Tingling/ Paresthesia

You may have experienced tingling in your extremities recently. **Tingling/ paresthesia** is a possible side effect associated with KEVEYIS treatment for Primary Periodic Paralysis (PPP).[1] This brochure can help you **talk with your healthcare team** about how to best manage treatment-related tingling.

Please see Important Safety Information on back and Full Prescribing Information in pocket.

KEVEYIS®
dichlorphenamide 50 mg tablets

What is **tingling**?

Often described as "pins and needles," you may feel burning, numbness, and/or prickling in your hands and fingers, or even feet and toes. The medical term for this is **paresthesia**. An example of this feeling is when your arm "falls asleep" after leaning for too long in the same position.

The tingling you are feeling may be related to KEVEYIS (dichlorphenamide), or it may be related to your PPP.[1,2]

Ask your doctor if reducing your KEVEYIS dose may lessen the tingling you feel.

The content included herein is not intended to be a substitute for professional medical advice or treatment. Always seek the advice of your doctor or other qualified healthcare provider with any questions you may have about a medical condition.

How to talk with your doctor.

Describe your tingling in detail. Where do you experience it? What does it feel like? How long does it last? The more information your doctor has about what you're feeling, the better.

Ask about a dose adjustment.

Your doctor may reduce your KEVEYIS dose, which could reduce the tingling.

The amount of KEVEYIS you will take is based on your specific needs. You should be sure to take KEVEYIS exactly as your doctor has recommended for you. And, if you begin to experience any new side effects, be sure to talk to your doctor right away.[1]

In some cases your numbness and tingling may go away on its own.

This information is provided by **Strongbridge Biopharma** as part of our commitment to providing patients a wide range of services and support.
For more information, call 844-538-3947.

KEVEYIS®
dichlorphenamide 50 mg tablets

What is KEVEYIS?

KEVEYIS (pronounced keh-VAY-iss) (dichlorphenamide) is a prescription drug used to treat primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and other similar diseases.

Important Safety Information

What should you tell your healthcare provider before taking KEVEYIS?

Tell your doctor if you are allergic to dichlorphenamide or other sulfa drugs; if you take high doses of aspirin, or if you have lung or liver disease; if you are pregnant, plan to become pregnant, or are breastfeeding or plan to breastfeed.

What should you know about KEVEYIS?

- Severe allergic and other reactions have happened with sulfonamides (drugs such as KEVEYIS) and have sometimes been fatal. Stop taking KEVEYIS at the first sign of skin rash, swelling, difficulty breathing, or any other unexpected side effect or reaction, and call 911 right away.
- Tell your healthcare provider if you take aspirin or if another healthcare provider instructs you to begin taking aspirin. High doses of aspirin should not be taken with KEVEYIS.
- KEVEYIS can cause your body to lose potassium, which can lead to heart problems. Your healthcare provider will measure the potassium levels in your blood before you start treatment and at certain times during treatment.
- Tell your healthcare provider about all other prescription and over-the-counter medicines you take, including supplements, as some medicines can interact with KEVEYIS.
- While taking KEVEYIS, your body may produce too much acid or may not be able to remove acid from the body. Your healthcare provider may run tests on a regular basis to check for signs of acid buildup.
- KEVEYIS may increase your risk of falling. Tell your healthcare provider right away if you experience a fall while taking KEVEYIS.
- The risks of falls and acid buildup are greater in elderly patients.
- It is not known whether KEVEYIS is safe or effective for people younger than 18 years of age.

What are the most common side effects with KEVEYIS?

The most common side effects are a feeling of numbness, tingling or burning ("pins and needles") in the toes, feet, hands or fingers; trouble with memory or thinking; feeling confused; and unpleasant taste in the mouth.

These are not all of the possible side effects of KEVEYIS. Call your healthcare provider for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Full Prescribing Information in the pocket.

References. 1. KEVEYIS [package insert]. Feasterville-Trevose, PA: Strongbridge Biopharma; 2017. **2.** Charles G, Zheng C, Lehmann-Horn F, Jurkat-Rott K, Levitt J. Characterization of hyperkalemic periodic paralysis: a survey of genetically diagnosed individuals. *J Neurol*. 2013;260:2606–2613. **3.** Peripheral neuropathy caused by chemotherapy. American Cancer Society. https://www.cancer.org/content/dam/CRC/PDF/Public/7509.pdf. Accessed August 22, 2018.

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KEVEYIS®
dichlorphenamide 50 mg tablets

STRONGBRIDGE BIOPHARMA

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 Strongbridge Biopharma at 1-855-324-8912, 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: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 “D” above the score and “50” below the score, the other side is plain, 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.

KEVEYIS 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 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.

5.3 Hypokalemia

KEVEYIS increases potassium excretion and can cause hypokalemia. The risk of hypokalemia is greater when KEVEYIS 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 KEVEYIS treatment are recommended.

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

5.4 Metabolic Acidosis

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

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

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

5.5 Falls

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

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 ≥ 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 ≥ 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

KEVEYIS 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 KEVEYIS and high dose aspirin is contraindicated. KEVEYIS 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/m^2) basis. A no-effect dose has not been established. KEVEYIS 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

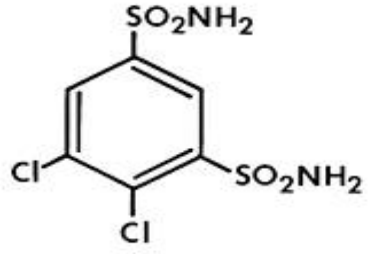
Symptoms of overdosage or toxicity may include drowsiness, anorexia, nausea, vomiting, dizziness, paresthesias, ataxia, tremor, and tinnitus.

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

KEVEYIS (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 $C_6H_6Cl_2N_2O_4S_2$ 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.

KEVEYIS (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 KEVEYIS 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 KEVEYIS 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 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 KEVEYIS (dichlorphenamide) tablet, 50 mg is round, white, scored on one side, engraved with “D” above the score and “50” below the score. The other side is plain.
KEVEYIS (dichlorphenamide) tablets are supplied as follows:
Bottles of 100 …….NDC 71090-001-01

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

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