KALBITOR- ecallantide injection, solution
Takeda Pharmaceuticals America, Inc.

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

KALBITOR (ecallantide) injection, for subcutaneous use
Initial U.S. Approval: 2009

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning

Anaphylaxis has been reported after administration of KALBITOR®. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR [*see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6)*].

INDICATIONS AND USAGE

KALBITOR is a plasma kallikrein inhibitor indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If an attack persists, an additional dose of 30 mg may be administered within a 24 hour period. (2.1)
- KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. (2.2).

DOSAGE FORMS AND STRENGTHS

Single use glass vial containing 10 mg/mL of ecallantide as a solution for injection. (3)

CONTRAINDICATIONS

Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis: Anaphylaxis has occurred in 4% of treated patients. Administer KALBITOR in a setting equipped to manage anaphylaxis and hereditary angioedema. Given the similarity in hypersensitivity symptoms and acute HAE symptoms, monitor patients closely for hypersensitivity reactions (5).

ADVERSE REACTIONS

The most common adverse reactions occurring in ≥3% of KALBITOR-treated patients and greater than placebo are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2021

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FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

Anaphylaxis has been reported after administration of KALBITOR. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR. [*see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6)*]

1 INDICATIONS AND USAGE

KALBITOR® (ecallantide) is indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of KALBITOR is 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.

2.2 Administration Instructions

KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.

KALBITOR should be refrigerated and protected from the light. KALBITOR is a clear, colorless liquid; visually inspect each vial for particulate matter and discoloration prior to administration. If there is particulate matter or discoloration, the vial should not be used.

Using aseptic technique, withdraw 1 mL (10 mg) of KALBITOR from the vial using a large bore needle. Change the needle on the syringe to a needle suitable for subcutaneous injection. The recommended needle size is 27 gauge. Inject KALBITOR into the skin of the abdomen, thigh, or upper arm. Repeat the procedure for each of the 3 vials comprising the KALBITOR dose. The injection site for each of the injections may be in the same or in different anatomic locations (abdomen, thigh, upper arm). There is no need for site rotation. Injection sites should be separated by at least 2 inches (5 cm) and away from the anatomical site of attack.

The same instructions apply to an additional dose administered within 24 hours. Different injection sites or the same anatomical location (as used for the first administration) may be used.

3 DOSAGE FORMS AND STRENGTHS

KALBITOR is a clear, colorless liquid free of preservatives. Each vial of KALBITOR contains ecallantide at a concentration of 10 mg/mL.

4 CONTRAINDICATIONS

Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR. [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions, Including Anaphylaxis

Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with KALBITOR. In 255 HAE patients treated with intravenous or subcutaneous KALBITOR in clinical studies, 10 patients (4%) experienced anaphylaxis.

For the subgroup of 187 patients treated with subcutaneous KALBITOR, 5 patients (3%) experienced anaphylaxis. Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension. These reactions occurred within the first hour after dosing.

Other adverse reactions indicative of hypersensitivity reactions included the following: pruritus (5%), rash (3%), and urticaria (2%).

Patients should be observed for an appropriate period of time after administration of KALBITOR, taking into account the time to onset of anaphylaxis seen in clinical trials. Given the similarity in hypersensitivity symptoms and acute HAE symptoms, patients should be monitored closely in the event of a hypersensitivity reaction.

KALBITOR should not be administered to any patients with known clinical hypersensitivity to KALBITOR [*see Contraindications (4)*].

6 ADVERSE REACTIONS

Hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with KALBITOR [*see Contraindications (4) and Warnings and Precautions (5.1)*].

6.1 Clinical Trials 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.

The safety data described below reflect exposure to KALBITOR in 255 patients with HAE treated with either intravenous or subcutaneous KALBITOR. Of the 255 patients, 66% of patients were female and 86% were Caucasian. Patients treated with KALBITOR were between the ages of 10 and 78 years.

Overall, the most common adverse reactions in 255 patients with HAE were headache (16%), nausea (13%), fatigue (12%), diarrhea (11%), upper respiratory tract infection (8%), injection site reactions (7%), nasopharyngitis (6%), vomiting (6%), pruritus (5%), upper abdominal pain (5%), and pyrexia (5%).

Anaphylaxis was reported in 4% of patients with HAE. Injection site reactions were characterized by local pruritus, erythema, pain, irritation, urticaria, and/or bruising.

The incidence of adverse reactions below is based upon 2 placebo-controlled, clinical trials (EDEMA3® and EDEMA4®) in a total of 143 unique patients with HAE. Patients were treated with KALBITOR 30 mg subcutaneous or placebo. Patients were permitted to participate sequentially in both placebo-controlled trials; safety data collected during exposure to KALBITOR was attributed to treatment with KALBITOR, and safety data collected during exposure to placebo was attributed to treatment with placebo. Table 1 shows adverse reactions occurring in ≥3% of KALBITOR-treated patients that also occurred at a higher rate than in the placebo-treated patients in the two controlled trials (EDEMA3 and EDEMA4) of the 30 mg subcutaneous dose.

Table 1: Adverse Reactions Occurring at ≥3% and Higher than Placebo in 2 Placebo Controlled Clinical Trials in Patients with HAE

	Treated with KALBITOR	
	KALBITOR N=100	**Placebo N=81**
Adverse Reactions	**n (%)** *	**n (%)***
Headache	8 (8%)	6 (7%)
Nausea	5 (5%)	1 (1%)
Diarrhea	4 (4%)	3 (4%)
Pyrexia	4 (4%)	0
Injection site reactions	3 (3%)	1 (1%)
Nasopharyngitis	3 (3%)	0

* Patients experiencing more than 1 event with the same preferred term are counted only once for that preferred term.

Some patients in EDEMA3 and EDEMA4 received a second, open-label 30 mg subcutaneous dose of KALBITOR within 24 hours following the initial dose. Adverse reactions reported by these patients who received the additional 30 mg subcutaneous dose of KALBITOR were consistent with those reported in the patients receiving a single dose.

6.2 Immunogenicity

In the KALBITOR HAE program, patients developed antibodies to KALBITOR. Rates of seroconversion increased with exposure to KALBITOR over time. Overall, 20.2% of patients seroconverted to anti-ecallantide antibodies. Neutralizing antibodies to ecallantide were determined *in vitro* to be present in 8.8% of patients and were not associated with loss of efficacy.

Anti-ecallantide IgE antibodies were detected at a rate of 4.7% for tested patients, and anti-*P. pastoris* IgE antibodies were also detected at a rate of 20.2%. Patients who seroconvert may be at a higher risk of a hypersensitivity reaction. The long-term effects of antibodies to KALBITOR are not known.

The test results for the ecallantide program were determined using one of two assay formats: ELISA and bridging electrochemiluminescence (ECL). As with all therapeutic proteins, there is a potential for immunogenicity with the use of KALBITOR. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to KALBITOR with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

Similar adverse reactions have been observed postmarketing as described for clinical trial experience. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or to establish a causal relationship with drug exposure.

7 DRUG INTERACTIONS

No formal drug interactions studies were performed. No *in vitro* metabolism studies were performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from the pharmacovigilance database for Kalbitor have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In an animal reproduction study, increased early fetal deaths resulting in decreased live fetuses were observed in rats following treatment during the period of organogenesis at an intravenous dose approximately 1.6 times the maximum recommended human dose (MRHD) in the presence of maternal toxicity. There were no effects on embryofetal survival or structural abnormalities in rats and rabbits following treatment during the period of organogenesis with intravenous doses up to approximately 1.1 and 6 times the MRHD, respectively, or rats treated with subcutaneous doses up to 2.4 times the MRHD. In a pre- and post-natal development study with rats, there were no effects on pup survival and development with subcutaneous doses up to approximately 2.7 times the MRHD.

The estimated 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

<u>Animal Data</u>

In an embryofetal development study with rats, ecallantide administered by the intravenous route during the period of organogenesis from gestation days 7 to 17 at a dose approximately 1.6 times the MRHD (on a mg/m^2 basis at a maternal intravenous dose of 15 mg/kg/day) caused increased numbers of early resorptions and percentages of resorbed conceptuses per litter resulting in decreased numbers of live fetuses in the presence of mild maternal toxicity. No effects on embryofetal survival or structural abnormalities were observed in rats with intravenous doses up to approximately 1.1 times the MRHD (on a mg/m^2 basis with maternal intravenous dose of 10 mg/kg/day). In an embryofetal development study with rats, ecallantide administered by the subcutaneous route during the period of organogenesis from gestation days 7 to 17 at doses up to approximately 2.4 times the MRHD (on an AUC basis with maternal subcutaneous doses up to 20 mg/kg/day) had no effects on embryofetal survival or structural abnormalities. In an embryofetal development study with rabbits, ecallantide administered by the intravenous route during the period of organogenesis from gestation days 7 to 19 at doses up to approximately 6 times the MRHD (on an AUC basis with maternal intravenous doses up to 5 mg/kg/day in rabbits) had no effects on embryofetal survival or structural abnormalities.

In a pre- and post-natal development study with rats, ecallantide administered by the subcutaneous route from gestation day 7 through lactation day 20 at doses up to

approximately 2.7 times the MRHD (on a mg/m^2 basis with maternal subcutaneous doses up to 25 mg/kg/day) had no effects on pup survival and behavioral or physical development.

8.2 Lactation

Risk Summary

There are no data on the presence of ecallantide in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KALBITOR and any potential adverse effects on the breastfed child from KALBITOR or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of KALBITOR have been established in patients 12 to 17 years of age. The efficacy of KALBITOR in the 12-15 year age group is extrapolated from efficacy in patients 16 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and adolescents *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*. The safety profile observed in pediatric patients 12-17 years of age was similar to the adverse reactions observed in the overall clinical trial population *[see Adverse Reactions (6.1)]*.

Safety and effectiveness of KALBITOR in patients less than 12 years of age have not been established.

8.5 Geriatric Use

Clinical trials of KALBITOR did not include sufficient numbers of subjects aged 65 and over 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.

10 OVERDOSAGE

There have been no reports of overdose with KALBITOR. HAE patients have received single doses up to 90 mg intravenously without evidence of dose-related toxicity.

11 DESCRIPTION

KALBITOR (ecallantide) is a human plasma kallikrein inhibitor for injection for subcutaneous use. Ecallantide is a 60-amino-acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

KALBITOR is a clear and colorless, sterile, and nonpyrogenic solution. Each vial contains 10 mg ecallantide as the active ingredient, and the following inactive ingredients: 0.76 mg disodium hydrogen orthophosphate (dihydrate), 0.2 mg monopotassium phosphate, 0.2 mg potassium chloride, and 8 mg sodium chloride in water for injection, USP. KALBITOR is preservative free, with a pH of approximately 7.0. A 30 mg dose is supplied as 3 vials each containing 1 mL of 10 mg/mL KALBITOR. Vials are intended for single use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hereditary angioedema (HAE) is a rare genetic disorder caused by mutations to C1-esterase-inhibitor (C1-INH) located on Chromosome 11q and inherited as an autosomal dominant trait. HAE is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is therefore not present. During attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

KALBITOR is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. KALBITOR binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin. By directly inhibiting plasma kallikrein, KALBITOR reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.

12.2 Pharmacodynamics

No exposure-response relationships for KALBITOR to components of the complement or kallikrein-kinin pathways have been established.

The effect of KALBITOR on activated partial thromboplastin time (aPTT) was measured because of potential effect on the intrinsic coagulation pathway. Prolongation of aPTT has been observed following intravenous dosing of KALBITOR at doses ≥20 mg/m^2. At 80 mg administered intravenously in healthy subjects, aPTT values were prolonged approximately two-fold over baseline values and returned to normal by 4 hours post-dose.

For patients taking KALBITOR, no significant QT prolongation has been seen. In a randomized, placebo-controlled trial (EDEMA4) studying the 30 mg subcutaneous dose versus placebo, 12-lead ECGs were obtained at baseline, 2 hours and 4 hours post-dose (covering the time of expected C_{max}), and at follow-up (day 7). ECGs were evaluated for PR interval, QRS complex, and QTc interval. KALBITOR had no significant effect on the QTc interval, heart rate, or any other components of the ECG.

12.3 Pharmacokinetics

Following the administration of a single 30 mg subcutaneous dose of KALBITOR to healthy subjects, a mean (± standard deviation) maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2 to 3 hours post-dose. The mean area under the concentration-time curve was 3017 ± 402 ng*hr/mL. Following administration, plasma concentration declined with a mean elimination half-life of 2.0 ± 0.5 hours. Plasma clearance was 153 ± 20 mL/min and the volume of distribution was 26.4 ± 7.8 L.

Based on a population pharmacokinetic analysis, body weight, age, and gender were not found to affect KALBITOR exposure significantly. Ecallantide is a small protein (7054 Da) and renal elimination in the urine of treated subjects has been demonstrated.

No pharmacokinetic data are available in patients or subjects with hepatic or renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year study was conducted in rats to assess the carcinogenic potential of KALBITOR. No evidence of tumorigenicity was observed in rats at ecallantide doses up to 10 mg/kg administered subcutaneously every three days (approximately 2-fold greater than the MRHD on an AUC basis).

KALBITOR had no effects on fertility and reproductive performance in rats at maternal subcutaneous doses up to 25 mg/kg/day (approximately 2.7 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

The safety and efficacy of KALBITOR to treat acute attacks of hereditary angioedema in adolescents and adults were evaluated in 2 randomized, double-blind, placebo-controlled trials (EDEMA4 and EDEMA3) in 168 patients with HAE. Patients having an attack of hereditary angioedema, at any anatomic location, with at least 1 moderate or severe symptom, were treated with 30 mg subcutaneous KALBITOR or placebo. Because patients could participate in both trials, a total of 143 unique patients participated. Of the 143 patients, 94 were female, 123 were Caucasian, and the mean age was 36 years (range 11-77). There were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks.

In both trials, the effects of KALBITOR were evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). These endpoints evaluated attack severity (MSCS) and patient response to treatment (TOS) for an acute HAE attack.

MSCS score is a point-in-time measure of symptom severity. At baseline, and post-dosing at 4 hours and 24 hours, patients rated the severity of each affected symptom on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe). Patient-reported severity was based on each patient's assessment of symptom impact on their ability to perform routine activities. Ratings were averaged to obtain the MSCS score. The endpoint was reported as the change in MSCS score from baseline. A decrease in MSCS score reflected an improvement in symptom severity; the maximum possible change toward improvement was -3.

TOS is a measure of symptom response to treatment. At 4 hours and 24 hours post-dosing, patient assessment of response for each anatomic site of attack involvement was recorded on a categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100]). The response at each anatomic site was weighted by baseline severity and then the weighted scores across all involved sites were averaged to calculate the TOS. A TOS value >0 reflected an improvement in

symptoms from baseline. The maximum possible score was +100.

EDEMA4

EDEMA4 was a randomized, double-blind, placebo-controlled trial in which 96 patients were randomized 1:1 to receive KALBITOR 30 mg subcutaneous or placebo for acute attacks of HAE. The primary endpoint was the change from baseline in MSCS score at 4 hours, and the TOS at 4 hours was a key secondary endpoint. Patients treated with KALBITOR demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo and the results were statistically significant (Table 2). At 24 hours, patients treated with KALBITOR also demonstrated a greater decrease from baseline in the MSCS than placebo (-1.5 vs. -1.1; p = 0.04) and a greater TOS (89 vs. 55, p = 0.03).

Table 2: Change in MSCS Score and TOS at 4 Hours

	EDEMA4		**EDEMA3**	
	KALBITOR (N=48)	**Placebo (N=48)**	**KALBITOR (N=36)**	**Placebo (N=36)**
Change in MSCS Score at 4 Hours				
n	47	42	34	35
Mean	-0.8	-0.4	-1.1	-0.6
95% CI	-1.0, -0.6	-0.6, -0.1	-1.4, -0.8	-0.8, -0.4
P-value	0.010		0.041	
TOS at 4 Hours				
n	47	42	34	35
Mean	53	8	63	36
95% CI	39, 68	-12, 28	49, 76	17, 54
P-value	0.003		0.045	

MSCS: Mean Symptom Complex Severity
TOS: Treatment Outcome Score
CI: confidence interval

More patients in the placebo group (24/48, 50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the KALBITOR-treated group (16/48, 33%).

Some patients reported improvement following a second 30 mg subcutaneous dose of KALBITOR, administered within 24 hours following the initial dose for symptom persistence or relapse, but efficacy was not systematically assessed for the second dose.

EDEMA3

EDEMA3 was a randomized, double-blind, placebo-controlled trial in which 72 patients were randomized 1:1 to receive KALBITOR or placebo for acute attacks of HAE. EDEMA3 was similar in design to EDEMA4 with the exception of the order of the prespecified efficacy endpoints. In EDEMA3, the primary endpoint was the TOS at 4 hours, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hours. As in EDEMA4, patients treated with KALBITOR demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients treated with placebo

and the results were statistically significant (Table 2).

In addition, more patients in the placebo group (13/36, 36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the KALBITOR-treated group (5/36, 14%).

16 HOW SUPPLIED/STORAGE AND HANDLING

KALBITOR (ecallantide) is supplied as three 10 mg/mL single-use vials packaged in a carton. Each vial contains 10 mg of ecallantide. Each vial contains a slight overfill.

- NDC (47783-101-01): 3 single-use vials in 1 carton

KALBITOR should be kept refrigerated (2°C to 8°C/36°F to 46°F). Vials removed from refrigeration should be stored below 86°F/30°C and used within 14 days or returned to refrigeration until use.

Protect vials from light until use.

Do not use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

- Advise patients that KALBITOR may cause anaphylaxis and other hypersensitivity reactions. Advise patients that KALBITOR should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Instruct patients who have known clinical hypersensitivity to KALBITOR not to receive additional doses of KALBITOR. [*see Boxed Warning*, *Contraindications (4), and Warnings and Precautions (5.1)*]
- Advise patients to consult the Medication Guide for additional information regarding the risk of anaphylaxis and other hypersensitivity reactions.

For more information, visit www.kalbitor.com or call 1-800-828-2088.

Manufactured by:
Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421

U.S. License No. 1898

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Medication Guide

KALBITOR® (KAL-bi-tor)
(ecallantide)

Read this Medication Guide before you start receiving KALBITOR and before each treatment. There may be new information. This Medication Guide does not take the place

of talking to your doctor about your medical condition or your treatment.

What is the most important information that I should know about KALBITOR?

Serious allergic reactions may happen in some people who receive KALBITOR. These allergic reactions can be life-threatening and usually happen within 1 hour after receiving KALBITOR.

- KALBITOR should be given to you by a doctor or nurse in a healthcare setting where serious allergic reactions and hereditary angioedema (HAE) can be treated.
- Symptoms of a serious allergic reaction to KALBITOR can be similar to the symptoms of HAE, the condition that you are being treated for. Your doctor or nurse should watch you for any signs of a serious allergic reaction after treatment with KALBITOR.
- **Tell your doctor or nurse right away if you have any of these symptoms of a serious allergic reaction during or after treatment with KALBITOR:**
  - wheezing, shortness of breath, cough, chest tightness, or trouble breathing
  - dizziness, fainting, fast or weak heartbeat, or feeling nervous
  - reddening of the face, itching, hives, or feeling warm
  - swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing
  - runny nose, nasal congestion, or sneezing

What is KALBITOR?

KALBITOR is a prescription medicine used to treat sudden attacks of hereditary angioedema (HAE) in people 12 years of age and older.

KALBITOR is not a cure for HAE.

It is not known if KALBITOR is safe and effective in children under 12 years of age.

Who should not receive KALBITOR?

Do not receive KALBITOR if you are allergic to KALBITOR.

What should I tell my doctor before I receive KALBITOR?

Before receiving KALBITOR, tell your doctor if you:

- have ever had an allergic reaction to KALBITOR. See "Who should not receive KALBITOR?"
- are pregnant or plan to become pregnant. It is not known if KALBITOR will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if KALBITOR passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine.

How will I receive KALBITOR?

For each dose, you will receive 3 injections just under the skin (subcutaneous or SC injections) of your abdomen, thigh, or upper arm.

What are the possible side effects?

KALBITOR can cause serious allergic reactions. See "What is the most important information I should know about KALBITOR?"

Common side effects of KALBITOR include:

- headache
- nausea
- diarrhea
- fever
- injection site reactions, such as redness, rash, swelling, itching, or bruising
- stuffy nose

Call your doctor for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about KALBITOR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide gives you the most important information about KALBITOR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALBITOR that is written for health professionals.

What are the ingredients of KALBITOR?

Active Ingredient: ecallantide

Inactive ingredients: disodium hydrogen orthophosphate (dihydrate), monopotassium phosphate, potassium chloride, sodium chloride in water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

For more information, visit www.kalbitor.com or call 1-800-828-2088.

Manufactured by:
Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421

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Revised: 11/2021

PRINCIPAL DISPLAY PANEL - 10 mg/mL Vial Carton

ATTENTION: Dispense the enclosed Medication Guide to each patient.
NDC# 47783-101-01

KALBITOR®

ecallantide

10 mg/mL

Injection
For Subcutaneous Use Only
Single Use; Discard Unused Portion
Net Quantity: 3 Vials

Rx Only

ATTENTION: Dispense the enclosed Medication Guide to each patient.
NDC# 47783-101-01

KALBITOR®
ecallantide

10 mg/mL
Injection
For Subcutaneous Use Only
Single Use: Discard Unused Portion
Net Quantity: 3 Vials

Rx Only

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874042R5

For questions, call
1-866-888-0660

KALBITOR®
ecallantide

KEEP REFRIGERATED (36–46°F/2–8°C)

DO NOT FREEZE

PROTECT FROM LIGHT

DOSAGE: 30 mg
All 3 vials must be injected to receive the recommended 30 mg dose

Each vial contains a slight overfill

Rx Only

Rx Only

KALBITOR®
ecallantide

Mfd. by: Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421

License: 1898
1-866-888-0660
www.kalbitor.com
Product of the United Kingdom

N
3 47783-101-01 3

www.kalbitor.com

KALBITOR®
ecallantide

ATTENTION: Dispense the enclosed Medication Guide to each patient.

KALBITOR®
ecallantide

KEEP REFRIGERATED (36–46°F/2–8°C)

DO NOT FREEZE

PROTECT FROM LIGHT

See package insert for ingredient information

Ecallantide is a protein produced in yeast cells

No US standard of potency

Sterile product/no preservatives

Rx Only

KALBITOR

ecallantide injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:47783-101
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Ecallantide (UNII: 5Q6TZN2HNM) (Ecallantide - UNII:5Q6TZN2HNM)	Ecallantide	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE (UNII: 94255I6E2T)	0.76 mg in 1 mL
Monobasic Potassium Phosphate (UNII: 4J9FJ0HL51)	0.2 mg in 1 mL
Potassium Chloride (UNII: 660YQ98I10)	0.2 mg in 1 mL
Sodium Chloride (UNII: 451W47IQ8X)	8 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47783-101-01	3 in 1 CARTON	02/02/2010	
1		1 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125277	02/02/2010	

Labeler - Takeda Pharmaceuticals America, Inc. (039997266)

Establishment

Name	Address	ID/FEI	Business Operations
Fujifilm Diosynth Biotechnologies UK Limited		778997119	API MANUFACTURE(47783-101)

Establishment

Name	Address	ID/FEI	Business Operations

Jubilant HollisterStier LLC		069263643	MANUFACTURE(47783-101) , PACK(47783-101) , LABEL(47783-101)