HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IGALMI safely and effectively. See full prescribing information for IGALMI.

IGALMI® (dexmedetomidine) sublingual film, for sublingual or buccal use
Initial U.S. Approval: 1999

---------- RECENT MAJOR CHANGES ----------
- Indications and Usage (1) 11/2026
- Dosage and Administration (2.1, 2.2, 2.3, 2.4) 11/2026
- Warnings and Precautions (5.1, 5.3, 5.4) 11/2026

---------- INDICATIONS AND USAGE ----------
IGALMI is a central alpha-2 adrenergic receptor agonist indicated for the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder in adults. (1)

Limitations of Use: IGALMI is not indicated for preventive treatment of agitation or for the underlying psychiatric disorder. The safety and effectiveness of chronic, daily use of IGALMI have not been studied. (1)

----------DOSAGE AND ADMINISTRATION ----------
- Prior to treatment, assess heart rate and blood pressure, including orthostatic measurements, and the risk of syncope and falls. During treatment, monitor for hypotension, orthostatic hypotension, presyncope, syncope, and falls. (2.1)
- Administer sublingually or buccally. Do not chew or swallow. (2.1)
- Recommended dosage in the healthcare supervised setting (2.2):

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
*See Full Prescribing Information for recommendations on administering up to two additional doses and maximum recommended dosages.		

- Recommended dosage in the unsupervised setting: 120 mcg. If agitation recurs, an additional 120 mcg dose may be administered after at least 12 hours. Do not administer more than one dose within a 12-hour period. Use in the unsupervised setting is not recommended in geriatric patients (65 years of age and older) or patients with mild, moderate, or severe hepatic impairment. (2.3)
- In the healthcare supervised setting, IGALMI 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively. (2.2, 2.4)
- See Full Prescribing Information for preparation and administration instructions. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
Sublingual film: 120 mcg (healthcare supervised and unsupervised settings) and 180 mcg (healthcare supervised setting only). (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND 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. Warn patients of the risk of syncope and falls. In the healthcare supervised setting, ensure that patients are alert and not experiencing orthostatic or symptomatic hypotension prior to resuming ambulation. (5.1)
- QT Interval Prolongation: IGALMI prolongs the QT interval; avoid use in patients with risk factors for prolonged QT interval. (5.2)
- 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. (5.3)

---------- ADVERSE REACTIONS ----------
- In the healthcare supervised setting: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) are somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension. (6.1)
- In the unsupervised setting: The most common adverse reactions (incidence ≥5% and greater than placebo) are somnolence, dry mouth, dizziness, and oral paresthesia or oral hypoesthesia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------
- Drugs that Prolong the QT Interval: Avoid concomitant use. (5.2, 7.1)
- Anesthetics, Sedatives, Hypnotics, and Opioids: Consider reducing the dose of IGALMI (healthcare supervised setting) or the concomitant drug. Concomitant use may increase the risk of CNS depression. (2.2, 7.2) Avoid concomitant use of IGALMI (unsupervised setting). with sedative, hypnotic, or opioid. Concomitant use may increase the risk of CNS depression. (2.3, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder in adults.

Limitations of Use

IGALMI is not indicated for preventive treatment of agitation or for the underlying psychiatric disorder. The safety and effectiveness of chronic, daily use of IGALMI have not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to and During Treatment with IGALMI

Prior to treatment with IGALMI:

- Assess heart rate and blood pressure, including orthostatic measurements.
- Assess for history of hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or syncope.
- Assess for risk of orthostatic hypotension, syncope, and falls and warn patients of the risk.

During treatment with IGALMI:

- Monitor for hypotension and orthostatic hypotension.
- Monitor for presyncope, syncope, and falls.

[see Warnings and Precautions (5.1)].

IGALMI is a film for sublingual or buccal administration. Do not chew or swallow the film. Do not eat or drink for at least 15 minutes after sublingual administration, or at least 1 hour after buccal administration.

2.2 Recommended Dosage in the Healthcare Supervised Setting

Table 1 includes dosage recommendations for IGALMI in the healthcare supervised setting based on agitation severity for adults, patients with hepatic impairment, and geriatric patients. Lower dosages are recommended for patients with hepatic impairment and geriatric patients *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)]*. Consider reducing the dosage of IGALMI when used concomitantly with anesthetics, sedatives, hypnotics, or opioids *[see Drug Interactions (7.2)]*.

If agitation persists after the initial dose, up to two additional doses may be administered at least two hours apart. The dosage recommendations for additional doses vary depending upon the patient population and agitation severity *(see Table 1)*. Assess vital signs including orthostatic measurements prior to the administration of any subsequent doses.

Due to risk of hypotension, additional half-doses are not recommended in patients with systolic blood pressure (SBP) less than 90 mmHg, diastolic blood pressure (DBP) less than 60 mmHg,

heart rate (HR) less than 60 beats per minute, or postural decrease in SBP ≥ 20 mmHg or in DBP ≥ 10 mmHg.

Table 1: IGALMI Dosage Recommendations for Adult Patients in the Healthcare Supervised Setting

Patient Population	Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Adults	Mild or Moderate	120 mcg	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	120 mcg	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 *[see Dosage and Administration (2.2, 2.4)]*.
† Hepatic impairment: Mild (Child-Pugh Class A); Moderate (Child-Pugh Class B); Severe (Child-Pugh Class C)

2.3 Recommended Dosage in the Unsupervised Setting

The recommended dosage of IGALMI in the unsupervised setting is 120 mcg administered once for agitation. If agitation recurs, an additional 120 mcg dose may be administered after at least 12 hours have passed since the previous dose. Do not administer more than one dose within a 12-hour period.

Use of IGALMI in the unsupervised setting is not recommended in the following patients:

- geriatric patients (65 years of age and older)
- patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment

[see Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)].

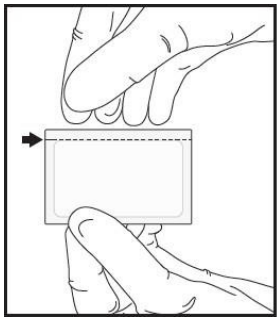
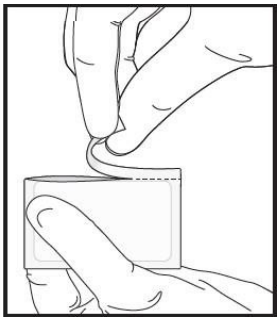
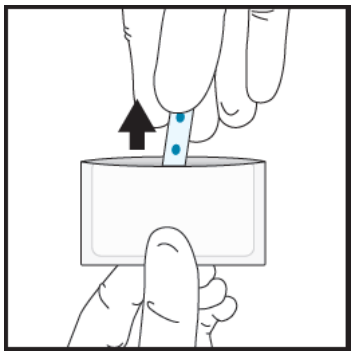
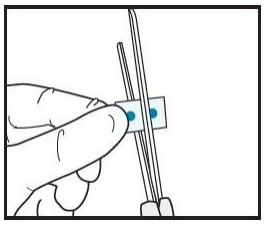
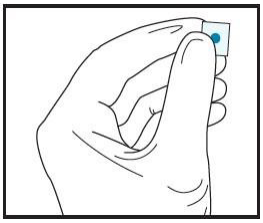
Patients treated with IGALMI should also receive appropriate therapy for the underlying schizophrenia, schizoaffective disorder, or bipolar I or II disorder. If IGALMI is used frequently, reassess the adequacy of treatment for the underlying psychiatric disorder.

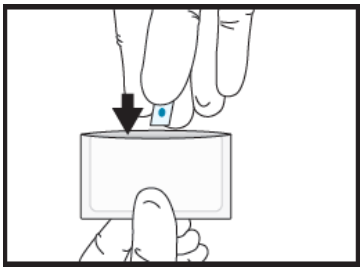
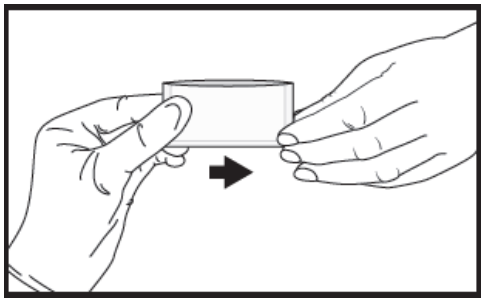
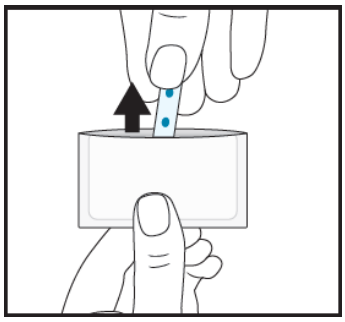
2.4 Preparation and Administration Instructions

Keep IGALMI in the foil pouch until ready to administer. IGALMI should be immediately administered once the pouch is opened and the dose prepared.

Healthcare Supervised Setting

Prepare and administer IGALMI under the supervision of a healthcare provider as follows:

<table>
<tr><th colspan="3">Healthcare Professional: Prepare IGALMI Dose for Patient</th></tr>
<tr><td>1</td><td>Open the sealed foil pouch by tearing straight across at the notch.</td><td> </td></tr>
<tr><td colspan="3">• Perform Steps 2a, 2b, 2c, and 2d only if a 60 mcg or 90 mcg dose (half of a film) is needed, then proceed to Step 3.
• If administering a full dose (1 film), proceed directly to Step 3.</td></tr>
<tr><td>2a</td><td>Remove the film from the pouch with clean dry hands.</td><td></td></tr>
<tr><td>2b</td><td>Cut the film in half between the dots with clean, dry scissors.</td><td> </td></tr>
<tr><td>2c</td><td colspan="2">Discard unused half in waste container.</td></tr>
</table>

2d	Place the half film for administration to the patient back into the pouch.	
3	Immediately give the pouch to the patient.	
4	Instruct patient to remove the film from the pouch with clean dry hands.	

5	**For sublingual administration:** Instruct patient to place film under the tongue. The film will stick in place. **Note:** Patient may not eat or drink for 15 minutes after sublingual administration.	
	For buccal administration: Instruct patient to place film behind lower lip. The film will stick in place. **Note:** Patient may not eat or drink for one hour after buccal administration.	
6	Instruct patient to: • Close their mouth. • Allow the film to dissolve. • Do not chew or swallow the film.	

Unsupervised Setting

Advise patients on the following:

- Read the Instructions for Use before taking IGALMI.
- Wash and dry hands prior to removing the film from the pouch, place the film under the tongue (sublingual administration) or between the lower lip and gum (buccal administration), and allow the film to dissolve completely.
- Do not split, cut, chew, or swallow the film.
- Do not eat or drink for at least 15 minutes after sublingual administration, or at least 1 hour after buccal administration.

3 DOSAGE FORMS AND STRENGTHS

Sublingual film

- *For use in the healthcare supervised setting:* 120 mcg or 180 mcg dexmedetomidine, blue, rectangular sublingual film with two darker blue spots on one side.
- *For use in the unsupervised setting:* 120 mcg dexmedetomidine, blue, rectangular sublingual film imprinted with "D12" in black on one side and featuring two darker blue spots on the same side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension, Orthostatic Hypotension, and Bradycardia

IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In Studies 1 and 2, 18%, 16%, and 9% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced orthostatic hypotension (defined as SBP decrease ≥ 20 mmHg or DBP decrease ≥ 10 mmHg after 1, 3, or 5 minutes of standing) at 2 hours post-dose. In those studies, 7%, 6%, and 1% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced HR ≤ 50 beats per minute within 2 hours of dosing *[see Adverse Reactions (6.1)].* In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics, or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension.

Reports of hypotension and bradycardia, including some resulting in fatalities, have been associated with the use of another dexmedetomidine product given intravenously (IGALMI is for sublingual or buccal use and is not approved for intravenous use). Clinically significant episodes of bradycardia and sinus arrest have been reported after administration of this other dexmedetomidine product to young, healthy adult volunteers with high vagal tone and when this product was given by rapid intravenous or bolus administration.

Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients *[see Dosage and Administration (2.2, 2.3) and Use in Specific Populations (8.5)]*.

Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. Warn patients of the risk of syncope and falls. After IGALMI administration, advise patients to hydrate and to sit or lie down until vital signs are within normal range. If patients are unable to remain seated or lying down, take precautions to reduce the risk of falls. In the healthcare supervised setting, ensure that patients are alert and not experiencing orthostatic or symptomatic hypotension prior to allowing patients to resume ambulation *[see Dosage and Administration (2.1)]*.

5.2 QT Interval Prolongation

IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5.3 Somnolence

IGALMI can cause somnolence. In placebo-controlled Studies 1 and 2 in adults with agitation

associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder, somnolence (including fatigue and sluggishness) was reported in 23% and 22% of patients treated with IGALMI 180 mcg and 120 mcg, respectively, compared to 6% of placebo-treated patients. 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 *[see Adverse Reactions (6.1)]*.

5.4 Risk of Withdrawal Reactions

Symptoms of withdrawal have been observed after treatment with another dexmedetomidine product administered as a continuous intravenous infusion in the intensive care unit for another indication. In a clinical study of this product, 12 (5%) adult patients who received intravenous dexmedetomidine up to 7 days (regardless of dose) experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing dexmedetomidine and 7 (3%) adult patients who received intravenous dexmedetomidine experienced at least 1 event related to withdrawal 24 to 48 hours after discontinuing dexmedetomidine. The most common withdrawal reactions were nausea, vomiting, and agitation. In these patients, tachycardia and hypertension requiring intervention occurred at a frequency of <5% in the 48 hours following intravenous dexmedetomidine discontinuation. Withdrawal symptoms have been reported in pediatric patients who received another dexmedetomidine product intravenously for another indication. IGALMI is not approved for pediatric use.

Withdrawal symptoms reported in published literature include cardiovascular symptoms, such as hypertension, tachycardia, arrhythmias, and in severe cases, hypertensive crisis; neurological symptoms, such as agitation, anxiety, tremors, seizures, and altered mental status; and autonomic symptoms such as diaphoresis, nausea, vomiting, hyperthermia, and mydriasis.
In a randomized, double-blind, placebo-controlled, multiple ascending dose study assessing IGALMI at doses up to 120 mcg per day administered over 7 days in healthy volunteers, elevated heart rate and systolic blood pressure and vomiting occurred at a higher frequency upon abrupt discontinuation of 120-mcg doses of IGALMI as compared to placebo. There may be a risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated *[see Dosage and Administration (2.2, 2.3) and Drug Abuse and Dependence (9.3)]*.

5.5 Tolerance and Tachyphylaxis

Use of another dexmedetomidine product administered intravenously beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions. There may be a risk of tolerance and tachyphylaxis if IGALMI is administered at higher doses or for a longer duration than were evaluated, or in a manner other than indicated *[see Dosage and Administration (2.2, 2.3) and Drug Abuse and Dependence (9.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Hypotension, Orthostatic Hypotension, and Bradycardia *[see Warnings and Precautions (5.1)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.2)]*
- Somnolence *[see Warnings and Precautions (5.3)]*
- Risk of Withdrawal Reactions *[see Warnings and Precautions (5.4)]*

- Tolerance and Tachyphylaxis *[see Warnings and Precautions (5.5)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Studies in the Healthcare Supervised Setting

The safety of IGALMI was evaluated in 507 adult patients with agitation associated with schizophrenia or schizoaffective disorder (N=255) or bipolar I or II disorder (N=252) in two randomized, placebo-controlled studies (Studies 1 and 2) *[see Clinical Studies (14)]*. In both studies, patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment. Patients were 18 to 71 years of age (mean age was 46 years old); 45% were female and 55% were male; 66% were Black, 31% were White, 2% were multiracial, and 1% were other.

In these studies, patients received an initial dose of IGALMI 180 mcg (N=252), IGALMI 120 mcg (N=255), or placebo (N=252). Patients who were hemodynamically stable (i.e., those with systolic blood pressure (SBP) > 90 mmHg, diastolic blood pressure (DBP) > 60 mmHg, and heart rate (HR) > 60 beats per minute) and without orthostatic hypotension (i.e., reduction in SBP < 20 mmHg or DBP < 10 mmHg upon standing) were eligible for an additional dose after 2 hours. An additional half dose (90 mcg, 60 mcg, or placebo) was given to 7% (18/252), 23% (58/255), and 44% (111/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg, and placebo arms, respectively. After at least an additional 2 hours, an additional second half dose (total IGALMI dose of 360 mcg, total IGALMI dose of 240 mcg, or placebo, respectively) was given to 3% (8/252), 9% (24/255), and 21% (53/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg, and placebo arms, respectively.

In these studies, one patient discontinued treatment due to an adverse reaction of oropharyngeal pain.

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

Table 2 presents the adverse reactions that occurred in IGALMI-treated patients at a rate of at least 2% and at a higher rate than in placebo-treated patients in Studies 1 and 2.

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 Schizoaffective Disorder 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*	23	22	6
Paresthesia oral 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	0	1

*Somnolence includes the terms fatigue and sluggishness.
†Abdominal discomfort includes dyspepsia and gastroesophageal reflux disease.

Hypotension, Orthostatic Hypotension, and Bradycardia in Two Placebo-Controlled Studies
In clinical studies, patients were excluded if they were treated with alpha-1 noradrenergic blockers, benzodiazepines, antipsychotic drugs, or other hypnotics four hours prior to study drug administration; had a history of syncope or syncopal attacks; their SBP was less than 110 mmHg; their DBP was less than 70 mmHg; their HR was less than 55 beats per minute; or they had evidence of hypovolemia or orthostatic hypotension. In these studies, vital signs were monitored (at 30 minutes and 1, 2, 4, 6, and 8 hours post-dose), including orthostatic vital signs at 2, 4, and 8 hours post-dose. Maximum positional decreases in SBP and DBP after standing were observed at two hours post-dose. Maximal reductions in BP and HR were observed two hours post-dose.

Table 3 presents the mean BP and HR decrease across all patients from both studies at 2 hours post dose.

Table 3: Mean Blood Pressure and Heart Rate Decrease at 2 Hours Post-Dose

	IGALMI 180 mcg N=252	IGALMI 120 mcg N=255	Placebo N=252
Mean SBP Decrease (mmHg)	15	13	1
Mean DBP Decrease (mmHg)	8	7	<1
Mean Heart Rate Decrease (bpm)	9	7	3

In the clinical studies:

- 13%, 8%, and < 1% of patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, experienced SBP ≤ 90 mmHg and a decrease ≥ 20 mmHg of SBP within 24 hours of dosing.
- 19%, 17%, and 2% of the patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a DBP ≤ 60 mmHg and a DBP decrease ≥ 10 mmHg

within 24 hours of dosing.

- 4%, 3%, and 0% of patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute within 24 hours of dosing.

At 8 hours post-dose, 2% of patients in the IGALMI 180 mcg group experienced a SBP ≤ 90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 24 hours, none of the patients in the IGALMI 180 mcg group experienced a SBP ≤ 90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 8 hours post-dose, none of the patients in the IGALMI 180 mcg group had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute compared with one patient in the 120 mcg group (<1%) and none in the placebo group.

Study in the Unsupervised Setting

The safety of IGALMI 120 mcg was evaluated in 208 adult patients with agitation associated with schizophrenia or schizoaffective disorder (N=111 [53%]) or bipolar I or II disorder (N=97 [47%]) in one randomized, 12-week, outpatient, placebo-controlled study (Study 3). Of these patients, 102 received IGALMI and 106 received placebo.

Of the patients treated with IGALMI, about half (48%) of the patients were male; 53% were White and most were neither Hispanic nor Latino (69%). The median age was 47 years.

The most common adverse reactions (incidence ≥ 5% and greater than placebo) were: somnolence, dry mouth, dizziness, and oral paresthesia or oral hypoesthesia.

Table 4 presents the adverse reactions that occurred in IGALMI-treated patients at a rate of at least 2% and at a higher rate than in placebo-treated patients in Study 3.

Table 4: Adverse Reactions Reported in ≥2% of IGALMI-Treated Patients and Greater than Placebo in a 12-Week Placebo-Controlled At-Home Study of Agitated Adult Patients with Schizophrenia or Schizoaffective Disorder or Bipolar I or II Disorder (Study 3)

Adverse Reaction	IGALMI 120 mcg N=102 %	Placebo N=106 %
Somnolence*	55	42
Dry mouth	15	4
Dizziness	11	3
Paresthesia oral or hypoesthesia oral	5	2
Nausea	4	1
Restless legs syndrome	3	0
Increased appetite	2	0
Dysarthria	2	1

Adverse reactions were reported within 24 hours of dosing.
*Somnolence includes the terms fatigue and sedation.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of another dexmedetomidine product given intravenously (IGALMI is not approved for intravenous use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and Lymphatic System Disorders:* Anemia
- *Cardiac Disorders:* Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia
- *Eye Disorders:* Photopsia, visual impairment
- *Gastrointestinal Disorders:* Abdominal pain, diarrhea, nausea, vomiting
- *General Disorders and Administration Site Conditions:* Chills, hyperpyrexia, pain, pyrexia, thirst
- *Hepatobiliary Disorders:* Hepatic function abnormal, hyperbilirubinemia
- *Investigations:* Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram QT prolonged, electrocardiogram T wave inversion, gamma-glutamyltransferase increased
- *Metabolism and Nutrition Disorders:* Acidosis, hyperkalemia, hypernatremia, hypoglycemia, hypovolemia
- *Nervous System Disorders:* Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder
- *Psychiatric Disorders:* Agitation, confusional state, delirium, hallucination, illusion
- *Renal and Urinary Disorders:* Oliguria, polyuria
- *Respiratory, Thoracic and Mediastinal Disorders:* Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis
- *Skin and Subcutaneous Tissue Disorders:* Hyperhidrosis, pruritus, rash, urticaria
- *Surgical and Medical Procedures:* Light anesthesia
- *Vascular Disorders:* Blood pressure fluctuation, hemorrhage, hypertension, hypotension

7 DRUG INTERACTIONS

7.1 Drugs that Prolong the QT Interval

Avoid concomitant use of IGALMI with other drugs known to prolong the QTc interval. Concomitant use of IGALMI with other products that prolong the QTc interval may result in additive QTc prolongation and increase the risk of cardiac arrhythmia *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

7.2 Anesthetics, Sedatives, Hypnotics, and Opioids

In the healthcare supervised setting, consider reducing the dosage of IGALMI or the concomitant anesthetic, sedative, hypnotic, or opioid, and monitor for central nervous system (CNS) depression *[see Dosage and Administration (2.2)]*.

In the unsupervised setting, avoid concomitant use of IGALMI with sedative, hypnotic, or opioid. *[see Dosage and Administration (2.3) and Patient Counseling Information (17)]*.

Reference ID: 5904216

Due to additive pharmacologic effects, concomitant use of IGALMI with anesthetics, sedatives, hypnotics, or opioids may increase the risk of CNS depression, including sedation and somnolence.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on IGALMI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal effects. Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects or miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

In animal reproductive studies fetal toxicity occurred in the presence of maternal toxicity with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 5 times the maximum recommended human dose (MRHD) of 360 mcg/day based on mg/m^2 body surface area. Adverse developmental effects, including early implantation loss and decreased viability of second generation offspring, occurred when pregnant rats were subcutaneously administered doses less than or equal to the MRHD based on mg/m^2 from late pregnancy through lactation and weaning *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Increased post-implantation losses and reduced live pups in the presence of maternal toxicity (decreased body weight) occurred in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine of 200 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis [Gestation Day (GD) 5 to 16]. No embryo-fetal toxicity was observed at 20 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2). No malformations were reported at any dose level.

No malformation or embryo-fetal toxicity was observed in a rabbit embryo-fetal development study in which pregnant dams were administered dexmedetomidine intravenously at doses up to 96 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring weights and grip strength were reported in a rat developmental

toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at 8 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2) during late pregnancy through lactation and weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second generation offspring and an increase in early implantation loss along with delayed motor development occurred at 32 mcg/kg/day (equivalent to the MRHD of 360 mcg/day based on mg/m^2) when first generation offspring were mated. This study limited dosing to hard palate closure (GD 15-18) through weaning instead of standard dosing from implantation (GD 6-7) to weaning (PND 21).

8.2 Lactation

Risk Summary

Available published literature reports the presence of dexmedetomidine in human milk following intravenous administration. There is no information regarding the effects of dexmedetomidine on the breastfed child or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IGALMI and any potential adverse effects on the breastfed child from IGALMI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of IGALMI have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of IGALMI-treated patients in clinical studies for the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder, 33 of 1,027 (3%) patients were 65 years of age and older and 1 (<1%) was 75 years of age and older *[see Clinical Studies (14)]*.

In the healthcare supervised setting, the recommended initial dose in geriatric patients is 120 mcg *[see Dosage and Administration (2.2)]*. IGALMI is not recommended in geriatric patients in the unsupervised setting *[see Dosage and Administration (2.3)]*. There was a higher incidence of bradycardia and hypotension observed in geriatric patients compared to younger adult patients after intravenous administration of another dexmedetomidine product *[see Warnings and Precautions (5.1)]*. The pharmacokinetic profile of intravenous dexmedetomidine was not altered in geriatric subjects *[see Clinical Pharmacology (12.3)]*.

Clinical studies of IGALMI did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in the effectiveness of IGALMI in the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder compared to younger adult patients.

8.6 Hepatic Impairment

Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). In the healthcare supervised setting, reduced doses are recommended in patients with mild, moderate, or severe hepatic impairment. In the unsupervised setting, IGALMI is not recommended for patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment *[see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

IGALMI contains dexmedetomidine, which is not a controlled substance.

9.3 Dependence

Physical Dependence

Dexmedetomidine is an alpha-2 adrenergic agonist and has been associated with physical dependence, as manifested by a withdrawal syndrome with abrupt drug discontinuation, particularly after prolonged continuous intravenous use in critical care settings. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal signs and symptoms associated with physical dependence produced by dexmedetomidine, as reported in the literature, include cardiovascular findings, such as hypertension, tachycardia, arrhythmias, and in severe cases, hypertensive crisis; neurological findings, such as agitation, anxiety, tremors, seizures, and altered mental status; and autonomic findings, such as diaphoresis, nausea, vomiting, hyperthermia, and mydriasis.

The potential for IGALMI to produce a withdrawal syndrome was evaluated in two clinical studies. The first was a single-arm, open-label clinical study that evaluated adult patients diagnosed with agitation associated with schizophrenia or schizoaffective disorder or bipolar disorder after a 7-day IGALMI treatment period. This study demonstrated that, with a mean of 3 doses (min, max: 1, 7; SD: 1.69) administered in the 7-day treatment period and with no patient receiving more than a single 180 mcg daily dose, there was no evidence of dexmedetomidine withdrawal signs or symptoms.

The second was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in healthy volunteers that assessed IGALMI 30 to 120 mcg daily administered over 7 days. The findings from this study are suggestive of dexmedetomidine withdrawal symptoms (e.g., increased heart rate and systolic blood pressure, vomiting) upon abrupt discontinuation with the hemodynamic changes being more frequently reported in the 120-mcg single daily dose group as compared to placebo. There may be an increased risk of physical dependence and a withdrawal syndrome if IGALMI is administered at higher doses or for a longer duration than were evaluated or is used in a manner other than indicated *[see Dosage and Administration (2.1, 2.2, 2.3) and Warnings and Precautions (5.4)]*.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

There may be a risk for tolerance if IGALMI is administered in a manner other than indicated *[see Dosage and Administration (2.1, 2.2, 2.3) and Warnings and Precautions (5.5)]*.

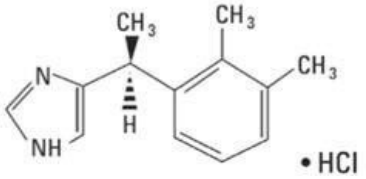
10 OVERDOSAGE

In a tolerability study of intravenous dexmedetomidine in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hour, the maximum blood concentration was approximately 13 times the upper boundary of the therapeutic range for the intravenous dexmedetomidine (IGALMI is not approved for intravenous use). The most notable effects observed in two subjects who achieved the highest doses were first-degree atrioventricular block and second-degree heart block.

Five adult patients received an overdose of intravenous dexmedetomidine in intensive care unit sedation studies. Two patients who received a 2 mcg/kg loading dose (twice the recommended loading dose) over 10 minutes experienced bradycardia and/or hypotension.
One patient who received a loading intravenous bolus dose of undiluted dexmedetomidine (19.4 mcg/kg) had cardiac arrest from which he was successfully resuscitated.
Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations for IGALMI.

11 DESCRIPTION

IGALMI contains dexmedetomidine, a central alpha-2 adrenergic receptor agonist, present as dexmedetomidine hydrochloride, the S-enantiomer of medetomidine chemically described as 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride. The empirical formula is $C_{13}H_{16}N_2$•HCl with a molecular weight of 236.7 g/mol. The structural formula of dexmedetomidine hydrochloride is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in octanol/water at pH 7.4 is 2.89.

IGALMI is for sublingual or buccal use. Each IGALMI sublingual film contains 120 mcg or 180 mcg of dexmedetomidine equivalent to 141.8 mcg and 212.7 mcg of dexmedetomidine hydrochloride, respectively.

IGALMI for use in the healthcare supervised setting contains the following inactive ingredients: FD&C Blue #1 colorant, hydroxypropyl cellulose, peppermint oil, polyethylene oxide, and sucralose.

IGALMI for use in the unsupervised setting contains the following inactive ingredients: Black Ink (shellac, black iron oxide), FD&C Blue #1 colorant, hydroxypropyl cellulose, peppermint oil, polyethylene oxide, and sucralose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmedetomidine is a central alpha-2 adrenergic receptor agonist. The mechanism of action of

IGALMI in the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder is thought to be due to activation of presynaptic alpha-2 adrenergic receptors.

12.2 Pharmacodynamics

Dexmedetomidine acts as an agonist at alpha-2 adrenergic receptors with binding affinities (Ki values) of 4 to 6 nM at the alpha-2 adrenergic receptor subtypes.

Cardiac Electrophysiology

IGALMI exhibits a concentration-dependent QT prolongation. Table 5 shows the mean (upper 90% confidence interval) QTcF increase from baseline for respective dosing regimens *[see Warnings and Precautions (5.2)]*.

Table 5: QTcF Increase from Baseline by Dosage of IGALMI

IGALMI Dosage	Mean QTcF Increase from Baseline (upper 90% confidence interval)
120 mcg single dose	6 (7) msec
120 mcg + 2 additional doses of 60 mcg 2 hours apart (total 3 doses)	8 (9) msec
180 mcg single dose	8 (11) msec
180 mcg + 2 additional doses of 90 mcg 2 hours apart (total 3 doses)	11 (14) msec

12.3 Pharmacokinetics

Dexmedetomidine exposure (C_{max} and AUC) increased in a dose proportional manner in the dose range of 20 mcg (0.17 times the recommended initial dose of 120 mcg in adults) to 180 mcg after single sublingual administration of IGALMI.

The mean time for film to dissolve in the mouth was about 6 to 8 minutes and 18 minutes following sublingual and buccal administration, respectively. Dexmedetomidine was quantifiable in plasma generally after 5 to 20 minutes post dosing.

Absorption

The absolute bioavailability of dexmedetomidine was about 72% and 82% following sublingual and buccal administration of IGALMI, respectively. When water was taken at two hours post dose, comparable exposures of dexmedetomidine were observed when IGALMI was administered by both routes.

Mean maximal plasma concentrations of dexmedetomidine were reached approximately two hours after sublingual or buccal administration of IGALMI. Following sublingual administration of 40 mcg of IGALMI (0.33 times the recommended initial dose of 120 mcg in adults) with water drinking at two hours post dose and 20 mcg dexmedetomidine intravenous infusion for 90 minutes in healthy volunteers:

- The mean peak plasma concentration (C_{max}) of dexmedetomidine was 143 ng/L and 144 ng/L, respectively.
- The mean area under concentration curve (AUC) of dexmedetomidine was 851 ng•h/L

and 584 ng•h/L, respectively.

Effect of Drinking Water on Absorption
Compared to drinking water at two hours post sublingual administration of IGALMI, early water intake (as early as 15 minutes post dose) had minimal effects on the rate or extent of absorption of dexmedetomidine.

Effects of early water intake (i.e., before two hours post dose) on the absorption of dexmedetomidine have not been evaluated following buccal administration.

Distribution
The steady-state volume of distribution (Vss) of dexmedetomidine following intravenous administration was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin, and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of dexmedetomidine IV were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline, and digoxin by dexmedetomidine hydrochloride injection was explored in vitro and none of these compounds appeared to be significantly displaced by intravenous dexmedetomidine.

Elimination
Metabolism
Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450-mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6 with a minor role of CYP1A2, CYP2E1, CYP2D6, and CYP2C19) of dexmedetomidine to generate 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide.

Excretion
The mean terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2.8 hours following sublingual or buccal administration of IGALMI. Clearance is estimated to be approximately 39 L/h following intravenous administration.

A mass balance study demonstrated that after nine days, an average of 95% of the radioactivity, following intravenous administration of radiolabeled dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products

Reference ID: 5904216

of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide accounted for approximately 18% of the dose in urine. The N-methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Specific Populations

Male and Female Patients

There was no observed difference in the pharmacokinetics of intravenous dexmedetomidine due to sex.

Geriatric Patients

The pharmacokinetic profile of intravenous dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of intravenous dexmedetomidine in young (18–40 years), middle age (41–65 years), and geriatric (>65 years) subjects.

Patients with Hepatic Impairment

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 *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].* After an intravenous infusion of 0.6 mcg/kg of dexmedetomidine 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.

Patients with Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V) were not significantly different in patients with creatinine clearance <30 mL/minute compared to subjects with normal renal function.

Drug Interaction Studies

In vitro studies in human liver microsomes demonstrated no evidence of cytochrome P450-mediated drug interactions that are likely to be of clinical relevance. In vitro studies using expressed major human transporter proteins demonstrated no evidence of transporter-mediated drug interactions which are likely to be of any clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Dexmedetomidine did not increase the incidence of tumors in male and female Tg ras H2 mice treated for 26 weeks twice daily (BID) into the oral cavity at doses of 20, 80, and 180 mcg/kg/day or 30, 100, and 240 mcg/kg/day, respectively.

Mutagenesis

Dexmedetomidine was not mutagenic in the in vitro Ames bacterial reverse mutation test or mammalian mouse lymphoma cell forward mutation assay. Dexmedetomidine was not clastogenic in the in vitro human lymphocyte chromosome aberration test in the absence or presence of human liver S9 metabolic activation; however, a weak clastogenic response was noted in the presence of rat liver S9 metabolic activation. Dexmedetomidine was not clastogenic in the in vivo bone marrow micronucleus test in CD-1 mice, although there was some evidence for clastogenicity in NMRI mice.

Impairment of Fertility

Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (1.5 times the MRHD of 360 mcg/day on a mg/m^2 basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.

13.2 Animal Toxicology and/or Pharmacology

Dexmedetomidine was administered sublingually, twice a day (BID) to rats and dogs in repeat dose toxicity studies up to 26 weeks and 39 weeks, respectively. In dogs, a sublingual lesion (inflammation, necrosis, myofiber degeneration, and hemorrhage) occurred in a single male dog (out of 32 treated dogs) in a 28-day study dosed 320 mcg/day (equivalent to the MRHD of 360 mcg/day). Similar findings were not observed in dogs from longer duration toxicity studies up to 39 weeks; however, the high dose was 280 mcg/day (less than the MRHD of 360 mcg/day).

14 CLINICAL STUDIES

The effectiveness of IGALMI for the acute treatment of agitation associated with schizophrenia, schizoaffective disorder, or bipolar I or II disorder in adults was established in two randomized, double-blind, placebo-controlled, fixed-dose studies (Studies 1 and 2):

- Study 1 (NCT04268303) included 380 patients who met DSM-5 criteria for schizophrenia, schizoaffective or schizophreniform disorder. The population was 18 to 71 years of age (mean age was 46 years old); 37% female and 63% male; 78% Black, 20% White, 1% multiracial, and 1% Asian.
- Study 2 (NCT04276883) included 378 patients who met DSM-5 criteria for bipolar I or II disorder. The population was 18 to 70 years of age (mean age was 47 years old); 55% female and 45% male; 56% Black, 41% White, 1% Asian, 1% multiracial, and 1% other.

The Positive and Negative Syndrome Scale-Excited Component (PEC) is an investigator-rated instrument consisting of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is scored on a scale from 1 to 7 (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate-severe, 6=severe, 7=extremely severe). The total PEC score ranges from 5 to 35, with higher scores reflecting greater overall symptom severity. For enrollment in the studies, patients had to be judged to be clinically agitated with a total PEC score of ≥ 14, with at least one individual item score ≥ 4. In both studies, patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment.

Patients were randomized to receive a single sublingual dose of 180 mcg of IGALMI, 120 mcg

of IGALMI, or placebo. The primary efficacy endpoint in both studies was the change from baseline in the PEC score, assessed two hours following the initial dose. The key secondary endpoint was the time to effect onset, assessed by measuring the change from baseline in PEC score at 10, 20, 30, 45, 60, and 90 minutes after the initial dose administration.

In both studies, mean baseline PEC scores were similar in all treatment groups (Table 6). The mean change from baseline in the PEC total score at two hours after the first dose in patients treated with 180 mcg and 120 mcg of IGALMI was statistically greater than patients who received placebo (Table 6).

Examination of population subsets (race and sex) on the primary endpoint did not show evidence for differential responsiveness between White and Black or female and male patients. The clinical studies did not include enough patients of other races or patients ≥65 years of age to determine whether there were differences in effectiveness for those groups.

Table 6: Primary Efficacy Results for Change from Baseline in the PEC Score at Two Hours in Agitated Patients with Schizophrenia or Schizoaffective Disorder or Bipolar I or II Disorder (Studies 1 and 2)

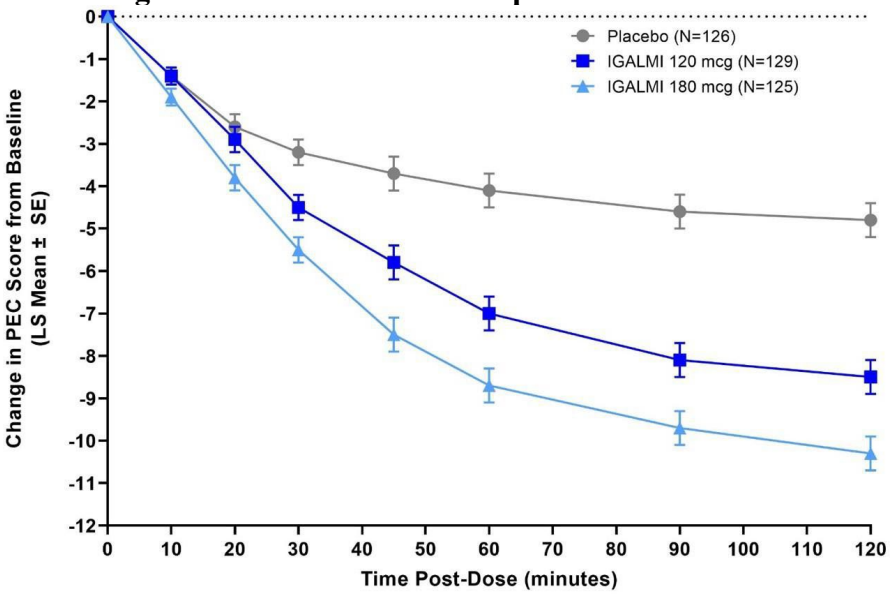
Study	**Treatment Group**	**Number of Patients**	**Mean Baseline PEC Score** (SD)	**LS Mean Change from Baseline to 2 Hours Post First Dose** (SE)	**LS Mean Difference** (95% CI)
Study 1	IGALMI 180 mcg*	125	17.6 (2.7)	-10.3 (0.4)	-5.5 (-6.5, -4.4)
	IGALMI 120 mcg*	129	17.5 (2.5)	-8.5 (0.4)	-3.7 (-4.8, -2.7)
	Placebo	126	17.6 (2.3)	-4.8 (0.4)	-
Study 2	IGALMI 180 mcg*	126	18.0 (3.0)	-10.4 (0.4)	-5.4 (-6.5, -4.3)
	IGALMI 120 mcg*	126	18.0 (2.7)	-9.1 (0.4)	-4.1 (-5.1, -3.0)
	Placebo	126	17.9 (2.9)	-5.0 (0.4)	-

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=unadjusted confidence interval; PEC=Positive and Negative Syndrome Scale-Excited Component
*IGALMI doses that were statistically significantly superior to placebo after adjusting for multiplicity.

Figures 1 and 2 show the changes from baseline in PEC score at each time point assessed up to two hours following the initial dose. In Study 1, the decrease in agitation with IGALMI, compared to placebo, was statistically significant beginning at 20 minutes following dosing with the 180 mcg dose and 30 minutes after the 120 mcg dose. In Study 2, the decrease in agitation with IGALMI, compared to placebo, was statistically significant beginning at 20 minutes after treatment with both 120 mcg and 180 mcg doses.

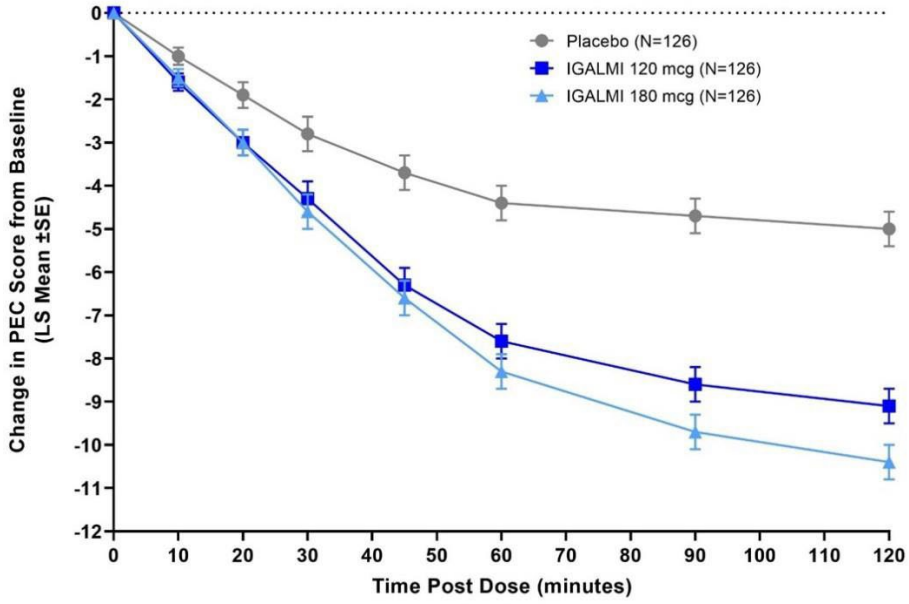
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Figure 1: Mean Change from Baseline in PEC Score through Two Hours after a Single Dose in Agitated Patients with Schizophrenia or Schizoaffective Disorder (Study 1)



LS = least square; PEC = Positive and Negative Syndrome Scale – Excited Component;
SE = standard error
PEC baseline scores were: 17.6, 17.5, and 17.6 in the placebo, IGALMI 120 mcg, and IGALMI 180 mcg groups , respectively

Figure 2: Mean Change from Baseline in PEC Score through Two Hours after a Single Dose in Agitated Patients with Bipolar I or II Disorder (Study 2)



LS = least square; PEC = Positive and Negative Syndrome Scale – Excited Component;
SE = standard error
PEC baseline scores were: 17.9, 18.0, and 18.0 in the placebo, IGALMI 120 mcg, and IGALMI 180 mcg groups, respectively

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IGALMI (dexmedetomidine) sublingual film is supplied as a blue, rectangular sublingual film

containing two darker blue spots. The film for use in the unsupervised setting is also imprinted with “D12” in black. Films are packaged individually in heat-sealed foil pouches.

IGALMI is available in configurations intended for use in either the unsupervised setting or the healthcare supervised setting. The available strengths and package configurations for each setting are provided in Table 7 (Healthcare Supervised) and Table 8 (Unsupervised).

Table 7: IGALMI Sublingual Film Packaging Configurations – Healthcare Supervised Setting

Strength	Film Description	Package Configuration	NDC
120 mcg	Blue rectangular film with two darker blue spots	Carton of 10 individual foil-pouch films	81092-1120-1
120 mcg	Blue rectangular film with two darker blue spots	Carton of 30 individual foil-pouch films	81092-1120-3
180 mcg	Blue rectangular film with two darker blue spots	Carton of 10 individual foil-pouch films	81092-1180-1
180 mcg	Blue rectangular film with two darker blue spots	Carton of 30 individual foil-pouch films	81092-1180-3

Table 8: IGALMI Sublingual Film Packaging Configurations – Unsupervised Setting

Strength	Film Description	Package Configuration	NDC
120 mcg	Blue rectangular film with two darker blue spots and black imprint “D12”	Carton of 10 individual foil-pouch films, child-resistant	81092-0120-1

16.2 Storage and Handling

Store IGALMI at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*.

Keep IGALMI in the foil pouch until ready to administer.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Advise patients to place IGALMI under the tongue, close to the base of the tongue, on the left or right side (sublingual) or between the lower lip and gum (buccal).

Advise patients not to chew or swallow IGALMI. Also, advise patients not to eat or drink for at least 15 minutes after sublingual administration, or at least 1 hour after buccal administration *[see Dosage and Administration (2.1, 2.4)]*.

Unsupervised Setting: Advise patients to take IGALMI once for agitation. If agitation recurs, patients may be advised to take an additional dose after at least 12 hours have passed since the

previous dose. Advise patients not to take more than one dose within a 12-hour period and to wash and dry hands before handling the film *[see Dosage and Administration (2.3, 2.4)]*.

Advise patients to continue treatment for their underlying psychiatric disorder and to tell their healthcare provider if they are using IGALMI frequently *[see Dosage and Administration (2.2, 2.3)]*.

Hypotension, Orthostatic Hypotension, and Bradycardia
Advise patients that IGALMI can cause dose-dependent hypotension, orthostatic hypotension, and bradycardia. Warn patients of the risk of syncope and falls. Advise patients to hydrate and to sit or lie down after IGALMI administration. Advise patients to tell their healthcare provider if they experience dizziness, lightheadedness, fainting, or other symptoms of hypotension or bradycardia *[see Warnings and Precautions (5.1)]*.

QT Interval Prolongation
Inform patients to consult their healthcare provider immediately if they feel faint or have heart palpitations *[see Warnings and Precautions (5.2)]*.

Somnolence
Advise patients that IGALMI can cause somnolence and may impair the ability to perform tasks that require complex motor and mental skills. Advise patients that they should avoid doing activities that require them to be alert, such as driving a car or operating machinery, for at least eight hours after taking IGALMI *[see Warnings and Precautions (5.3)]*.

Risk of Withdrawal Reactions and Tolerance
Advise patients to use IGALMI only as prescribed. Inform patients that using IGALMI more often or at higher doses than prescribed may increase the risk of withdrawal reactions and tolerance *[see Warnings and Precautions (5.4, 5.5)]*.

Lactation
Advise women who are breastfeeding to monitor the breastfed infant for irritability *[see Use in Specific Populations (8.2)]*.

Storage
Advise patients to keep IGALMI in the foil pouch until ready to administer *[see How Supplied/Storage and Handling (16.2)]*.

Manufactured for:
Teva Neuroscience, Inc.
Parsippany, NJ 07054

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MEDICATION GUIDE
IGALMI® (i-GAL-mee)
(dexmedetomidine) sublingual film
for sublingual or buccal use

What is the most important information I should know about IGALMI?

IGALMI can cause serious side effects, including:

Low blood pressure (hypotension), **low blood pressure when standing after sitting or lying** (orthostatic hypotension) and **slow heart rate** (bradycardia). IGALMI can lower your blood pressure and heart rate. Lightheadedness or fainting may happen when standing up too quickly from a sitting or lying position. You should drink fluids and sit or lie down after taking IGALMI. Get up slowly after taking IGALMI to help prevent your risk of fainting or falling. Tell your healthcare provider right away if you get any of the following signs and symptoms:

- dizziness
- lightheadedness
- fainting
- tiredness or weakness
- feeling that your heart is pounding or racing (palpitations)
- shortness of breath
- chest pain

Before and during treatment with IGALMI your healthcare provider will check your blood pressure, heart rate, and your risks for fainting and falling.

See **"What are the possible side effects of IGALMI?"** for more information about side effects.

What is IGALMI?

IGALMI is a prescription medicine used for the treatment of sudden (acute) agitation in adults with schizophrenia schizoaffective disorder, or bipolar I or bipolar II disorder.

It is not known if IGALMI is safe and effective in children.

Before taking IGALMI, **tell your healthcare provider about all of your medical conditions, including if you**:

- have heart problems
- have a slow heart rate
- have low blood pressure (hypotension)
- have long-term (chronic) high blood pressure
- have a history of fainting
- have low blood or fluid levels in your body (hypovolemia)
- have diabetes
- have low blood potassium or magnesium levels
- are 65 years of age or older
- have liver problems
- are pregnant or plan to become pregnant. It is not known if IGALMI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. IGALMI passes into breast milk. If you breastfeed during treatment with IGALMI, tell your healthcare provider if the baby is irritable. Talk to your healthcare provider about the best way to feed your baby during treatment with IGALMI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
IGALMI and other medicines may affect each other causing possible serious side effects. IGALMI may affect the way other medicines work, and other medicines may affect how IGALMI works.

Especially tell your healthcare provider if you take:

- blood pressure medicines
- medicines for heart problems
- medicines that make you sleepy, such as sleeping or pain (opioids) medicines

Know the medicines that you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine. **Do not start any new medicine during treatment with IGALMI without talking to your healthcare provider first.**

How should I take IGALMI?

- **See the Instructions for Use that come with IGALMI for information about the right way to take IGALMI.**
- Take IGALMI exactly as your healthcare provider tells you to take it.
- IGALMI is for sublingual (under the tongue) or buccal (between the lower lip and gum) use.
- Allow the film to dissolve completely.
- **Do not** split, cut, chew, or swallow the film.
- **Do not** eat or drink:
  - for at least 15 minutes after placing the film under the tongue, or
  - for at least 1 hour after placing the film between the lower lip and gum.

- **Do not** take more than 1 (one) dose in a 12-hour period. If agitation comes back, you may take another dose of IGALMI **after at least 12 hours** from taking the previous dose.
- You should continue treatment for mental health problems and tell your healthcare provider if you are using IGALMI frequently.
- If you take too much IGALMI, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking IGALMI?

- **Do not** drive, operate machinery, or do dangerous activities for at least 8 hours after taking IGALMI. IGALMI may make you sleepy, drowsy, and affect your judgement, thinking, or motor skills.

What are the possible side effects of IGALMI?

IGALMI may cause serious side effects, including:

- **See "What is the most important information I should know about IGALMI?"**
- **Changes in electrical activity of your heart** (QT prolongation). IGALMI can cause a heart problem called QT prolongation that can lead to abnormal heart rhythms and sudden death. You have an increased risk of QT prolongation if you have heart problems and if you take IGALMI with other medicines that affect your heart rhythm. Your healthcare provider may do tests during treatment with IGLAMI to check the electrical activity of your heart (EKG) and your body salts (electrolytes). Tell your healthcare provider right away if you get signs and symptoms of QT prolongation including:
  - dizziness
  - fainting
  - feeling that your heart is pounding or racing (palpitations)
  - chest pain
- **Sleepiness or drowsiness.** IGALMI can cause sleepiness, tiredness and sluggishness. See "**What should I avoid while taking IGALMI**?"
- **Risk of withdrawal reactions and tolerance.** Your body can become used to IGALMI and become less effective (tolerance). Taking IGALMI more often or at higher doses than prescribed may increase the risk of withdrawal reactions and tolerance. Tell your healthcare provider if you feel IGALMI is not working as well as it used to.

The most common side effects of IGALMI in the healthcare supervised setting include:

- sleepiness or drowsiness
- numbness or tingling in the mouth
- dizziness
- dry mouth
- low blood pressure
- low blood pressure when standing after sitting or lying down

The most common side effects of IGALMI in the unsupervised setting include:

- sleepiness or drowsiness
- dry mouth
- dizziness
- numbness or tingling in the mouth

These are not all the possible side effects of IGALMI.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store IGALMI?

- Store IGALMI at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep IGALMI in the foil pouch until you are ready to take your dose.
- IGALMI comes in a child-resistant pouch (unsupervised setting).

Keep IGALMI and all medicines out of the reach of children.

General information about the safe and effective use of IGALMI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use IGALMI for a condition for which it was not prescribed. Do not give IGALMI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IGALMI that is written for health professionals.

What are the ingredients in IGALMI?

Active ingredient: dexmedetomidine hydrochloride
Inactive ingredients of IGALMI for use in the healthcare supervised setting: FD&C Blue #1 colorant, hydroxypropyl cellulose, peppermint oil, polyethylene oxide, and sucralose.
Inactive ingredients of IGALMI for use in the unsupervised setting: Black ink (shellac, black iron oxide) FD&C Blue #1 colorant, hydroxypropyl cellulose, peppermint oil, polyethylene oxide, and sucralose.

Manufactured for:
Teva Neuroscience, Inc.
Parsippany, NJ 07054
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This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 11/2026

INSTRUCTIONS FOR USE

IGALMI® (i-GAL-mee)

(dexmedetomidine) sublingual film

for sublingual or buccal use

These Instructions for Use contain information on how to take IGALMI.

Important Information You Need to Know Before Taking IGALMI.

- **Do not** take IGALMI until:
  - you have read and understand these instructions.
  - you have reviewed the steps with your healthcare provider on how to take it.
- If you are not sure about how or when to take IGALMI, **call your healthcare provider.**
- IGALMI is a film for sublingual (under your tongue) or buccal (between your lower lip and gum) use.
- Allow the film to dissolve completely.
- **Do not** split, cut, chew, or swallow the film.
- **Do not** take more than 1 (one) dose in a 12-hour period.
- Each IGALMI film comes in a sealed child-resistant pouch. **Do not** open the pouch until you are ready to take your dose of IGALMI.
- Check the expiration date printed on the pouch. **Do not** take IGALMI if it is expired or if the pouch has been previously cut or pierced. Throw away IGALMI in your household trash and get a new pouch that is not expired or damaged.

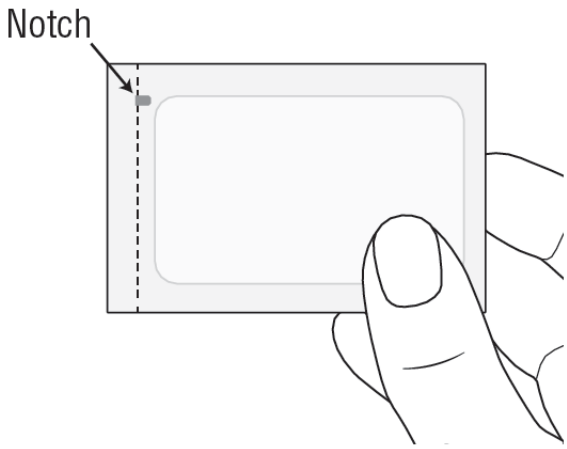
Step 1. Preparing to Take IGALMI

- Make sure your hands are clean and dry. Take one pouch of IGALMI out of the carton.

Step 2. Folding the IGALMI Pouch

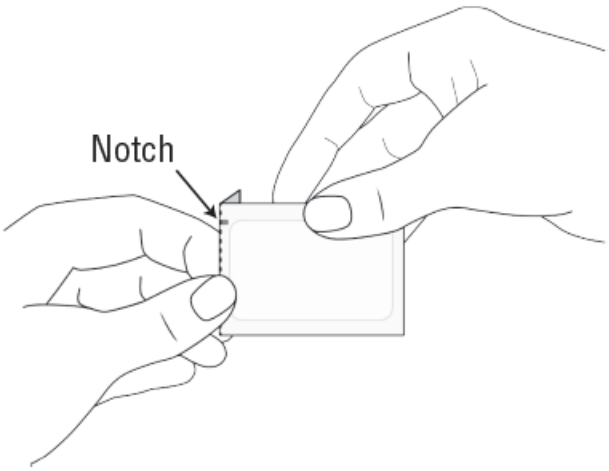
- Locate the notch on the pouch (**See Figure A**)

Figure A



- Fold the sealed foil pouch across the dotted line (**See Figure B**).

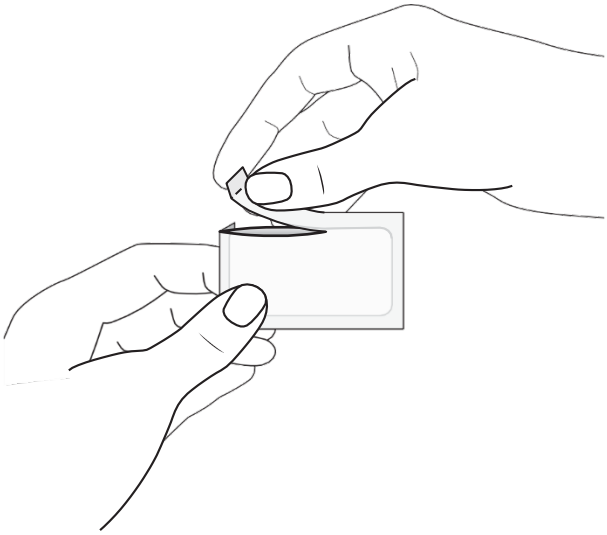
Figure B



Step 3. Opening the pouch

- Tear the pouch at notch. (see **Figure C**).

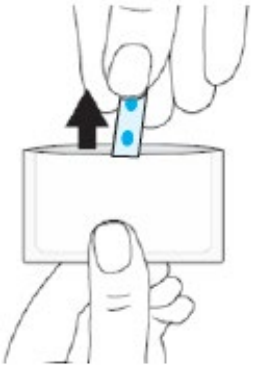
Figure C



Step 4. Removing IGALMI from the pouch

- Remove the film from the pouch (see **Figure D**).

Figure D



- **If the film tears or dissolves in your hands** (hands were not dry enough) when it is removed from the pouch, throw away (dispose of) the film as described below (see Throwing away (disposing of) IGALMI) and get a new film. **Repeat steps 1 to 3** with the new film.

Step 5: Administering IGALMI

- Take the IGALMI film right away after opening the pouch and removing the film.
- **Do not** split, cut, chew, or swallow the film.
- Administer the film as described in Figure E or Figure F. Note different waiting times before eating and drinking.

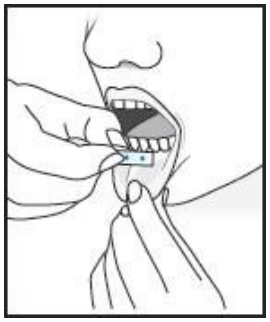
Figure E: Sublingual Administration **Or** **Figure F: Buccal Administration**

Place the film under the tongue. The film will stick in place.



Do not eat or drink for 15 minutes.

Place the film between the lower lip and gum. The film will stick in place.



Do not eat or drink for one hour.

- Close the mouth and allow the film to dissolve.

Throwing away (disposing of) IGALMI

- Throw away (dispose of) any unused or expired IGALMI in your household trash.
- Throw away the empty pouches in your household trash.

Storing IGALMI

- Store IGALMI at room temperature between 68°F to 77°F (20°C to 25°C).
- IGALMI comes in a child-resistant foil pouch (unsupervised setting). Keep IGALMI in the foil pouch until you are ready to take your dose.

Keep IGALMI and all medicines out of the reach of children.

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