®)**
**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

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Agitation Severity</th>
<th>Initial Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Mild or Moderate</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>180</td>
</tr>
<tr>
<td>Mild or Moderate Hepatic Impairment</td>
<td>Mild or Moderate</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>120</td>
</tr>
<tr>
<td>Severe Hepatic Impairment</td>
<td>Mild or Moderate</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>90</td>
</tr>
<tr>
<td>Geriatric Patients (≥ 65 years old)</td>
<td>Mild, Moderate, or Severe</td>
<td>120</td>
</tr>
</tbody>
</table>

- 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**

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

<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>72 % (SL), 82 % (buccal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.8 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver: Major via glucuronidation &amp; hydroxylation N-methylation: Major</td>
</tr>
<tr>
<td>Excretion</td>
<td>Primarily renal (95%); feces (4%)</td>
</tr>
</tbody>
</table>

**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:**

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>Dosing Regimen</th>
<th>Cost per Dose (WAC)</th>
<th>Formulary Status BHRS</th>
<th>Formulary Status CareAdvantage</th>
<th>Formulary Status DHCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igalmi (dexmedetomidine)</td>
<td>60 mcg to <strong>180 mcg</strong> sublingually or buccally as an initial dose. Maximum dose of 360 mcg daily.</td>
<td>Brand: $105</td>
<td></td>
<td></td>
<td>PA required</td>
</tr>
</tbody>
</table>
| 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

- Elliott, William, and James Chan. "Dexmedetomidine Sublingual Film (Igalmi)." Internal Medicine Alert 44.9 (2022).
- Highmark Medication Review: New Dosage Form Bipolar Agents: Bipolar Agents, Other Igalmi (dexmedetomidine) [BioXcel Therapeutics] April 2022
- Mina Antonius. New Dosage Form Bipolar Agents: Bipolar Agents, Other Igalmi (dexmedetomidine). Highmark Clinical Pharmacy Strategies. April 2022
- Pacheco, Eli. "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."