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

KHINDIVI® (hydrocortisone) oral solution
Initial U.S. Approval: 1952

----------INDICATIONS AND USAGE----------
KHINDIVI is a corticosteroid indicated as replacement therapy in pediatric patients 5 years of age and older with adrenocortical insufficiency. (1)

Limitations of Use
KHINDIVI is not approved for increased dosing during periods of stress or acute events. Use a different hydrocortisone-containing drug product for stress dosing *[see Warnings and Precautions (5.1)]*.

----------DOSAGE AND ADMINISTRATION----------
- Individualize the dose, using the lowest possible dosage. (2.1)
- When stress dosing is needed use a different hydrocortisone containing drug product. (2.1)
- The recommended starting replacement dosage of KHINDIVI is 8 to 10 mg/m^{2}daily. Higher doses may be needed based on the patient's age and symptoms of the disease. Use of lower starting doses may be sufficient in patients with residual but decreased endogenous cortisol production. (2.2)
- Divide the total daily dose into 3 doses and administer 3 times daily. Older patients may have their daily dose divided by 2 and administered twice daily. (2.2)
- KHINDIVI contains the inactive ingredients polyethylene glycol 400, propylene glycol, and glycerin. If patients experience adverse reactions (i.e., hyperosmolarity, metabolic acidosis, hypoglycemia, hepato-renal injury, central nervous system toxicity, and gastrointestinal adverse reactions), consider discontinuation of KHINDIVI and switch to another hydrocortisone product. (2.3)
- When switching from other oral hydrocortisone formulations, use the same total daily hydrocortisone dosage. If symptoms of adrenal insufficiency occur, increase total daily dosage. (2.4)
- See the Full Prescribing Information for detailed dosing and administration instructions. (2)

----------DOSAGE FORMS AND STRENGTHS----------
- Oral solution: 1 mg/mL. (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to hydrocortisone or any component of KHINDIVI. (4)

----------WARNINGS AND PRECAUTIONS----------
- Adrenal Crisis: Undertreatment, sudden discontinuation of therapy, or switching from another oral hydrocortisone formulation may leadto adrenocortical insufficiency, adrenal crisis and death. Adrenal crisis may also be induced by stress events such as infections or surgery. During periods of stress switch to another oral hydrocortisone product and increase the dose. Switch patients who are vomiting, severely ill or unable to take oral medications to parenteral corticosteroid formulations. (5.1)
- Systemic Adverse Reactions Due to Inactive Ingredients: KHINDIVI contains the inactive ingredients polyethylene glycol 400, propylene and glycol, and glycerin, which may cause hyperosmolarity, metabolic acidosis, hypoglycemia, hepato-renal injury, central nervous toxicity, gastrointestinal adverse reactions. Discontinue KHINDIVI and switch to another hydrocortisone product if these adverse reactions occur. (5.2)
- Immunosuppression and Increased Risk of Infection with Use of a Dosage Greater Than Replacement: Use of a greater than replacement dosage can suppress the immune system and increase the risks of new infections or exacerbation of latent infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. Monitor patients for signs and symptoms of infections. (5.3)
- Growth Retardation: Long-term use in excessive doses may cause growth retardation. Use the minimum dosage of KHINDIVI to achieve desired clinical response and monitor the patient's growth. (5.4)
- Cushing's Syndrome Due to Use of Excessive Doses of Corticosteroids: Prolonged use with supraphysiologic doses may cause Cushing's syndrome. Monitor patients for signs and symptoms of Cushing's syndrome every 6 months. (5.5)
- Decrease in Bone Mineral Density: Corticosteroids decrease bone formation and increase bone resorption which may lead to inhibitionof bone growth and development of osteoporosis. Use the minimum dosage of KHINDIVI to achieve desired clinical response.(5.6)
- Psychiatric Adverse Reactions: Use may be associated with severe psychiatric adverse reactions such as euphoria, mania, psychosis with hallucinations and delirium or depression. Symptoms typically emerge within a few days or weeks of starting the treatment. Most reactions resolve after either dose reduction or withdrawal, although specific treatment may be necessary. Monitor patients for behavioral and mood disturbances during treatment. Instruct caregivers and/or patients to seek medical advice if psychiatric symptoms develop. (5.7)
- Ophthalmic Adverse Reactions: Cataracts, glaucoma and central serous chorioretinopathy have been reported with prolonged use of high doses. Monitor patients for blurred vision or other visual disturbances and if they occur, refer them to an ophthalmologist. (5.8)
- Gastrointestinal Adverse Reactions: Increased risk in patients with certain gastrointestinal disorders. Signs and symptoms may be masked. (5.9)

----------ADVERSE REACTIONS----------
Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. at 1-855-224-0233 or FDA at 1-800-FDA-1088or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CYP3A4 Inhibitors: concomitant administration may require a decrease in the KHINDIVI dose. (7)
- CYP3A4 Inducers: concomitant administration may require an increase in the KHINDIVI dose. (7)
- Estrogen and Estrogen-Containing Products: concomitant administration may require an increase in the KHINDIVI dose. (7)
- Antidiabetic agents: excessive doses may increase blood glucose concentrations. Dose adjustment of antidiabetic agents may be required. (7)
- NSAIDs: concomitant administration increases risk of gastrointestinal adverse reactions. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Revised: 5/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KHINDIVI is indicated as replacement therapy in pediatric patients 5 years of age and older with adrenocortical insufficiency.

Limitations of Use

KHINDIVI is not approved for increased dosing during periods of stress or acute events. Use a different hydrocortisone-containing drug product for stress dosing *[(see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Considerations for Dosing

- Individualize the dose for each patient, using the lowest possible dosage.
- Monitor patients for symptoms of under and/or overtreatment including signs and symptoms of adrenocortical insufficiency, linear growth, and weight gain. Adjust doses accordingly.
- When stress dosing is needed (during episodes of acute febrile illness, gastroenteritis, surgery or major trauma) use a different hydrocortisone-containing drug product. *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage and Administration

- The recommended starting replacement dosage of KHINDIVI is 8 to 10 mg/m^2 daily administered orally with or without food. Higher doses may be needed based on the patient's age and symptoms of the disease. Use of lower starting dose may be sufficient in patients with residual but decreased endogenous cortisol production.
- Round the dose to the nearest 0.5 mg or 1 mg.
- Divide the total daily dose into 3 doses and administer 3 times daily. Older pediatric patients may have their daily dose divided by 2 and administered twice daily.
- Administer KHINDIVI using the oral syringe provided by the pharmacy.
- KHINDIVI may be administered through a gastric tube. Flush gastric tube with 20 mL of water to ensure the entire dose is delivered.

2.3 Discontinue KHINDIVI Due to Adverse Reactions Associated with Inactive Ingredients

- KHINDIVI contains the inactive ingredients polyethylene glycol 400, propylene glycol, and glycerin, which have been associated with hyperosmolarity, metabolic acidosis, hypoglycemia, hepato-renal injury, central nervous system toxicity, and gastrointestinal adverse reactions. If patient presents with adverse reactions that could be related to these conditions, monitor the patient, and consider discontinuation of KHINDIVI and switching to another hydrocortisone product *[see Warnings and Precautions (5.2)]*.

2.4 Switching to KHINDIVI from Other Oral Hydrocortisone Formulations

- When switching patients to KHINDIVI from other oral hydrocortisone formulations to KHINDIVI use the same total daily hydrocortisone dosage. After switching to KHINDIVI, monitor patients for symptoms of adrenocortical insufficiency. If symptoms of adrenal insufficiency occur after switching, increase the total daily dosage of KHINDIVI *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1, 5.2)].*

3 DOSAGE FORMS AND STRENGTHS

KHINDIVI oral solution, 1 mg/mL is a clear, colorless to slightly yellow colored viscous oral

solution.

4 CONTRAINDICATIONS

KHINDIVI is contraindicated in patients with hypersensitivity to hydrocortisone or to any component of KHINDIVI. Reactions have included anaphylaxis in patients receiving corticosteroids *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Crisis

Undertreatment with KHINDIVI or sudden discontinuation of therapy with KHINDIVI may lead to adrenocortical insufficiency, adrenal crisis, and death. Adrenal crisis may also be induced by stress events such as infections or surgery when patients require higher doses ofcorticosteroids. Symptoms of adrenocortical insufficiency include poor feeding, fatigue, low muscle tone, joint pain, nausea, vomiting, hypoglycemia, low blood pressure and electrolyte disturbances.

During periods of stress (e.g., infections, surgery), switch to another oral hydrocortisone product and increase the dose, if oral medications are tolerated. Switch patients who are vomiting, severely ill, or unable to take oral medications to parenteral corticosteroid formulations without delay. Once the patient recovers, gradually reduce the steroid dosage used during the acute event and do not switch back to KHINDIVI until the maintenance dosage can be resumed.

KHINDIVI is not approved for stress dosing. KHINDIVI contains inactive ingredients polyethylene glycol 400, propylene glycol, and glycerin at levels that individually or in combination may result in hyperosmolarity, metabolic acidosis, hypoglycemia, hepato-renal injury, central nervous system toxicity (e.g., seizure and coma) and/or gastrointestinal adverse reactions *[see Warnings and Precautions (5.2)]*. Use of KHINDIVI for stress dosing will result in a greater exposure to inactive ingredients and may increase the risk of these adverse reactions.

When switching patients to KHINDIVI from other oral hydrocortisone formulations, consider the potential for dosing inaccuracy if other oral hydrocortisone formulations have been manipulated (e.g., split or crushed tablets, compounded formulations). Manipulation of oral hydrocortisone formulations may result in a relative difference in hydrocortisone exposure when using the same dosage to initiate KHINDIVI treatment. Monitor patients after switching to KHINDIVI to ensure KHINDIVI is providing the same level of hydrocortisone exposure as the previously used oral hydrocortisone formulation. If symptoms of adrenal insufficiency occur, increase the total daily dosage of KHINDIVI.

5.2 Systemic Adverse Reactions Due to Inactive Ingredients

<u>Hyperosmolarity</u>

KHINDIVI is not approved in pediatric patients less than 5 years of age. KHINDIVI contains the inactive ingredients polyethylene glycol 400, propylene glycol, and glycerin, which undergo substantial systemic absorption. These inactive ingredients, individually or in combination may increase plasma osmolarity in all pediatric patients, especially in pediatric patients less than 5 years of age due to incomplete maturity of the alcohol dehydrogenase enzyme that metabolizes propylene glycol and polyethylene glycol 400.

Monitor pediatric patients using KHINDIVI for signs and symptoms consistent with hyperosmolarity. Discontinue KHINDIVI and switch to another hydrocortisone formulation if this occurs.

Metabolic Acidosis and Other Adverse Reactions

KHINDIVI contains the inactive ingredient polyethylene glycol 400 and propylene glycol that may result in metabolic acidosis, hypoglycemia, hepato-renal injury, and central nervous system toxicity (e.g., seizure and coma). These adverse reactions may increase the risk of adrenal crisis *[see Warnings and Precautions (5.1)]*. Monitor laboratory values and for physical signs and symptoms of these adverse reactions. Discontinue KHINDIVI and switch to another hydrocortisone formulation if these adverse reactions occur.

Laxative Effects Due to Inactive Ingredients

KHINDIVI contains the inactive ingredients polyethylene glycol 400 and glycerin, which alone or in combination, may cause gastrointestinal irritation resulting in vomiting and/or diarrhea. These gastrointestinal reactions may increase the risk of adrenal crisis in patients with adrenal insufficiency *[see Warnings and Precautions (5.1)]*. Monitor for signs or symptoms of gastrointestinal irritation and associated fluid and electrolyte abnormalities. Discontinue KHINDIVI and switch to another hydrocortisone formulation if these adverse reactions occur.

5.3 Immunosuppression and Increased Risk of Infection with Use of a Dosage Greater Than Replacement

Use of the recommended dosage of KHINDIVI *[see Dosage and Administration (2.1, 2.2)]* as a replacement therapy in pediatric patients with adrenocortical insufficiency is not expected to cause immunosuppression or increase the risk of infection. The use of a greater than replacement dosage can suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. The use of KHINDIVI at greater than replacement dosage can:

- Reduce resistance to new infections
- Exacerbate existing infections
- Increase the risk of disseminated infections
- Increase the risk of reactivation or exacerbation of latent infections
- Mask some signs of infection

Infections associated with the use of corticosteroids at a greater than replacement dosage range from mild to severe or fatal, and the rate of infectious complications increases with increasing corticosteroid dosages.

Monitor for the development of infection and consider KHINDIVI dosage reduction as needed *[see Warnings and Precautions (5.1)].*

5.4 Growth Retardation

Long-term use of corticosteroids in excessive doses may cause growth retardation in pediatric patients. Historical cohorts of adults treated from childhood for congenital adrenal hyperplasia have been found to have growth retardation. Effects on linear growth are less likely when using corticosteroids as replacement therapy. Use the minimum dosage of KHINDIVI to achieve desired clinical response and monitor the patient's growth.

5.5 Cushing's Syndrome Due to Use of Excessive Doses of Corticosteroids

Prolonged use of corticosteroids in supraphysiologic doses may cause Cushing's syndrome. Symptoms and signs of Cushing's syndrome include weight gain, decreased height velocity, hyperglycemia, hypertension, edema, easy bruising, muscle weakness, red round face, depression, or mood swings. Monitor patients for signs and symptoms of Cushing's syndrome

every 6 months.

5.6 Decrease in Bone Mineral Density
Corticosteroids decrease bone formation and increase bone resorption which may lead to development of osteoporosis. Historical cohorts of adults treated from childhood for congenital adrenal hyperplasia have been found to have reduced bone mineral density and increased fracturerates. Use the minimum dosage of KHINDIVI to achieve desired clinical response.

5.7 Psychiatric Adverse Reactions
Corticosteroid use may be associated with severe psychiatric adverse reactions. Euphoria, mania, psychosis with hallucinations and delirium or depression have been seen in patients at replacement doses of hydrocortisone *[see Adverse Reactions (6)].* Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses, although dose levels do not allow prediction of the onset, type, severity, or duration of reactions. Most reactions resolve after either dose reduction or withdrawal, although specific treatment may be necessary. Monitor patients for behavioral and mood disturbances during treatment with KHINDIVI. Instruct caregivers and/or patients to seek medical advice if psychiatric symptoms develop.

5.8 Ophthalmic Adverse Reactions
Ophthalmic effects, such as cataract, glaucoma or central serous chorioretinopathy have been reported with prolonged use of corticosteroids in high doses. Monitor patients for blurred vision or other visual disturbances. If patients develop ophthalmic adverse reactions, refer them to an ophthalmologist for further evaluation.

5.9 Gastrointestinal Adverse Reactions

Gastrointestinal Perforation
There is an increased risk of gastrointestinal perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation may be masked in patients receiving corticosteroids. Corticosteroids should be used with caution if there is a probabilityof impending perforation, abscess, or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

Concomitant Use with Non-Steroidal Anti-Inflammatory Drugs
Concurrent administration of corticosteroids with non-steroidal anti-inflammatory drugs (NSAIDS) may increase the risk of gastrointestinal adverse reactions. Monitor patients receiving corticosteroidsand concomitant NSAIDS for gastrointestinal adverse reactions *[see Drug Interactions (7)].*

5.10 Risk of Kaposi's Sarcoma with Use of a Dosage Greater Than Replacement
Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions at a dosage greater than replacement (supraphysiologic dosage). If patients take a supraphysiologic chronic dosage of KHINDIVI, they are at increased risk of developing Kaposi's sarcoma.

5.11 Vaccination
Administration of live vaccines may be acceptable in KHINDIVI-treated pediatric patients with adrenocortical insufficiency who receive replacement corticosteroids.

6 ADVERSE REACTIONS

The following serious adverse reactions are described here and elsewhere in the label:

- Adrenal Crisis *[see Warnings and Precautions (5.1)]*
- Systemic Adverse Reactions Due to Inactive Ingredients *[see Warnings and Precautions (5.2)]*
- Immunosuppression and Increased Risk of Infection with Use of a Dosage Greater Than Replacement *[see Warnings and Precautions (5.3)]*
- Growth Retardation *[see Warnings and Precautions (5.4)]*
- Cushing's Syndrome Due to Use of Excessive Doses of Corticosteroids *[see Warnings and Precautions (5.5)]*
- Decrease in Bone Mineral Density *[see Warnings and Precautions (5.6)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.7)]*
- Ophthalmic Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.9)]*
- Risk of Kaposi's Sarcoma with Use of Dosage Greater than Replacement *[see Warnings and Precautions (5.10)]*
- Vaccinations *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical studies 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 of oral hydrocortisone was evaluated in an uncontrolled, open-label, single-arm clinical study in 18 pediatric patients with adrenocortical insufficiency treated with oral hydrocortisone granules. Adrenocortical insufficiency was due to congenital adrenal hyperplasia in 17 patients and to hypopituitarism in one patient. All patients received at least one dose of hydrocortisone granules. The age ranged from 36 days to 5.7 years at start of treatment; 8 patients were female and 10 were male; 100% were White. Adverse reactions that were reported in two or more patients (≥ 11%) are shown in Table 1.

Table 1: Adverse Reactions Occurring in ≥11% of Pediatric Patients with Adrenocortical Insufficiency Treated with Hydrocortisone Granules for up to 29 Months

Adverse Reactions	**N=18 n (%)**
Pyrexia	10 (56)
Gastroenteritis	9 (50)
Viral upper respiratory tract infection	8 (44)
Vomiting	7 (39)
Viral infection	6 (33)
Conjunctivitis	5 (28)
Otitis media viral	3 (17)
Tonsillitis	3 (17)
Body temperature increased	2 (11)
Bronchitis	2 (11)
Dental caries	2 (11)
Diarrhea	2 (11)
Genitourinary operation	2 (11)
Pharyngitis	2 (11)
Respiratory tract infection	2 (11)
Rhinitis	2 (11)

6.2 Postmarketing Experience

The following adverse reactions seen in pediatric and adult patients associated with the use of corticosteroids were identified in the literature and from postmarketing reports. Because some of 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.

Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Allergic Reactions: Anaphylaxis, angioedema

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scalp, edema, facial erythema, hyper or hypo-pigmentation, impaired wound healing, increased sweating, petechiae and ecchymoses, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria

Endocrine: Abnormal fat deposits, decreased carbohydrate tolerance, development of Cushingoid state, hirsutism, manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycemic agents in diabetics, menstrual irregularities, moon faces, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgeryor illness), suppression of growth in pediatric patients

Fluid and Electrolyte Disturbances: Fluid retention, potassium loss, hypertension, hypokalemic alkalosis, sodium retention

Gastrointestinal: Abdominal distention, elevation in serum liver enzymes levels (usually reversible upon discontinuation), hepatomegaly, hiccups, malaise, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, ulcerative esophagitis

General: Increased appetite and weight gain

Metabolic: Negative nitrogen balance due to protein catabolism

Musculoskeletal: Osteonecrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy,tendon rupture, vertebral compression fractures

Neurological: Arachnoiditis, convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually following discontinuation of treatment, insomnia, meningitis, mood swings, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, personality changes, sensory disturbances, vertigo

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, and central serous chorioretinopathy

Reproductive: Alteration in motility and number of spermatozoa

7 DRUG INTERACTIONS

Table 2: Drug Interactions with KHINDIVI

CYP3A4 Inhibitors	
Clinical Impact:	Hydrocortisone is metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant administration of inhibitors of CYP3A4 may lead to increases in serum concentrations of KHINDIVI and increase the risk of adverse reactions associated with the use of excessive doses.
Intervention:	Concomitant use of CYP3A4 inhibitors may require a decrease in the KHINDIVI dose.
Examples:	*Anti-fungals:* itraconazole, posaconazole, voriconazole *Antibiotics:* erythromycin and clarithromycin *Antiretrovirals:* ritonavir Grapefruit juice
CYP3A4 Inducers	
Clinical Impact:	Hydrocortisone is metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant administration of inducers of CYP3A4 may lead to decreases in serum concentrations of KHINDIVI and increase the risk of adverse reactions, including adrenal crisis.
Intervention:	Concomitant use of CYP3A4 inducers may require an increase in the KHINDIVI dose.
Examples:	*Anticonvulsants*: phenytoin, carbamazepine and oxcarbazepine *Antibiotics*: rifampicin and rifabutin *Barbiturates:* phenobarbital and primidone *Antiretrovirals*: efavirenz and nevirapine
Estrogen and Estrogen-Containing Products	
Clinical Impact:	Oral estrogen and estrogen-containing oral contraceptives may interact with hydrocortisone by increasing serum cortisol-binding globulin (CBG) concentration. Concomitant use may reduce the efficacy of KHINDIVI by binding and delaying or preventing absorption.
Intervention:	Concomitant use of estrogen/estrogen containing products may require an increase in the KHINDIVI dose.
Antidiabetic Agents	
Clinical Impact:	Corticosteroids in supraphysiologic doses may increase blood glucose concentrations.
Intervention:	Use of KHINDIVI in supraphysiologic doses may require a dose adjustment of antidiabetic agents.
Anticoagulant Agents	
Clinical Impact:	Concomitant use of warfarin and corticosteroids usually results in inhibition of response to warfarin, although there have been some conflicting reports.
Intervention:	Monitor coagulation indices in patients receiving KHINDIVI andconcomitant warfarin to maintain the desired anticoagulant effect.
Cyclosporine	
Clinical Impact:	Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use.
Intervention:	Monitor patients receiving KHINDIVI and concomitantcyclosporine.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	

Clinical Impact:	Concomitant use of NSAIDs and corticosteroids increases the risk of gastrointestinal adverse reactions. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids; this could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn.
Intervention:	Monitor patients receiving KHINDIVI and concomitant NSAIDs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Untreated adrenocortical insufficiency in pregnancy can result in a high rate of complications, including maternal mortality. The use of physiologic doses of hydrocortisone is not expected to cause major birth defects, miscarriage and adverse maternal and fetal outcomes. Available data from observational studies with hydrocortisone use in pregnancy have not identified a clear drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population isunknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Human Data

Available data from observational studies with hydrocortisone use in pregnant women have not identified a clear drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Evidence from published epidemiologic studies suggest that there may be a small increased risk of cleft lip with or without cleft palate associated with first trimester systemic corticosteroid use in pregnant patients. However, the data are limited and report inconsistent findings,and studies have important methodological limitations, including non-randomized design, retrospective data collection, lack of dose-response data and the inability to control for confounders, such as underlying maternal disease and use of concomitant medications. In addition, unlike other corticosteroids, hydrocortisone is enzymatically deactivated by the placenta and therefore limits fetal exposure.

Animal Data

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalentto the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats and rabbits without adrenocortical insufficiency have yielded an increased incidence of cleft palate in the offspring.

8.2 Lactation

Risk Summary

Cortisol is present in human milk. The use of hydrocortisone at a physiologic dose for adrenocortical insufficiency is not expected to adversely affect the breastfed infant or milk production. There are no data on the presence of hydrocortisone in breast milk, the effect on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KHINDIVI and any potential adverse effects on the breastfed infant from KHINDIVI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of KHINDIVI have been established in pediatric patients 5 years of age and older for replacement therapy of adrenocortical insufficiency and the information on this use is discussed throughout the labeling. Use of KHINDIVI for this indication is supported by findings of safety and efficacy in other approved hydrocortisone products, including supportive pharmacokinetic and safety data in pediatric patients with adrenocortical insufficiency.

KHINDIVI is not approved in pediatric patients less than 5 years of age. KHINDIVI contains the inactive ingredients polyethylene glycol 400, propylene glycol, and glycerin, which undergo substantial systemic absorption. These inactive ingredients, individually or in combination, may increase plasma osmolarity in all pediatric patients, especially in pediatric patients less than 5 years of age due to incomplete alcohol dehydrogenase maturity *[see Warnings and Precautions (5.2)].*

When prescribing KHINDIVI in pediatric patients 5 years of age and older, consider the combined daily amount of polyethylene glycol 400, propylene glycol, and glycerin from all sources including KHINDIVI and other drugs with inactive ingredients utilizing the same metabolic pathways as these inactive ingredients, which may increase exposure and lead to an increased risk of systemic toxicity *[see Warnings and Precautions (5.2)]*.

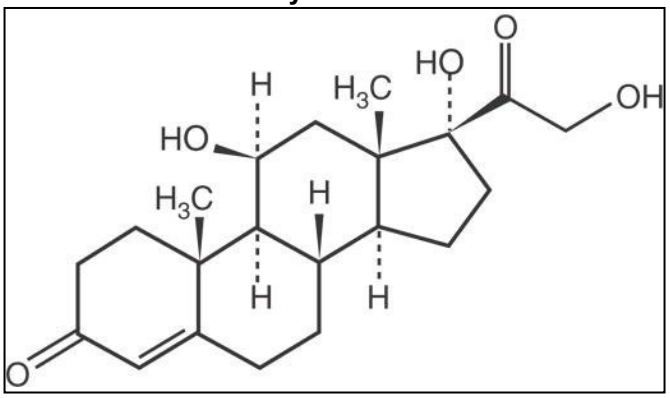
10 OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy.

11 DESCRIPTION

KHINDIVI contains hydrocortisone, a corticosteroid, also known as cortisol. The chemical name of hydrocortisone is 11β,17α,21-trihydroxy-pregn-4-ene-3,20-dione and it has the chemical formula of $C_{21}H_{30}O_5$, and molecular weight of 362 $g \cdot mol^{-1}$. Hydrocortisone is a white or almost white powder soluble in the pH range of 1-7.

Structural formula of hydrocortisone:



KHINDIVI is a clear, colorless to slightly yellow colored viscous solution of hydrocortisone available for oral administration in a concentration of 1 mg/mL. The inactive ingredients are berry flavor, butylated hydroxyanisole, ethyl maltol, glycerin (623 mg/mL), methylparaben, propylparaben, polyethylene glycol 400 (500 mg/mL), propylene glycol (50 mg/mL), and sucralose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocortisone is a glucocorticoid. Glucocorticoids, adrenocortical steroids, cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

12.2 Pharmacodynamics
Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states.

12.3 Pharmacokinetics
Absorption
Following oral administration of KHINDIVI (5 mg) in dexamethasone-suppressed healthy adult volunteers under fasted conditions, mean (range) C_{max} of hydrocortisone is 152 (98-210) ng/mL. Mean (range) T_{max} is 0.5 (0.25-0.75) hours.

Effect of Food
No clinically significant differences in KHINDIVI pharmacokinetics were observed following administration of a high-fat meal.

Distribution
90% or more of circulating hydrocortisone is reversibly bound to protein.

The binding is accounted for by two protein fractions. One, corticosteroid-binding globulin is a glycoprotein; the other is albumin.

Following administration of 5 mg Hydrocortisone oral solution in dexamethasone-suppressed healthy adult volunteers under fasted conditions, mean (range) Vd/F of hydrocortisone is 23 (5-59) L.

Elimination
Hydrocortisone is metabolized in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol which are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

Following administration of 5 mg Hydrocortisone oral solution in dexamethasone-suppressed healthy adult volunteers under fasted conditions, mean (range) terminal half-life of hydrocortisone is about 0.95 (0.3-2.3) hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No adequate studies in animals have been conducted with hydrocortisone to evaluate carcinogenic or mutagenic potential. Corticosteroids have been shown to impair fertility in male rats.

16 HOW SUPPLIED/STORAGE AND HANDLING
KHINDIVI is supplied as a colorless to slightly yellow colored, clear viscous solution:

Strength	Volume in Bottle	NDC
1 mg/mL	473 mL	71863-116-16

Store at 2°C to 25°C (36°F to 77°F). Excursions permitted to 30°C (86°F) [see USP refrigerated and controlled room temperature]. Protect from light and heat.

Product must be used within 120 days of first opening. If not used within 120 days, the unused

portion must be discarded.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or caregivers to read the FDA-approved patient labeling (Medication Guide).

Administration Information

Instruct patients and/or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients and/or caregivers that oral dosing syringes may be obtained from their pharmacy.

Advise patients and/or caregivers to take a sip of water immediately following administration to ensure all the solution has been swallowed.

For administration through a gastric tube, flush with 20 mL of water to ensure that the entire dose is delivered *[see Dosage and Administration (2.2)].*

Adrenal Crisis

Inform patients and/or caregivers that undertreatment or sudden discontinuation of KHINDIVI or switching to KHINDIVI from another oral hydrocortisone formulation, may lead to adrenocortical insufficiency, adrenal crisis, and death.

Inform patients and/or caregivers to switch to another oral hydrocortisone product and increase the dose during periods of stress, and not to use KHINDIVI for increased dosing during period of stress or acute events due to increased risk of systemic and gastrointestinal adverse reactions.

Inform the caregiver that potential dosing inaccuracy of the manipulated oral hydrocortisone formulation (e.g., split or crushed tablets, compounded formulations) may result in dosing differences when switching to KHINDIVI which may require dose adjustments. Advise caregivers to watch the patient for symptoms of adrenocortical insufficiency during the days after switching to KHINDIVI. Inform patient and/or caregiver to contact their healthcare provider if they have symptoms of adrenocortical insufficiency, prolonged vomiting, are severely ill or are unable to take oral medications *[see Warnings and Precautions (5.1)]*.

Systemic Adverse Reactions Due to Inactive Ingredients

Inform patients and/or caregivers that some inactive ingredients in KHINDIVI may increase the risk for hyperosmolarity, metabolic acidosis, loose stools, diarrhea, and other systemic adverse reactions, which may increase the risk of adrenal crisis. Patients and/or caregivers should contact the healthcare provider if patients have altered mental status, abnormal urine output, or are severely ill *[see Warnings and Precautions (5.2)]*.

Immunosuppression and Increased Risk of Infections

Advise patients and/or caregivers that greater than replacement dosage of corticosteroids can suppress the immune system and increase the risk of infections. Instruct patients and/or caregivers to contact their healthcare provider if they develop any infections *[see Warnings and Precautions (5.3)]*.

Growth Retardation

Discuss with caregivers that long-term use of corticosteroids in excessive doses may cause growthretardation in pediatric patients *[see Warnings and Precautions (5.4)]*.

Cushing’s Syndrome

Inform patients and/or caregivers that prolonged use of corticosteroids in supraphysiologic doses may cause Cushing’s syndrome and that symptoms and signs include weight gain, decreased

height velocity, hyperglycemia, hypertension, edema, easy bruising, muscle weakness, red round face, depression, or mood swings *[see Warnings and Precautions (5.5)]*.

Decrease in Bone Mineral Density
Inform patients and/or caregivers that corticosteroids decrease bone formation and increase bone resorption that may lead to osteoporosis *[see Warnings and Precautions (5.6)]*.

Psychiatric Adverse Reactions
Advise patients and/or caregivers that corticosteroid use may be associated with severe psychiatric adverse reactions such as euphoria, mania, psychosis with hallucinations or depression. Instruct caregivers and/or patients to seek medical advice if psychiatric symptoms develop *[see Warnings and Precautions (5.7)]*.

Ophthalmic Adverse Reactions

Inform patients and/or caregivers that ophthalmic effects such as cataract, glaucoma or central serous chorioretinopathy have been reported with prolonged use of high-dose corticosteroids. Instruct patients or caregivers to report any blurred vision or visual disturbances to their healthcare provider *[see Warnings and Precautions (5.8)]*.

Gastrointestinal Adverse Reactions
Discuss with patients and/or healthcare providers that use of corticosteroids may increase risk of gastrointestinal perforation in certain gastrointestinal disorders *[see Warnings and Precautions (5.9)]*.

Risk of Kaposi's Sarcoma
Inform patients that they are at risk of developing Kaposi's sarcoma *[see Warnings and Precautions (5.10)]*.

Vaccination
Inform patients and/or caregivers that administration of live vaccine may be acceptable *[see Warnings and Precautions (5.11)]*.

KHINDIVI is manufactured for Eton Pharmaceuticals, Inc. by Tulex Pharmaceuticals, Inc., 5 Cedarbrook Dr., Cranbury, NJ 08512, USA.

KHINDIVI® is a registered trademark of Eton Pharmaceuticals, Inc.

KHINDIVI is covered by the following US patents: 11,904,046, and 12,133, 914.