Ecballantide Subcutaneous Injection (Kalbitor)

**Manufacturer:** Dyax Corporation, Cambridge, Mass.

**Indication:** Ecballantide is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

**Drug Class:** Ecballantide is a human plasma kallikrein inhibitor injection for subcutaneous (SQ) use. It is a 60-amino-acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

**Uniqueness of Product:** As a potent selective, reversible inhibitor of plasma kallikrein (Kᵢ = 25 pM), ecballantide binds to plasma kallikrein and blocks its binding site. This action inhibits the conversion of high-molecular-weight kininogen to bradykinin. Ecballantide thus helps to treat symptoms during acute episodic attacks of HAE.

**Boxed Warning:** Anaphylaxis has been reported after the administration of ecballantide. Because of this potential risk, this agent should be administered only by a health care professional with appropriate medical support to manage anaphylaxis and HAE. Physicians should be aware of the similarity of symptoms between hypersensitivity reactions and HAE, and patients should be monitored closely. Patients with a known clinical hypersensitivity to ecballantide should not receive it.

**Warning:** Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients receiving ecballantide. In 255 patients with HAE who received intravenous (IV) or SQ ecballantide in clinical studies, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with SQ ecballantide, five patients (2.7%) experienced anaphylaxis. Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rash, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension. These reactions occurred within the first hour after dosing.

Patients should be observed for an appropriate period of time after administration of ecballantide, 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. Ecballantide should not be given to any patients with a known clinical hypersensitivity to it.

**Dosage and Administration:** The product should be refrigerated and protected from light. Ecballantide is a clear, colorless liquid, and each vial should be visually inspected for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, the vial should not be used.

The recommended dose is 30 mg (3 mL), administered in three 10-mg (1-mL) SQ injections. If the HAE attack persists, an additional dose of 30 mg may be given within 24 hours. Only health care professionals with appropriate medical support to manage anaphylaxis and HAE should administer ecballantide. With aseptic technique, the clinician should use a large-bore needle to withdraw 10 mg (1 mL) of ecballantide from the vial. The needle on the syringe should be changed to a needle suitable for an SQ injection. The recommended needle size is 27 gauge.

Ecballantide is injected into the skin of the abdomen, thigh, or upper arm. The procedure is repeated for each of the three vials comprising the ecballantide dose. The site for each of the injections may or may not be in the same anatomical locations; 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 the attack. The same instructions apply if an additional dose is administered within 24 hours. Different injection sites or the same anatomical location as in the first administration may be used.

**Commentary:** HAE is a rare genetic disorder caused by mutations to C1 esterase inhibitor (C1-INH), located on chromosome 11q. It is inherited as an autosomal dominant trait. HAE is characterized by low levels of C1-INH activity and low levels of C4, a complement component. C1-INH regulates 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 inflammatory and coagulation pathways. A critical aspect of this pathway is the conversion of high-molecular-weight kininogen to bradykinin by the protease plasma kallikrein. In patients with HAE, normal regulation of plasma kallikrein and the classical complement cascade is not present. During HAE attacks, unregulated activity of plasma kallikrein results in the excessive generation of bradykinin. Bradykinin is a vasodilator that might be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. The drug’s inhibition of plasma kallikrein aids in treating the symptoms during acute, episodic attacks of HAE.

**Source:** www.kalbitor.com

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**Capsaicin 8% Patch (Qutenza)**

**Manufacturer:** NeurogesX, Inc., San Mateo, Calif.

**Indication:** The patch is indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN).

**Drug Class:** In this localized dermal delivery system, the capsaicin is a synthetic equivalent of the naturally occurring compound found in chili peppers. The single-use patch is stored in a foil pouch. Each patch is 14 cm × 20 cm (280 cm²). The patch consists of a polyester backing film, coated with a drug-containing silicone adhesive mixture, and is covered with a removable polyester release liner. The empirical formula is C₁₈H₂₇NO₃, and the molecular weight is 305.42. Capsaicin ([E]-8-methyl-N-vanillyl-6-nonenamide) is an activating ligand for transient receptor potential vanilloid-1 receptor (TRPV1).

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Pharmaceutical Approval Update

**Uniqueness of Drug:** Capsaicin is an agonist for TRPV1, an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin. Topical administration of capsaicin initially enhances stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations. This is followed by pain relief, which is thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings. Over the course of several months, painful neuropathy may gradually re-emerge; some experts believe that this recurrence results from TRPV1 nerve fiber reinnervation of the treated area.

**Warnings and Precautions:**

**Eye and mucous membrane exposure.** The capsaicin 8% patch should not be applied to the face or scalp. If the patient’s eyes or mucous membranes become irritated, they should be flushed with cool water.

**Aerosolization.** A fine mist or small droplets can occur if the patch is rapidly removed from the skin. The patch should be removed gently and slowly by rolling the adhesive side inward. If the eyes or airways become irritated, the patient should be removed from the vicinity of the patch, and the eyes and mucous membranes should be flushed with cool water. Inhalation of airborne capsaicin can result in coughing or sneezing. Supportive medical care should be provided if shortness of breath develops.

**Unintended skin exposure.** If skin that was not intended to be treated comes in contact with the capsaicin patch, the cleansing gel that was supplied with the product can be applied for one minute and wiped off with dry gauze. After the gel has been removed, the area should be washed with soap and water.

**Pain.** Even when a local anesthetic has been given before the patch is applied, patients may experience pain. The clinician should be prepared to treat acute pain, during and following the application procedure, with local cooling, such as an ice pack, or with an appropriate analgesic medication, such as opioids. However, opioids may affect the patient’s ability to perform potentially hazardous activities such as driving or operating machinery.

**Increase in blood pressure.** Increases in blood pressure have occurred during or shortly after exposure to the patch. Although the changes averaged less than 10 mmHg, greater increases occurred in some patients, and these changes lasted for approximately two hours after patch removal. The increases were related not to the patient’s blood pressure before therapy but to treatment-related increases in pain. Blood pressure should be monitored periodically during treatment, and adequate support should be provided for treatment-related pain.

Patients with unstable or poorly controlled hypertension or a recent history of cardiovascular or cerebrovascular events may be at an increased risk of adverse cardiovascular effects. These factors should be considered before the patient is treated with this patch.

**Dosage and Administration:** The patch should be applied only to dry, intact skin. Only physicians, or health care professionals under the close supervision of a physician, should administer the capsaicin 8% patch. The clinician should wear only nitrile gloves when handling the patch and when cleaning capsaicin residue from the skin. Latex gloves do not provide adequate protection. Immediately afterward, the used and unused patches, the cleansing gel, and other treatment materials should be discarded in accordance with local biomedical waste procedures.

The recommended dose is a single, 60-minute application of up to four patches. Treatment may be repeated every three months, or as warranted by the return of pain, but not more frequently than every three months.

**Commentary:**

The capsaicin 8% patch is used to treat peripheral neuropathic pain or PHN in nondiabetic adults. It can be used alone or with other analgesics. The patch is applied to the most painful areas of the skin, as determined and marked by the physician. The patch should be applied only to unbroken, non-irritated skin.

Patches can be cut to match the area to be covered. No more than four patches should be applied to the patient at the same time. The area should be pretreated with a local anesthetic to reduce discomfort. The patch should remain in place for 30 minutes for the feet and 60 minutes for other parts of the body.

After the patch is removed, the area is cleaned with the cleansing gel provided. It may take from one day to two weeks for the patch to have an effect. In clinical studies, PHN pain was reduced for up to 12 weeks following a single one-hour treatment.

**Source:** www.qutenza.com

**Romidepsin Injection (Istodax)**

**Manufacturer:** Gloucester Pharmaceuticals, Cambridge, Mass.

**Indication:** Romidepsin is indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

**Drug Class:** A histone deacetylase (HDAC) inhibitor, romidepsin is a bicyclic depsipeptide. Its molecular weight is 540.71.

**Uniqueness of Drug:** HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. In vitro, romidepsin causes acetylated histones to accumulate and induces cell cycle arrest and apoptosis of some cancer cell lines with IC_{50} values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin has not been fully characterized.

**Warnings and Precautions:**

**Monitoring of laboratory values.** Because of the risk of QT prolongation, the patient’s potassium and magnesium levels should be within the normal range before romidepsin is administered.

**Hematological effects.** Romidepsin therapy can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia. These hematological parameters should be monitored during therapy, and the dose should be modified as necessary.

**Electrocardiographic changes.** Several treatment-emergent morphological changes in electrocardiograms (ECGs), including T-wave and ST-segment changes, have been reported. The significance of these changes is unknown. For patients with congenital long QT syndrome, those with a history of significant cardiovascular disease, or patients who were taking antiarrhythmic regimens that led to QT prolongation,
appropriate monitoring of electrolytes and ECGs at baseline and periodically during treatment should be considered.

**Pregnancy.** No adequate or well-controlled studies of romidepsin have been conducted in pregnant women. However, in view of the drug's mechanism of action, romidepsin may cause fetal harm. A study of rats did not expose pregnant animals to enough romidepsin to fully evaluate adverse outcomes. If this drug is used during pregnancy or if the patient becomes pregnant while taking romidepsin, she should be apprised of the potential hazard to the fetus.

**Women of childbearing age.** Women should be advised that romidepsin may reduce the effectiveness of estrogen-containing contraceptives. An in vitro binding assay determined that romidepsin competes with beta-estradiol for binding to estrogen receptors.

**Dosage and Administration:**

**Recommendations.** The recommended dose of romidepsin is 14 mg/m² given intravenously over a four-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days as long as the patient continues to benefit from and tolerates the therapy.

**Dose Modifications:**

Nonhematological toxicities (except alopecia grade 2 or 3 toxicity). Romidepsin therapy should be delayed until toxicity returns to grade 1 or less or returns to baseline. Therapy may then be restarted at 14 mg/m². If grade 3 toxicity recurs, treatment should be delayed until toxicity returns to grade 1 or less or returns to baseline, and the dose should be permanently reduced to 10 mg/m².

**Grade 4 toxicity.** Treatment should be delayed until toxicity returns to grade 1 or less or returns to baseline. The dose should then be permanently reduced to 10 mg/m². Romidepsin should be discontinued if grade 3 or 4 toxicities recur after a dose reduction.

**Hematological toxicities:**

**Grade 3 or 4 neutropenia or thrombocytopenia.** Treatment with romidepsin should be delayed until the specific cytopenia returns to an absolute neutrophil count (ANC) of 1.5 × 10⁹/L or higher, to a platelet count of 75 × 10⁹/L or higher, or to baseline. Therapy may then be restarted at 14 mg/m².

**Grade 4 neutropenia or thrombocytopenia in patients with fever (38.5°C or 101.3°F or higher) who require a platelet transfusion.** Treatment should be delayed until the specific cytopenia returns to grade 1 or lower or returns to baseline. The dose should then be permanently reduced to 10 mg/m².

**Commentary:** Romidepsin is a member of a new class of cancer drugs known as histone deacetylase inhibitors. Many patients with CTCL, a type of non-Hodgkin’s lymphoma (NHL) have disfiguring tumors, itchy and infected skin, and lesions in other organs if the cancer is at an advanced stage. In contrast to most NHLs, which are generally of B-cell origin, CTCL is caused by a mutation of T cells. The malignant T cells involve the skin, causing plaques, patches, erythroderma, or tumors; they can also involve other organs, including the blood, lymph nodes, and viscera. In patients for whom present-day systemic therapies have proved inadequate, romidepsin may meet a significant, unmet need, providing hope for patients, their families, and their physicians.

**Source:** www.fda.gov