dichlorphenamide (Keveyis®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO121

Description

Dichlorphenamide (Keveyis) is a carbonic anhydrase inhibitor; however, the mechanism by which dichlorphenamide (Keveyis) exerts its therapeutic effects in periodic paralysis is unknown.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
dichlorphenamide (Keveyis)	Primary periodic paralysis	50 mg tablets	120 tablets/30 days

Initial Evaluation

I. **Dichlorphenamide (Keveyis)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist or provider with experience in primary periodic paralysis (e.g., physiatrist); **AND**
   B. Member is 18 years of age or older; **AND**
   C. A diagnosis of **primary hypokalemic or hyperkalemic periodic paralysis** when the following are met:
      1. Provider attestation that lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) have been maximized and have been ineffective or insufficient alone; **AND**
      2. Documentation of baseline attack frequency and average duration (required for renewal evaluation); **AND**
      3. Treatment with acetazolamide has been ineffective, or not tolerated; **AND**
         i. For hypokalemic periodic paralysis: treatment with a potassium-sparing diuretic (e.g., spironolactone, triamterene, eplerenone) in combination with acetazolamide has been ineffective, contraindicated, or not tolerated (Note: if acetazolamide is not tolerated, monotherapy with a potassium-sparing diuretic is required); **OR**
         ii. For hyperkalemic periodic paralysis: treatment with hydrochlorothiazide has been ineffective, contraindicated, or not tolerated.

II. Dichlorphenamide (Keveyis) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Glaucoma

III. Dichlorphenamide (Keveyis) is considered investigational when used for all other conditions, including but not limited to:
   A. Periodic paralysis not characterized as hyperkalemic or hypokalemic
   B. Pediatric periodic paralysis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) continue to be practiced; **AND**
IV. Documentation showing reduction in attack frequency, duration, or severity compared to baseline.

Supporting Evidence

I. Periodic paralysis (PP) is a rare neuromuscular disorder due to a defect in muscle ion channels, and is characterized by attacks of painless muscle paralysis and generalized weakness. The majority of PP cases are hereditary and not a result of hypo or hyperkalemia. Two types of PP include hypokalemic and hyperkalemic, pertaining to the serum level of potassium at the time of attack. Attacks may last minutes, hours, or days causing increased morbidity and impaired quality-of-life. Nonpharmacologic interventions may reduce frequency or severity of attacks. For hypokalemic PP, effective strategies may include a low sodium and low carbohydrate diet, supplementation with potassium, limiting vigorous exercise, minimizing stress, limiting alcohol intake, and avoidance of fasting. For hyperkalemic PP, effective strategies may include avoidance of potassium-rich foods, avoidance of fasting, minimizing exposure to cold, minimizing stress, and limiting vigorous exercise. When lifestyle modifications are ineffective or

insufficient for preventing attacks, medication therapy may be considered (e.g., diuretics, thiazides, carbonic anhydrase inhibitors).

II. Given the difficulty with diagnosing PP and specialized management and treatment of the condition, prescribing by, or in consultation with, a specialist is required.

III. Dichlorphenamide (Keveyis) is indicated for the treatment of primary hypokalemic and hyperkalemic PP and related variants; however, it has only been evaluated in hypokalemic and hyperkalemic PP.

IV. Dichlorphenamide (Keveyis) has been evaluated in Phase 3 clinical trials of adults with hypokalemic and hyperkalemic PP patients. Overall, trials showed that therapy may help reduce 2-4 attacks per week compared to placebo; however, the studies has several limitations: patients transitioning from acetazolamide to dichlorphenamide did not have a washout period before entering the study, hypokalemic patients could supplement with potassium as required for acute attacks, and adverse effects (e.g., dysgeusia, cognitive issues, and paresthesia) were more common in the dichlorphenamide group – which may have led to unblinding the trial. Given these considerations, therapeutic effects may not be fully attributable to dichlorphenamide (Keveyis).

V. Other treatment strategies:

- Dichlorphenamide (Keveyis) may have an advantage in the level of trials available (Phase 3); however, given trial shortcomings listed above as well as the cost of treatment, trial of acetazolamide and one additional therapy (see below) are required. Empiric treatment with acetazolamide is standard of care, and is significantly less costly ($2-8 per day vs. $330-1300 per day). Acetazolamide and dichlorphenamide are in the same medication class and are expected to have similar tolerance. Contraindications to acetazolamide are the same as those to dichlorphenamide (Keveyis). Additionally, it has not been proven that dichlorphenamide (Keveyis) is superior to acetazolamide in safety or efficacy, as there are no comparative studies.
- For hypokalemic PP prophylaxis, potassium-sparing diuretics (e.g., spironolactone, triamterene, eplerenone) may be effective pharmacotherapy. These may be used in conjunction with carbonic anhydrase inhibitors or as monotherapy in patients that did not tolerate or experienced efficacy with carbonic anhydrase inhibitors. It has not been proven that dichlorphenamide (Keveyis) is superior to potassium-sparing diuretics in safety and efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis) is more costly; thus, trial of a potassium-sparing diuretic is required before coverage consideration of dichlorphenamide (Keveyis). Use in addition to, or as second-line treatment after, acetazolamide may maximize efficacy of these therapies and is required prior to coverage consideration of dichlorphenamide (Keveyis).
- For hyperkalemic PP, hydrochlorothiazide may be effective pharmacotherapy. It has not been proven that dichlorphenamide (Keveyis) is superior to hydrochlorothiazide in safety or efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis)

is more costly; thus, trial of hydrochlorothiazide is required before coverage consideration of dichlorphenamide (Keveyis).

VI. Efficacy, if realized, should occur by two months of therapy. The prescribing information indicates that response should be evaluated after two months. Given variability of patient response, risk of therapy exacerbating the condition symptoms, and cost, documentation of improvement of attack frequency, severity or duration is required prior continuation of treatment. Of note, withdrawal from the study due to acute and severe worsening of symptoms occurred in two patients in clinical trials for dichlorphenamide (Keveyis). Without reduction in attack frequency, severity, or duration, therapy should not be continued. Three months is allowed for initial approval to allow time for assessment of response and continuity of care.

Investigational or Not Medically Necessary Uses

I. Dichlorphenamide (Keveyis) is not FDA-approved, or has not been sufficiently studied for safety and efficacy for the following conditions:
   A. Glaucoma: dichlorphenamide (Daranide) was FDA-approved for glaucoma in 1958, and it was subsequently thought to be effective, off-label, for periodic paralysis. Dichlorphenamide (Daranide) was discontinued in 2002, given lack of use for glaucoma and availability of many effective therapies for glaucoma. Therapy is now available from an alternative manufacturer, as brand Keveyis. Although dichlorphenamide has been utilized in glaucoma historically, at this time it is unproven if dichlorphenamide (Keveyis) is more likely to produce similar therapeutic results or is superior to other agents that could be utilized for glaucoma (i.e., ophthalmic carbonic anhydrase inhibitors). Additionally, it is not generally recognized as an appropriate treatment for this condition. Furthermore, dichlorphenamide (Keveyis) is significantly more costly that other therapies that could be utilized. Given these factors dichlorphenamide (Keveyis) is not medically necessary for treatment of gluacoma.
   B. PP not characterized as hypokalemic or hyperkalemic (i.e., Thyrotoxic PP, Andersen syndrome, etc.): dichlorphenamide (Keveyis) is indicated for the treatment of primary hyperkalemic PP, primary hypokalemic PP, and related variants; however, has only been evaluated in hypokalemic and hyperkalemic PP. Use for other variations of PP is considered experimental and investigational.
   C. Pediatric/adolescent PP: Dichlorphenamide (Keveyis) has not been sufficiently evaluated and is not FDA-approved in pediatric or adolescent patients. To date, one study has attempted to evaluate safety and efficacy of dichlorphenamide (Keveyis) in adolescent patients. The study included six adolescents that were exposed to therapy, five of which were evaluable for efficacy. Although median decrease from baseline in weekly attack frequency was numerically greater compared to placebo, the trial had multiple

shortcomings. It was not powered to statistically evaluate changes in attack frequency for the adolescent subgroup, the trial duration was only nine weeks long, few patients were evaluated, and the dose varied between patients. Safety concerns included skin rash, dizziness, numbness, lightheadedness, slow thinking, nausea, weakness, and weight loss among adolescent patients. This trial did not sufficiently determine consequences of therapy in adolescents, and safety and efficacy in this population remains unknown; thus, is considered experimental and investigational. Lifestyle modifications and alternative therapies may be considered.

References

1. Keveyis [Prescribing Information]. Hawthorne, NY: Taro Pharmaceuticals; November 2019.
2. Statland JM, Fontaine B, Hanna MG, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. Muscle Nerve. 2018;57(4):522-530.
3. Ciafaloni E, Cohen F, Griggs R. Efficacy and safety of dichlorphenamide for primary periodic paralysis in adolescents compared with adults. *Pediatr Neurol*. 2019;101:43-46.
4. Sansone VA, Burge J, McDermott MP, et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. Neurology. 2016;86(15):1408-1416.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria updated: Changed initial approval from two to three months, addition of age requirement, addition of requirement regarding lifestyle modifications, distinction between hyperkalemic and hypokalemic PP with additional associated medication trial. Updated renewal criteria to standard format and to allow only in the event of improvement in the condition. Update to latest policy format, addition of NMN and E/I indications.	07/2022
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations as response should be seen within two months of therapy. Addition of specialist requirements. **Addition of renewal criteria.**	12/2019
Policy created	09/2015