HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BREKIYA® safely and effectively. See full prescribing information for BREKIYA®.

BREKIYA® (dihydroergotamine mesylate) injection, for subcutaneous use

Initial U.S. Approval: 1946

WARNING: PERIPHERAL ISCHEMIA FOLLOWING COADMINISTRATION WITH STRONG CYP3A4 INHIBITORS

See full prescribing information for complete boxed warning.

Serious and/or life-threatening peripheral ischemia has been associated with the co-administration of dihydroergotamine with strong CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of BREKIYA with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.1)].*

----------INDICATIONS AND USAGE----------

BREKIYA is an ergotamine derivative indicated for the acute treatment of migraine with or without aura and the acute treatment of cluster headaches in adults. (1)

Limitations of Use

BREKIYA is not indicated for the preventive treatment of migraine or for the management of hemiplegic migraine or migraine with brainstem aura. (1)

----------DOSAGE AND ADMINISTRATION----------

- For subcutaneous injection only. (2.1)
- Recommended dosage is 1 mg administered subcutaneously as a single 1 mL autoinjector. (2.1)
- Do not exceed 3 mg (3 doses) in a 24-hour period. (2.1)
- Do not exceed 6 mg (6 doses) in a week. (2.1)
- Prior to initiation, a cardiovascular evaluation is recommended. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 1 mg/mL dihydroergotamine mesylate as a 1 mL single-dose autoinjector. (3)

----------CONTRAINDICATIONS----------

- Concomitant use of strong CYP3A4 inhibitors (4)
- Ischemic heart disease or coronary artery vasospasm (4)
- Uncontrolled hypertension, peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment (4)
- Concomitant use of other 5-HT_1 agonists or ergotamine-containing or ergot-type medications within 24 hours (4)
- Hypersensitivity to dihydroergotamine, ergot alkaloids, latex, or any of the ingredients in BREKIYA (4)
- Concomitant use with peripheral and central vasoconstrictors (4)

----------WARNINGS AND PRECAUTIONS----------

- *Myocardial Ischemia and/or Infarction, Other Cardiac Adverse Reactions, and Fatalities:* In patients with risk factors predictive of coronary artery disease, consider first dose administration under medical supervision with an electrocardiogram. (5.2)
- *Cerebrovascular Adverse Reactions and Fatalities:* Cerebrovascular hemorrhage, subarachnoid hemorrhage, and stroke have been reported; discontinue BREKIYA if suspected. (5.3)
- *Other Vasospasm Related Adverse Reaction:* BREKIYA may cause vasospasm or elevation in blood pressure. Discontinue if signs or symptoms of vasoconstriction develop. (5.4, 5.5)
- *Medication Overuse Headache:* Detoxification may be necessary. (5.6)
- *Preterm Labor:* Advise pregnant women of the risk. (5.7, 8.1)
- *Fibrotic Complication:* Pleural and retroperitoneal fibrosis have been reported following prolonged daily use of dihydroergotamine mesylate. Do not exceed the BREKIYA dosing guidelines or use for chronic daily administration. (5.8)

----------ADVERSE REACTIONS----------

Serious cardiac events (including fatal) that have been reported with dihydroergotamine mesylate injection use include coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- *Beta Blockers/Nicotine:* May potentiate/provoke vasoconstriction. (7.3, 7.5)
- *Selective Serotonin Reuptake Inhibitors:* Weakness, hyperreflexia, and incoordination may occur with coadministration. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Lactation: Advise not to use during breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PERIPHERAL ISCHEMIA FOLLOWING COADMINISTRATION WITH STRONG CYP3A4 INHIBITORS

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with strong CYP3A4 inhibitors. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of BREKIYA with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7.1)].*

1 INDICATIONS AND USAGE

BREKIYA is indicated for the acute treatment of migraine with or without aura and the acute treatment of cluster headaches in adults.

Limitations of Use

BREKIYA is not indicated for the preventive treatment of migraine.
BREKIYA is not indicated for the management of hemiplegic migraine or migraine with brainstem aura.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

BREKIYA autoinjector is for subcutaneous injection only.

The recommended dose of BREKIYA is 1 mg administered subcutaneously via a single 1 mL autoinjector. The dose may be repeated, as needed, at 1-hour intervals to a total maximum of 3 mg (3 doses) in a 24-hour period. Do not exceed 6 mg (6 doses) total in a week.

2.2 Assessment Prior to First Dose

Prior to initiation of BREKIYA, a cardiovascular evaluation is recommended *[see Warnings and Precautions (5.3)]*. For patients with risk factors predictive of coronary artery disease who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of BREKIYA take place in the setting of an equipped healthcare facility.

2.3 Important Administration Instructions

See the "Instructions for Use" for detailed steps for administering the subcutaneous injection using the autoinjector.

Preparation

- BREKIYA is a prefilled, single-dose disposable autoinjector intended to be given subcutaneously into the skin of the middle thigh.
- Rotate injection sites. Choose an injection site at least 2 inches away from the last injection site.
- Do not inject into moles, scars, birthmarks, or areas where the skin is tender, bruised, red, or hard.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Carefully examine the liquid medication for discoloration, cloudiness, floating flakes or particles. Administer only if clear and colorless.

Administration

- Remove the red needle cap by pulling it straight off.
- Position the autoinjector straight onto the cleaned injection site with the white safety guard resting on the skin. Push the autoinjector down and press and release the gray activation button to start the injection. A "click" will sound when the injection starts.
- The autoinjector takes approximately 10 seconds to deliver the dose; when the viewing window is fully blocked (completely blue), the full dose has been administered.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1 mg/mL dihydroergotamine mesylate as a clear, colorless solution in a 1 mL single-dose autoinjector.

4 CONTRAINDICATIONS

BREKIYA is contraindicated in patients:

- with concomitant use of strong CYP3A4 inhibitors *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*
- with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or patients who have clinical symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal's variant angina *[see Warnings and Precautions (5.4)]*
- with uncontrolled hypertension *[see Warnings and Precautions (5.5)]*
- with peripheral arterial disease
- with sepsis
- following vascular surgery
- with severe hepatic impairment
- with severe renal impairment
- with known hypersensitivity to dihydroergotamine, ergot alkaloids, latex, or any of the ingredients in BREKIYA *[see Warnings and Precautions (5.9)]*
- with recent use (i.e., within 24 hours) of other 5-HT1 agonists, ergotamine-containing or ergot-type medications *[see Drug Interactions (7.2)]*
- with concomitant use of peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Ischemia Following Coadministration with Strong CYP3A4 Inhibitors

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine and strong CYP3A4 inhibitors. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or and ischemia of the extremities is increased. Hence, concomitant use of BREKIYA with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4) and Drug Interactions (7.1)]*.

5.2 Myocardial Ischemia and/or Infarction, Other Cardiac Adverse Reactions, and Fatalities

The potential for cardiac adverse reactions exists with BREKIYA treatment. Serious adverse cardiac events, including some that have been fatal, have occurred following use of dihydroergotamine mesylate. These events have included acute myocardial infarction, life-threatening disturbances of cardiac rhythm (e.g., ventricular tachycardia and ventricular fibrillation), coronary artery vasospasm, and transient myocardial ischemia.

Prior to initiation of BREKIYA, a cardiovascular evaluation is recommended to determine if the patient is free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. If, during the cardiovascular evaluation, the patient's medical history (including risk factors), or electrocardiographic investigation findings are consistent with coronary artery vasospasm or myocardial ischemia, BREKIYA should not be administered *[see Contraindications (4)]*.

For patients with risk factors predictive of coronary artery disease (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of coronary artery disease, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age) who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of BREKIYA take place in the setting of an equipped healthcare facility, unless the patient has previously received dihydroergotamine. During the interval immediately following the first use of BREKIYA, an electrocardiogram is recommended in those patients with risk factors because ischemia can occur in the absence of clinical symptoms.

5.3 Cerebrovascular Adverse Reactions and Fatalities

The potential for adverse cerebrovascular events exists with BREKIYA treatment. Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the dihydroergotamine mesylate having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). Discontinue BREKIYA if a cerebrovascular event is suspected.

5.4 Other Vasospasm-Related Adverse Reactions

BREKIYA, like other ergot alkaloids, may cause vasospastic reactions other than coronary artery vasospasm. Myocardial, peripheral vascular, and colonic ischemia have been reported with dihydroergotamine mesylate.

Dihydroergotamine associated vasospastic phenomena may also cause muscle pains, numbness, coldness, pallor, and cyanosis of the digits. In patients with compromised circulation, persistent vasospasm may result in gangrene or death. BREKIYA should be discontinued immediately if signs or symptoms of vasoconstriction develop.

Patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT agonist, including BREKIYA, should be evaluated by a healthcare provider.

5.5 Increase in Blood Pressure

Significant elevation in blood pressure has been reported on rare occasions in patients with and without a history of hypertension treated with dihydroergotamine mesylate. BREKIYA is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4)]*.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamines, triptans, opioids, or a combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication

overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Preterm Labor

Based on the mechanism of action of dihydroergotamine and findings from the published literature, BREKIYA may cause preterm labor. Avoid use of BREKIYA during pregnancy *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.2)]*.

5.8 Fibrotic Complications

The potential for fibrotic complications exists with BREKIYA treatment. There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs has been associated with cardiac valvular fibrosis. Rare cases have also been reported in association with the use of dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with cardiac valvular fibrosis.

Administration of BREKIYA should not exceed the dosing guidelines and should not be used for chronic daily administration *[see Dosage and Administration (2.1)]*.

5.9 Hypersensitivity

The rigid needle shield of the BREKIYA autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex. BREKIYA is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids or latex.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Peripheral Ischemia Following Coadministration with Strong CYP3A4 Inhibitors *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Myocardial Ischemia and/or Infarction, Other Adverse Cardiac Events, and Fatalities *[see Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions and Fatalities *[see Warnings and Precautions (5.3)]*
- Other Vasospasm Related Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.5)]*
- Medication Overuse Headache *[see Warnings and Precautions (5.6)]*
- Preterm Labor *[see Warnings and Precautions (5.7)]*
- Fibrotic Complications *[see Warnings and Precautions (5.8)]*
- Hypersensitivity *[see Warnings and Precautions (5.9)]*

The following adverse reactions associated with the use of dihydroergotamine were identified in clinical studies or postmarketing reports. 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 the drug exposure.

Serious cardiac events, including some that have been fatal, have occurred following use of dihydroergotamine. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate *[see Warnings and Precautions (5.8)]*.

Vasospasm, paresthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, increased sweating, and pleural and retroperitoneal fibrosis occurred after long-term use of dihydroergotamine.

Cases of myocardial infarction and stroke have been reported following the use of dihydroergotamine *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

There have been rare reports of serious adverse events in connection with the coadministration of intravenous administration of dihydroergotamine and strong CYP3A4 inhibitors resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities *[see Warnings and Precautions (5.1)]*. The use of strong CYP3A4 inhibitors with BREKIYA is contraindicated *[see Contraindications (4)]*. Administer moderate CYP3A4 inhibitors with caution.

7.2 Triptans

Triptans (serotonin [5-HT 1B/1D receptor agonists) have been reported to cause coronary artery vasospasm, and its effect could be additive with BREKIYA. Therefore, triptans and BREKIYA should not be taken within 24 hours of each other *[see Contraindications (4)]*.

7.3 Beta Blockers

There have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by blocking the vasodilating property of epinephrine.

7.4 Vasoconstrictors

BREKIYA is contraindicated for use with peripheral and central vasoconstrictors because the combination may cause synergistic elevation of blood pressure *[see Warnings and Precautions (5.5)]*.

7.5 Nicotine

Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy *[see Warnings and Precautions (5.2, 5.4)]*.

7.6 Selective Serotonin Reuptake Inhibitors

Weakness, hyperreflexia, and incoordination have been reported rarely when 5-HT_1 agonists have been co-administered with selective serotonin reuptake inhibitors (SSRI's) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published literature indicate an increased risk of preterm delivery with dihydroergotamine, the active moiety in BREKIYA, use during pregnancy. Avoid use of BREKIYA during pregnancy *[see Warnings and Precautions (5.9)]*. Data collected over decades have shown no increased risk of major birth defects or miscarriage with the use of dihydroergotamine mesylate during pregnancy.

In animal reproduction studies, adverse effects on development were observed following administration of dihydroergotamine mesylate during pregnancy (decreased fetal body weight and/or skeletal ossification) in rats and rabbits or during pregnancy and lactation in rats (decreased body weight and impaired reproductive function in the offspring) at doses that were not associated with maternal toxicity *(see Data).*

The estimated rate of major birth defects (2.2% to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine. 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 miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

Intranasal administration of dihydroergotamine mesylate to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weight and/or skeletal ossification at doses of 0.16 mg/day or greater. A no-effect level for adverse effects on embryofetal toxicity was not identified in rats. Intranasal administration of dihydroergotamine mesylate to pregnant rabbits throughout organogenesis resulted in decreased skeletal ossification at 3.6 mg/day. The no-effect dose for adverse effects on embryofetal toxicity in rabbits was 1.2 mg/day.

Intranasal administration of dihydroergotamine mesylate to female rats throughout pregnancy and lactation resulted in decreased body weight and impaired reproductive function (decreased mating indices) in the offspring at doses of 0.16 mg/day or greater. A no-effect dose for adverse developmental effects in rats was not established. Effects on offspring development occurred at doses below those that produced evidence of maternal toxicity in these studies.

Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

8.2 Lactation

Risk Summary

There are no data on the presence of dihydroergotamine in human milk; however, ergotamine, a related drug, is excreted in human milk. There are reports of vomiting, diarrhea, weak pulse, and unstable blood pressure in breastfed infants exposed to ergotamine. BREKIYA may reduce milk supply because it may decrease prolactin levels.

Because of the potential for reduced milk supply and serious adverse events in the breastfed infant, including diarrhea, vomiting, weak pulse, and unstable blood pressure; advise patients not to breastfeed during treatment with BREKIYA and for 3 days after the last dose. Breast milk supply during this time should be pumped and discarded.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of dihydroergotamine products did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

BREKIYA contains dihydroergotamine (as the mesylate salt), which is not a controlled substance.

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Currently available data have not demonstrated drug abuse with dihydroergotamine. However, cases of drug abuse in patients on other forms of ergot therapy have been reported.

9.3 Dependence

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. Currently available data have not demonstrated physical or psychological dependence with dihydroergotamine. However, cases of psychological dependence in patients on other forms of ergot therapy have been reported.

10 OVERDOSAGE

Symptoms

Excessive doses of dihydroergotamine may result in peripheral signs and symptoms of ergotism.

In general, the symptoms of an acute BREKIYA overdose may be similar to those of an ergotamine overdose, although there may be less pronounced nausea and vomiting with BREKIYA. The symptoms of an ergotamine overdose include the following: numbness, tingling, pain, and cyanosis of the extremities associated with diminished or absent peripheral pulses; respiratory depression; an increase and/or decrease in blood pressure, usually in that order; confusion, delirium, convulsions, and coma; and/or some degree of nausea, vomiting, and abdominal pain.

In laboratory animals, dihydroergotamine was lethal when given at intravenous doses of 44 mg/kg in mice, 130 mg/kg in rats, and 37 mg/kg in rabbits.

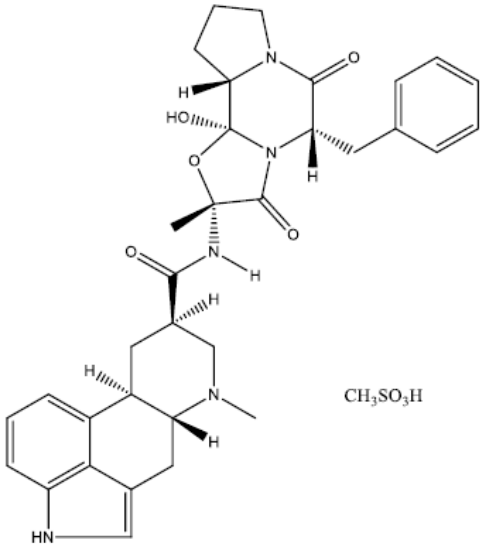
Treatment

Treatment includes discontinuance of the drug, local application of warmth to the affected area, the administration of vasodilators, and nursing care to prevent tissue damage. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

BREKIYA (dihydroergotamine mesylate) injection is an ergotamine derivative. Dihydroergotamine mesylate is a white or almost white, crystalline powder. It is slightly soluble in water and chloroform and sparingly soluble in methanol. The chemical name for dihydroergotamine mesylate is ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl) monomethanesulfonate (salt). Its molecular weight is 679.8g/mol and its molecular formula is $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$.

The chemical structure is



Dihydroergotamine mesylate

BREKIYA is a clear, colorless, sterile solution supplied in 1 mL single-dose autoinjector for subcutaneous administration. Each mL contains 1 mg dihydroergotamine mesylate, USP (equivalent to 0.86 mg of dihydroergotamine). BREKIYA also contains ethanol, USP 6.1% by volume; glycerin, USP 15% by weight; water for injection, USP; may contain methanesulfonic acid and/or sodium hydroxide, NF for pH adjustment. pH range is 3.4 to 4.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dihydroergotamine binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effects at 5-HT_{1D} receptors.

12.2 Pharmacodynamics

Significant elevation in blood pressure has been reported in patients treated with dihydroergotamine with and without a history of hypertension *[see Warnings and Precautions (5.5)]*.

Dihydroergotamine possesses oxytocic properties *[see Warnings and Precautions (5.7)]*.

12.3 Pharmacokinetics

Absorption

Following BREKIYA administration, the mean maximum plasma concentration was 3.8 ng/mL, and the median time from dosing to maximum plasma concentration was approximately 0.4 hours.

Distribution

Dihydroergotamine mesylate is 93% plasma protein bound. The apparent steady-state volume of distribution is approximately 800 liters.

Elimination

Metabolism

Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8′-β-hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several venoconstrictor activity models, *in vivo* and *in vitro*. The other metabolites (i.e., dihydrolysergic acid, dihydrolysergic amide, and a metabolite formed by oxidative opening of the proline ring) are of minor importance. Following nasal administration, total metabolites represent only 20% to 30% of plasma AUC. Quantitative pharmacokinetic characterization of the four metabolites has not been performed.

Excretion

The major excretory route of dihydroergotamine is via the bile in the feces. The total body clearance is 1.5 L/min which reflects mainly hepatic clearance. Only 6% to 7% of unchanged dihydroergotamine is excreted in the urine after intramuscular injection. The renal clearance (0.1 L/min) is unaffected by the route of dihydroergotamine administration. The decline of plasma dihydroergotamine after intramuscular or intravenous administration is multi-exponential with a terminal half-life of about 9 hours.

Specific Populations

No studies have been conducted on the effect of renal or hepatic impairment, gender, race, or ethnicity on dihydroergotamine pharmacokinetics *[see Contraindications (4)]*.

Drug Interaction Studies

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine) and macrolide antibiotics, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (e.g., clarithromycin, erythromycin), and in patients treated with dihydroergotamine and protease inhibitors (e.g., ritonavir), presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *[see Contraindications (4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year mouse carcinogenicity study, subcutaneous (SC) administration of dihydroergotamine mesylate (0,

0.5, 1.5 or 5 mg/kg/day) resulted in an increased incidence of fibrosarcoma at the injection sites in males and females at the high dose. The higher dose not associated with an increase in tumors (1.5 mg/kg/day) is approximately 2 times the recommended human dose (RHD) of 3 mg/day SC on a body surface area (mg/m^2) basis.

In a 2-year rat carcinogenicity study, intranasal administration of dihydroergotamine mesylate (0, 0.4, 0.8 or 1.6 mg/day for 13 weeks, followed by 0, 0.08, 0.24 or 0.8 mg/day for the remainder of the study) did not result in an increase in tumors.

Mutagenesis

Dihydroergotamine mesylate was negative in an in vitro mutagenicity (Ames) assay and positive in in vitro chromosomal aberration (V79 Chinese hamster cell assay with metabolic activation, and human peripheral blood lymphocyte) assays. Dihydroergotamine was negative in *in vivo* micronucleus assays in mouse and hamster.

Impairment of Fertility

Intranasal administration of dihydroergotamine to rats at doses up to 1.6 mg/day was not associated with adverse effects on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BREKIYA (dihydroergotamine mesylate) injection is a clear, colorless, sterile solution of 1 mg/mL dihydroergotamine mesylate available as:

Dosage Unit	Package Size	NDC #
1 mL prefilled single-dose autoinjector	Carton of 4	NDC 64896-509-02

Caution: The rigid needle shield of the BREKIYA autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex *[see Contraindications (4)* and *Warnings and Precautions (5.9)]*.

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Do not refrigerate or freeze. Protect from light. Retain in original pack until time of use.

17 PATIENT COUNSELING INFORMATION

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

Serious and/or Life-Threatening Reactions with Coadministration of CYP3A4 Inhibitors

Inform patients that serious and/or life-threatening peripheral ischemia (cerebral ischemia and/or ischemia of the extremities) has been associated with the coadministration of dihydroergotamine and strong CYP3A4 inhibitors, *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7.1)]*.

Myocardial Ischemia and/or Infarction, Other Cardiac Events, Cerebrovascular Events, and Fatalities

Inform patients of the risk for serious cardiac, cerebrovascular, and other vasospasm related events. Advise patients to notify their healthcare provider if they develop any risk factors or symptoms while taking BREKIYA. Inform patients that nicotine may provoke vasoconstriction predisposing to a greater ischemic response *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

Increase in Blood Pressure

Inform patients of the risk for significant elevation in blood pressure *[see Warnings and Precautions (5.5)]*.

Medication Overuse Headache

Inform patients that use of drugs to treat migraine attacks for 10 or more days per month may lead to an exacerbation of headache, and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) *[see Warnings and Precautions (5.6)]*.

Hypersensitivity

Inform patients that the rigid needle shield of the BREKIYA autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex, and can cause allergic reactions in latex-sensitive individuals *[see Warnings and Precautions (5.9)]*.

Drug Interactions

Advise patients to inform their healthcare providers if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions (7)]*.

Pregnancy

Advise patients of the risk for preterm birth. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.

Lactation

Advise patients not to breastfeed during treatment with BREKIYA *[see Use in Specific Populations (8.2)]*.

Important Administration Instructions

Advise patients on the proper use of BREKIYA prior to the initial use and instruct them to read the Instructions for Use *[see Dosage and Administration (2.3)]*.

For more information, call 1-877-835-5472.

BREKIYA® is a registered trademark of Amneal Pharmaceuticals LLC.

Distributed by:
Amneal Specialty, a division of Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Manufactured by:
Amneal Pharmaceuticals Pvt. Ltd.
Ahmedabad 382213, INDIA

Rev. 05-2025-01