BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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KEVEYIS™ (dichlorphenamide) oral

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 dictate 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.

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.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

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

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **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 or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Keveyis (dichlorphenamide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Congenital and Genetic Disease Specialist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Primary hyperkalemic periodic paralysis
     b. Primary hypokalemic periodic paralysis
     c. Paralysis in either of the related variants:
        i. Paramyotonia congenita with periodic paralysis
        ii. Andersen-Tawil syndrome
        iii. Congenital myasthenic syndrome
        iv. Potassium-associated myotonia

  4. Individual experiences one or more episodes of muscle weakness per week

  5. Individual has failed, or is intolerant to, or has a contraindication to **acetazolamide**

  6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate: **serum potassium and bicarbonate**

  7. There are **NO** contraindications:
     a. Contraindications include:
        i. Hepatic insufficiency
        ii. Severe pulmonary disease
        iii. Hypersensitivity to dichlorphenamide or other sulfonamides
        iv. Concomitant use with high dose aspirin

  Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Keveyis (dichlorphenamide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Congenital and Genetic Disease Specialist

  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. Reduction in severity of and number of attacks of muscle weakness per week

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3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Hypersensitivity, anaphylaxis
        ii. Persistent hypokalemia
        iii. Persistent metabolic acidosis (hyperchloremic, non-anion gap)
        iv. Persistent falls

5. There are no significant interacting drugs

Renewal duration: 12 months

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 paralysis

- 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 ion 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

- Therapy is directed by the type of periodic paralysis and instituting various lifestyle modifications according to type of disease
    - Carbonic anhydrase inhibitors are established therapies and their adverse effect profiles are 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 are also used off-label for periodic paralysis

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- Hypokalemic periodic paralysis (hypoKPP) is the most common disorder
    - It has autosomal dominant inheritance and is thought to be caused by a mutation in the voltage-gated calcium channel or voltage-gated sodium channel
    - Acquired cases of hypoKPP have been described in association with hyperthyroidism (thyrotoxic periodic paralysis)
    - Painless muscle weakness may be precipitated by heavy exercise, fasting, or high-carbohydrate meals
    - Acute attacks of hypoKPP are treated with oral potassium chloride 60-120 mEq
    - Non-pharmacological interventions include a low-carbohydrate diet and abstaining from vigorous exercise
        - Potassium supplementation, potassium-sparing diuretics, and carbonic anhydrase inhibitors are used when lifestyle changes are not effective
    - Prevention of hypoKPP is achieved by use of a carbonic anhydrase inhibitor, either acetazolamide 250 mg twice daily or dichlorphenamide 50 mg twice daily
        - Spironolactone 100 mg daily can be used as a supplement to carbonic anhydrase inhibitor or as an alternative to carbonic anhydrase inhibitor if a patient worsens or cannot tolerate the carbonic anhydrase inhibitor
        - Triamterene 150 mg daily may also be used

- Hyperkalemic periodic paralysis (hyperKPP)
    - It has autosomal dominant inheritance and is thought to be 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
    - Acute attacks with moderate or severe weakness and hyperkalemia can be treated by interventions that lower potassium levels such as:
        - Thiazides diuretics
        - Inhaled beta-adrenergic agonists
        - Intravenous calcium
    - Dietary modifications include avoiding foods rich in potassium and avoiding carbohydrate loading
        - Strenuous activity should also be avoided
    - Prophylaxis of hyperKPP is achieved with use of carbonic anhydrase inhibitors and/or hydrochlorothiazide

- Andersen-Tawil is characterized by a triad of periodic paralysis, ventricular dysrhythmias, and dysmorphic features such as short stature, hypertelorism, clinodactyly, micrognathia
    - Prolonged QT interval is also a feature
    - Paralytic attacks are commonly precipitated by rest after exercise
    - A dietary trigger is rarely identified
    - It is clinically and genetically distinct from other periodic paralyses
    - Carbonic anhydrase inhibitors are reported to limit attacks of weakness in some patients

- 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

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Definitions:

Periodic paralysis:

	Hypokalemic Periodic Paralysis	Hyperkalemic Periodic Paralysis	Andersen-Tawil Syndrome	Paramyotonia congenita
Age at onset	First or second decade	First decade	First or second decade	First decade
Attack frequency	Infrequent (a few times a year)	Frequent (up to several a day)	Monthly	
Attack duration	Hours to days	Minutes to hours	Days	Days to weeks
Precipitants	Exercise Carbohydrate load Stress	Exercise Fasting Stress K-rich food	Rest after exercise	Exercise Cold
Potassium level during attack	Low	Normal or elevated	Low, normal, or elevated	Low, normal, or elevated
Associated features	Later onset myopathy	Myotonia on examination and/or EMG Later onset myopathy	Dysmorphic features Ventricular arrhythmias Long QT interval	Myotonia of face or upper extremities, lower extremities are less affected, may also affect respiratory muscles
Etiology	Autosomal dominant inherited defect in calcium or sodium ion channel on muscle membrane	Autosomal dominant inherited defect of sodium ion	Autosomal dominant inherited defect of inward rectifying potassium channel	Autosomal dominant defect in a sodium channel
Preventive treatment	Carbonic anhydrase inhibitors Potassium-sparing diuretics	Carbonic anhydrase inhibitors Thiazide diuretics Inhaled beta-agonists as needed	Carbonic anhydrase inhibitors	Carbonic anhydrase inhibitors Thiazide diuretics or Loop diuretic

Resources:

Keveyis (dichlorphenamide) product information, revised by Strongbridge US, Inc. 11-2019, at DailyMed http://dailymed.nlm.nih.gov accessed January 29, 2021.

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Gutmann L, Conwit R. Hypokalemic periodic paralysis. In: UpToDate, Shefner JM, Wilterdink JL (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on January 29, 2021.

Gutmann L, Conwit R. Hyperkalemic periodic paralysis. In: UpToDate, Shefner JM, Wilterdink JL (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on January 29, 2021.