NEW DRUG APPROVAL

Brand Name	Igalmi™
Generic Name	dexmedetomidine
Drug Manufacturer	BioXcel Therapeutics, Inc

New Drug Approval

FDA approval date: April 05, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form, New Drug Application (NDA): 215390

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis. It is commonly associated with impairments in social and occupational functioning. It is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the top 10 illnesses contributing to the global burden of disease.

Characteristics of schizophrenia typically include positive symptoms, such as hallucinations or delusions; disorganized speech; negative symptoms, such as a flat affect or poverty of speech; and impairments in cognition, including attention, memory and executive functions.

Schizophrenia and bipolar disorder are mental health conditions that affect approximately 1.5 million (<1 1%) individuals and 7 million (2.8%) individuals in the United States, respectively.

- Patients with schizophrenia can experience psychotic symptoms including distortions of reality and emotions, accompanied by hallucinations and delusions.
- Bipolar disorder is a chronic and complex disorder of mood that can be subdivided into two main types: bipolar I disorder, which involves the occurrence of at least one lifetime manic episode (although depressive episodes are common); and bipolar II disorder, which includes the occurrence of at least one hypomanic episode and one major depressive episode.

Both schizophrenia and bipolar disorder can share the overlapping symptom of agitation. Agitation in bipolar and schizophrenia can include excessive motor and/or verbal activity, uncooperativeness, irritability, heightened responsiveness to stimuli, threatening gestures, and assault (verbal and/or physical).

There is a lack of clear epidemiological data describing the incidence of agitation in patients with schizophrenia and bipolar disorder. Some estimates suggest a prevalence of agitation in schizophrenia between 23.4% and 38.4% and in bipolar I disorder between 19.5% and 29%. These patients can experience over 10 agitation episodes per year.

Efficacy

The approval of Igalmi™ was based on two randomized, Phase 3, double-blind, placebo-controlled, fixed-dose studies, SERENITY I and SERENITY II. Patients were identified in outpatient clinics; mental health, psychiatric, or medical emergency services including medical/psychiatric observation units; or as newly admitted to a hospital

setting for acute agitation or already in hospital for chronic underlying conditions. For purposes of the study, patients were hospitalized or kept in a clinical research setting.

Table 1 provides a summary of the SERENITY I and SERENITY II trials.

Table 1. Igalmi™ Clinical Trials: Study Design Summary

	SERENITY I (N = 380)	SERENITY II (N = 378)
Study Population	Adult patients who met DSM-5 criteria for schizophrenia, schizoaffective, or schizophreniform disorder • Mean age: 46 years (range, 18–71 years) • 37% female, 63% male • 78% Black, 20% White, 1% multiracial, and 1% Asian	Adult patients who met DSM-5 criteria for bipolar I or II disorder • Mean age: 47 years (range, 18–70 years) • 45% female, 55% male • 56% Black, 41% White, 1% Asian, 1% multiracial, and 1% other
Key Inclusion Criteria	• Judged to be clinically agitated at screening (defined as PEC score* ≥14) • At least one individual item score on the PEC of ≥4	
Key Exclusion Criteria	• Agitation caused by acute intoxication (alcohol or drug of abuse, except THC). • Use of benzodiazepines, hypnotics, antipsychotic drugs in the 4 hours before study treatment. • Treatment with alpha-1 noradrenergic blockers. • Judged to be at significant risk of suicide. • Hydrocephalus, seizure disorder, or history of significant head trauma, stroke, transient ischemic attack, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, Parkinson's disease, or focal neurological findings. • History of syncope or other syncopal attacks, current evidence of hypovolemia, or orthostatic hypotension	
Interventions	Patients were randomized 1:1:1 to receive one of the following: • Sublingual dexmedetomidine 180 mcg • Sublingual dexmedetomidine 120 mcg • Matching placebo film	
Endpoints	• **Primary efficacy endpoint:** Change from baseline in PEC score, assessed at 2 hours after initial dose • **Key secondary endpoint:** Time to effect onset, measured by the change from baseline in PEC score at 10, 20, 30, 45, 60, and 90 minutes after the initial dose administration.	

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PEC, Positive and Negative Syndrome Scale-Excited Component; THC, tetrahydrocannabinol.

*The PEC is a subset of the Positive and Negative Syndrome Scale (PANSS) used to evaluate the degree of sedation or agitation in patients. The PEC consists of 5 items: excitement, tension, hostility, uncooperativeness, and poor

impulse control, which are rated from 1 (not present) to 7 (extremely severe), with total scores ranging from 5 to 35. Severe agitation is a score ≥20.

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) are somnolence, paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

WARNINGS & PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia:
Avoid use of Igalmi™ in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. Ensure that patients are alert and not experiencing orthostatic or symptomatic hypotension prior to resuming ambulation.

QT Interval Prolongation:
Igalmi™ increases in QT interval; avoid use in patients with risk factors for prolonged QT interval.

Somnolence:
Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery for at least eight hours after taking Igalmi™ .

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Dexmedetomidine is an alpha-2 adrenergic receptor agonist. The mechanism of action of Igalmi™ in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder is thought to be due to activation of presynaptic alpha-2 adrenergic receptors.

Dose & Administration

ADULTS

Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Mild or Moderate	120 mcg	60 mcg	240 mcg
Severe	180 mcg	90 mcg	360 mcg

* Igalmi™ 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively.

PEDIATRICS

None

GERIATRICS

Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Mild, Moderate, or Severe	120 mcg	60 mcg	240 mcg

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
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

* 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)

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Igalmi™ is a blue rectangular sublingual film containing on its surface two darker blue spots in dose strengths of 120 mcg and 180 mcg.