

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KEVEYIS™ (dichlorphenamide) tablets, for oral use
Initial U.S. Approval: 1958

-----**RECENT MAJOR CHANGES**-----

Indications and Usage: treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants (1) 8/2015
Dosage and Administration (2) 8/2015
Warnings and Precautions (5.1, 5.4, 5.5) 8/2015

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

KEVEYIS™ is an oral carbonic anhydrase inhibitor indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants (1)

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

- Initial dose: 50 mg twice daily (2)
- Titrate dose based on individual response (2)
- The maximum recommended dose is 200 mg daily (2)

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

Tablets: 50 mg (3)

-----**CONTRAINDICATIONS**-----

- Hepatic insufficiency (4)
- Severe pulmonary obstruction (4)
- Hypersensitivity to dichlorphenamide or other sulfonamides (4)
- Concomitant use with high dose aspirin (4)

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

- Hypersensitivity / Anaphylaxis / Idiosyncratic reactions: discontinue KEVEYIS™ at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction (5.1)
- Hypokalemia: baseline and periodic measurement of serum potassium are recommended; if hypokalemia develops or persists, consider reducing the dose or discontinuing KEVEYIS™ (5.3)
- Metabolic acidosis: baseline and periodic measurement of serum bicarbonate are recommended; if metabolic acidosis develops or persists, consider reducing the dose or discontinuing KEVEYIS™ (5.4)
- Falls: consider reducing the dose or discontinuing KEVEYIS™ in patients who experience falls (5.5)

-----**ADVERSE REACTIONS**-----

Most common adverse reactions (incidence at least 10% and greater than placebo) include paresthesias, cognitive disorder, dysgeusia, and confusional state (6)

To report SUSPECTED ADVERSE REACTIONS, contact Taro at 1-866-923-4914, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

Aspirin: Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin. The concomitant use of KEVEYIS™ and high dose aspirin is contraindicated. KEVEYIS™ should be used with caution in patients receiving low dose aspirin (4, 5.2, 7.1).

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

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2015

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1

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KEVEYIS™ is indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

2 DOSAGE AND ADMINISTRATION

Initiate dosing at 50 mg twice daily. The initial dose may be increased or decreased based on individual response, at weekly intervals (or sooner in case of adverse reaction). The maximum recommended total daily dose is 200 mg.

Primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants are a heterogeneous group of conditions, for which the response to KEVEYIS™ may vary. Therefore, prescribers should evaluate the patient's response to KEVEYIS™ after 2 months of treatment to decide whether KEVEYIS™ should be continued.

3 DOSAGE FORMS AND STRENGTHS

Round, white tablets, scored on one side, engraved with “TARO” on one side and on the other side “D” above the score and “50” below the score, 50 mg each.

4 CONTRAINDICATIONS

KEVEYIS™ is contraindicated in the following circumstances:

- Hypersensitivity to dichlorphenamide or other sulfonamides [*see Warnings and Precautions (5.1)*]
- Concomitant use of KEVEYIS™ and high dose aspirin [*see Warnings and Precautions (5.2)*]
- Severe pulmonary disease, limiting compensation to metabolic acidosis caused by KEVEYIS™ [*see Warnings and Precautions (5.4)*]
- Hepatic insufficiency: KEVEYIS™ may aggravate hepatic encephalopathy.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity / Anaphylaxis / Idiosyncratic Reactions

Fatalities associated with the administration of sulfonamides have occurred due to adverse reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Pulmonary involvement can occur in isolation or as part of a systemic reaction.

KEVEYISTM should be discontinued at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction.

5.2 Concomitant Use of Aspirin

Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorophenamide and high-dose aspirin. The concomitant use of KEVEYISTM and high dose aspirin is contraindicated. KEVEYISTM should be used with caution in patients receiving low dose aspirin.

5.3 Hypokalemia

KEVEYISTM increases potassium excretion and can cause hypokalemia. The risk of hypokalemia is greater when KEVEYISTM is used in patients with conditions associated with hypokalemia (e.g., adrenocortical insufficiency, hyperchloremic metabolic acidosis, or respiratory acidosis), and in patients receiving other drugs that may cause hypokalemia (e.g., loop diuretics, thiazide diuretics, laxatives, antifungals, penicillin, and theophylline).

Baseline and periodic measurement of serum potassium during KEVEYISTM treatment are recommended.

If hypokalemia develops or persists, consideration should be given to reducing the dose or discontinuing KEVEYISTM.

5.4 Metabolic Acidosis

KEVEYISTM can cause hyperchloremic non-anion gap metabolic acidosis. Concomitant use of KEVEYISTM with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis.

Baseline and periodic measurement of serum bicarbonate during KEVEYISTM treatment are recommended.

If metabolic acidosis develops or persists, consideration should be given to reducing the dose or discontinuing KEVEYISTM.

5.5 Falls

KEVEYISTM increases the risk of falls. The risk of falls is greater in the elderly and with higher doses of KEVEYISTM. Consider dose reduction or discontinuation of KEVEYISTM in patients who experience falls while treated with KEVEYISTM.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hypersensitivity / Anaphylaxis / Idiosyncratic reactions [see *Warnings and Precautions (5.1)*]
- Hypokalemia [see *Warnings and Precautions (5.3)*]
- Metabolic Acidosis [see *Warnings and Precautions (5.4)*]
- Falls [see *Warnings and Precautions (5.5)*]

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.

In a 9-week randomized controlled trial in adults with hyperkalemic or hypokalemic periodic paralysis (Study 1), the most common adverse reactions in patients treated with KEVEYIS™, with rates greater than placebo, were paresthesia, cognitive disorder, dysgeusia, and confusional state. The mean dose of KEVEYIS™ was 94 mg/day in patients with hypokalemic periodic paralysis and 82 mg/day in patients with hyperkalemic periodic paralysis.

Table 1 lists the incidence of adverse reactions that occurred in $\geq 5\%$ of patients treated with KEVEYIS™ and more commonly than in patients treated with placebo in Study 1.

Table 1: Adverse Reactions in Patients Treated with KEVEYIS™ with Incidence $\geq 5\%$ and more common than in Patients Treated with Placebo in Study 1

	Adverse Reaction	KEVEYIS™ N = 36 (%)	Placebo N = 29 (%)
Nervous system disorders	Paresthesia	44	14
	Cognitive disorder ¹	14	7
	Dysgeusia	14	0
	Confusional state	11	0
	Headache	8	7
	Hypoesthesia	8	0
	Lethargy	8	0
	Dizziness	6	0
Gastrointestinal disorders	Diarrhea	6	3
	Nausea	6	0
General disorders and administration site conditions	Fatigue	8	0
	Malaise	6	0
Investigations	Weight decreased	6	0
Musculoskeletal and connective tissue disorders	Muscle spasms	8	0
	Arthralgia	6	3
	Muscle twitching	6	0
Respiratory	Dyspnea	6	0
	Pharyngolaryngeal pain	6	0
Skin	Rash	8	0
	Pruritus	6	0

¹ Cognitive disorder combined cases with the preferred terms of *cognitive disorder*, *disturbance in attention*, and *mental impairment*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of dichlorphenamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following are adverse reactions which have been reported for dichlorphenamide that were serious adverse events or are not reported in the previous section of labeling [*see Clinical Trials Experience (6.1)*]: amnesia, cardiac failure, condition aggravated, convulsion, fetal death, hallucination, nephrolithiasis, pancytopenia, psychotic disorder, renal tubular necrosis, stupor, syncope, tremor.

7 DRUG INTERACTIONS

7.1 Aspirin and Salicylates

KEVEYISTM may cause an elevation in salicylate levels in patients receiving aspirin. Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin.

Concomitant use of KEVEYISTM and high dose aspirin is contraindicated. KEVEYISTM should be used with caution in patients receiving low dose aspirin. [*see Contraindications (4) and Warnings and Precautions (5.2)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Teratogenic effects (fetal limb reduction defects) were reported following oral administration of dichlorphenamide to pregnant rats during organogenesis at 350 mg/kg, or 17 times the maximum recommended human dose (200 mg/day) on a body surface area (mg/m²) basis. A no-effect dose has not been established. KEVEYISTM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether dichlorphenamide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dichlorphenamide is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

The risk of falls and of metabolic acidosis are greater in elderly patients.

10 OVERDOSAGE

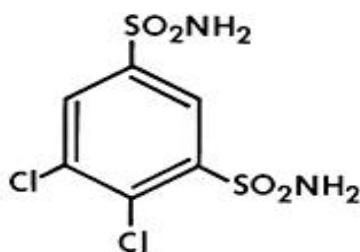
Symptoms of overdosage or toxicity may include drowsiness, anorexia, nausea, vomiting, dizziness, paresthesias, ataxia, tremor, and tinnitus.

In the event of overdosage, induce emesis or perform gastric lavage. The electrolyte disturbance most likely to be encountered from overdosage is hyperchloremic acidosis.

11 DESCRIPTION

KEVEYISTM (dichlorphenamide) tablets is an oral carbonic anhydrase inhibitor. Dichlorphenamide, a dichlorinated benzenedisulfonamide, is known chemically as 4, 5-dichloro-1,3-benzenedisulfonamide.

Its empirical formula is C₆H₆Cl₂N₂O₄S₂ and its structural formula is:



Dichlorphenamide USP is a white or practically white, crystalline compound with a molecular weight of 305.16. It is very slightly soluble in water but soluble in dilute solutions of sodium carbonate and sodium hydroxide. Dilute alkaline solutions of dichlorphenamide are stable at room temperature.

KEVEYISTM (dichlorphenamide) tablets is supplied as tablets, for oral administration, each containing 50 mg dichlorphenamide. Inactive ingredients are lactose monohydrate, magnesium stearate and pregelatinized maize starch.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dichlorphenamide is a carbonic anhydrase inhibitor. However, the precise mechanism by which dichlorphenamide exerts its therapeutic effects in patients with periodic paralysis is unknown.

12.3 Pharmacokinetics

The pharmacokinetic properties of dichlorphenamide after oral absorption are not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to assess the carcinogenic potential of dichlorphenamide have not been conducted.

Mutagenesis

Studies to assess the genotoxicity of dichlorphenamide have not been conducted.

Impairment of Fertility

Studies to assess the effects of dichlorphenamide on fertility have not been conducted.

14 CLINICAL STUDIES

The efficacy of KEVEYISTM was evaluated in two clinical studies, Study 1 and Study 2.

Study 1

Study 1 was a 9-week, double blind, placebo-controlled multi-center study. Study 1 consisted of two substudies: a substudy in patients with hypokalemic periodic paralysis (n=44), and a substudy in patients with hyperkalemic periodic paralysis (n=21). The primary efficacy endpoint in both substudies was the average number of self-reported attacks of muscle weakness per week over the final 8 weeks of the trial. Withdrawal from the study for acute severe worsening was also assessed as an endpoint.

In Study 1, the dose of KEVEYISTM was 50 mg b.i.d. for treatment-naïve patients. Patients already on dichlorphenamide prior to the study continued on the same dose while on

KEVEYIS™ during the study. In patients taking acetazolamide prior to the study, the dose of KEVEYIS™ was set at 20% of the acetazolamide dose. Dose reduction for tolerability was permitted.

Hypokalemic Periodic Paralysis Substudy of Study 1

In the hypokalemic periodic paralysis substudy, median age of patients was 45 years and 73% of patients were male. Patients treated with KEVEYIS™ (n=24) had 2.2 fewer attacks per week than patients (n=20) treated with placebo (p=0.02). None of the patients randomized to KEVEYIS™ reached the endpoint of acute worsening, vs. five patients randomized to placebo. The mean dose of KEVEYIS™ at Week 9 was 94 mg/day.

Hyperkalemic Periodic Paralysis Substudy of Study 1

In the Hyperkalemic Periodic Paralysis substudy, median age of patients was 43 years and 43% of patients were male. During the double-blind treatment period, patients treated with KEVEYIS™ (n=12) had 3.9 fewer attacks per week than patients (n=9) treated with placebo (p=0.08). None of the patients randomized to KEVEYIS™ reached the endpoint of acute worsening, vs. two patients randomized to placebo. The mean dose of KEVEYIS™ at Week 9 was 82 mg/day.

Study 2

Study 2 was a 35-week, double blind, placebo-controlled, multi-center, two-period crossover study. Study 2 also consisted of two substudies: a substudy in patients with hypokalemic periodic paralysis (n=42), and a substudy in patients with hyperkalemic periodic paralysis (n=31), including patients with Paramyotonia Congenita. The primary endpoint in the hypokalemic periodic paralysis substudy was the incidence of acute intolerable worsening (based on attack frequency or severity) necessitating withdrawal. The primary endpoint in the hyperkalemic periodic paralysis substudy was the average number of self-reported attacks of muscle weakness per week. Dosing was determined similarly to Study 1.

Hypokalemic Periodic Paralysis Substudy of Study 2

In the hypokalemic periodic paralysis substudy, mean age of patients was 38 years and 79% of patients were male. Acute intolerable worsening was observed in 2 patients on KEVEYIS™ vs. 11 patients on placebo (p=0.02). The mean dose of KEVEYIS™ at the end of the study was 96 mg/day.

Hyperkalemic Periodic Paralysis Substudy of Study 2

In the hyperkalemic periodic paralysis substudy, mean age of patients was 37 years and 79% of patients were male. Patients treated had 2.3 fewer attacks per week on KEVEYIS™ than on placebo (p=0.006). The mean dose of KEVEYIS™ at the end of the study was 73 mg/day.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each KEVEYISTM (dichlorphenamide) tablets, 50 mg – round, white tablet, scored on one side, engraved with “TARO” on one side and on the other side “D” above the score and “50” below the score.

KEVEYISTM (dichlorphenamide) tablets are supplied as follows:

Bottles of 100NDC 51672-4177-1

Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Worsening of Symptoms

Advise patients to notify their physician if they experience worsening of symptoms of periodic paralysis.

Driving and Operating Machinery

KEVEYISTM may cause drowsiness/fatigue in some patients. Caution patients on the potential for impaired ability to drive and operate machinery.

Mfd. by: Taro Pharmaceutical Industries Ltd., Haifa Bay, Israel 2624761

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