KEVEYIS™ (dichlorphenamide) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictated that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Keveyis (dichlorphenamide) is an oral carbonic anhydrase inhibitor used for the prevention of paralytic attacks associated with primary hypokalemic periodic paralysis (hypoKPP), hyperkalemic periodic paralysis (hyperKPP), and other related variants (such as paramyotonia congenita with periodic paralysis and Andersen-Tawil syndrome). The precise mechanism by which it exerts its therapeutic benefit in patients with periodic paralysis is not known.

Primary periodic paralyses are a group of rare neuromuscular disorders in the family of diseases called channelopathies. It is thought that they are caused by mutations in skeletal muscle channel genes. They are characterized by episodes of flaccid weakness affecting one or more limbs, lasting several hours to several days. There are a number of variants of primary periodic paralysis and secondary causes such as thyrotoxic periodic paralysis of hyperthyroidism have been identified.
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HypoKPP is the most common disorder caused by a mutation in the voltage-gated calcium channel or voltage-gated sodium channel. Painless muscle weakness may be precipitated by heavy exercise, fasting, or high-carbohydrate meals. It has autosomal dominant inheritance or may be acquired in association with hyperthyroidism (thyrotoxic periodic paralysis).

HyperKPP is caused by point mutations in the voltage-gated sodium channel. Transient episodes of paralysis are usually precipitated by cold exposure, rest after exercise, fasting, or ingestion of small amounts of potassium.

Paramyotonia congenita with periodic paralysis is caused by mutations in the sodium channel. It is generally characterized by muscle stiffness which is made worse by cold temperatures or physical activity, but patients also have attacks of weakness and/or paralysis.

Andersen-Tawil is characterized by a triad of periodic paralysis, ventricular dysrhythmias, and dysmorphic features. It is clinically and genetically distinct from other periodic paralyses.

Carbonic anhydrase inhibitors (such as dichlorphenamide and acetazolamide), are established therapies and their adverse event profiles have been well characterized. There are no trials that compare dichlorphenamide and acetazolamide and as such there is no evidence that one is safer or more effective than the other in preventing paralytic attacks. Clinical trials of dichlorphenamide have compared it to placebo. Use of acetazolamide has not been evaluated in clinical trials but has shown efficacy in improving muscle strength. Other diuretics used off-label for periodic paralysis have included spironolactone and hydrochlorothiazide.

There are no guidelines on the treatment of periodic paralysis; evidence on pharmacotherapy used in treatment is limited to case reports and small, non-randomized, open-label studies. Treatment is selected by type of periodic paralysis and instituting various lifestyle modifications according to type of disease. In hypokPP non-pharmacological interventions include a low-carbohydrate diet and abstaining from vigorous exercise. Symptomatic potassium supplementation, potassium-sparing diuretics, and carbonic anhydrase inhibitors are used when lifestyle changes are not effective. In hyperkPP dietary modifications include avoiding foods rich in potassium and avoiding carbohydrate loading. Strenuous activity should also be avoided. Prophylaxis with carbonic anhydrase inhibitors and/or hydrochlorothiazide may be used.

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.
**KEVEYS™ (dichlorphenamide) oral tablet (cont.)**

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**

Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**

Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.
KEVEYS™ (dichlorphenamide) oral tablet (cont.)

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Keveyis (dichlorphenamide) oral tablet requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Keveyis (dichlorphenamide) is considered *medically necessary* when ALL of the following criteria are met:

  1. Individual is 18 years of age or older
  2. Individual has medical record documentation that use is for prevention of a confirmed diagnosis of **ONE** of the following:
     - Primary hyperkalemic periodic paralysis
     - Primary hypokalemic periodic paralysis
     - Paralysis in either of the related variants:
       - Paramyotonia congenita with periodic paralysis
       - Andersen-Tawil syndrome
  3. Unable to use acetazolamide due to **ONE** of the following:
     - Not effective
     - Not tolerated
     - Contraindicated
  4. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Serum potassium level
     - Serum bicarbonate level
  5. Absence of **ALL** of the following contraindications:
     - Hepatic insufficiency
     - Severe pulmonary disease
     - Hypersensitivity to dichlorphenamide or other sulfonamides
     - Concomitant use with high dose aspirin

- **Continuation of coverage (renewal request):** Keveyis (dichlorphenamide) is considered *medically necessary* with documentation of **ALL** of the following:

  1. The individual has benefited from therapy but remains at high risk
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2. The condition has not progressed or worsened while on therapy

3. Individual has not developed any contraindications or other exclusions to its continued use

- Keveyis (dichlorphenamide) for all other indications not previously listed is considered experimental or investigational based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:

  - Use in acute episode of periodic paralysis

Resources:


FDA-approved indication and dosage:

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<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>KEVEYIS is an oral carbonic anhydrase inhibitor indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants</td>
<td>- Initial dose: 50 mg twice daily</td>
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<td>- Titrate dose based on individual response</td>
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<td>- The maximum recommended dose is 200 mg daily</td>
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