OVERVIEW
Keveyis, a carbonic anhydrase inhibitor, is indicated for the treatment of primary hyperkalemic periodic paralysis (HyperPP), primary hypokalemic periodic paralysis (HypoPP), and related variants.\(^1\) The primary periodic paralyses are rare muscle disorders caused by genetic mutations in ion channels.\(^2\) HypoPP is caused in 80% of cases by point mutations in the voltage-gated calcium channel gene on chromosome 1. Mutation in the CACNA1S, SCN4A, or KCNJ18 genes alter the usual structure and function of calcium or sodium channels.\(^3,4\) The altered channels cannot properly regulate the flow of ions into muscle cells, which reduces the ability of skeletal muscles to contract, leading to severe muscle weakness or paralysis.\(^3\) HyperPP and HypoPP are inherited in an autosomal dominant manner, so one copy of the altered gene in each cell is sufficient to cause the disorder.\(^5\) Other channelopathies include Andersen-Tawil syndrome, paramyotonia congenital, and potassium-aggravated myotonia.

The recommended initial dose of Keveyis is 50 mg twice daily (BID).\(^1\) The maximum recommended total daily dose is 200 mg. Primary HyperPP, primary HypoPP, 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 to decide whether it should be continued.

Efficacy Data
The efficacy of Keveyis was established in two Phase III studies.\(^1,6,9\) In both of these studies, when Keveyis was compared with placebo there was a statistically significant decrease in the attack frequency per week, severity-weighted attack rate, and the duration of attacks.

Other Drug Therapies
Oral potassium salts can be taken as maintenance/prophylactic therapy for patients with HypoPP; however, this does not completely prevent attacks.\(^4\) Although data are limited to case reports and single-blind trials, acetazolamide, another carbonic anhydrase inhibitor, has been used historically for primary periodic paralysis. In one Keveyis published study, 40% of patients (n = 29/73) were receiving prophylactic treatment at baseline; 76% of these patients (n = 22/29) were taking acetazolamide and the rest were taking dichlorphenamide.\(^6\) Acetazolamide treatment is beneficial in approximately 50% of patients with HypoPP and it has no effect in 30% of affected patients.\(^4\) It can also exacerbate symptoms in 20% of patients. Keveyis has been reported to be 30 times more potent than acetazolamide \textit{in vitro}.\(^9\) Prior to initiating Keveyis it is important to verify if the patient has had exacerbation with acetazolamide, since Keveyis is considered to be more potent and may potentially lead to more exacerbations.\(^7\)

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Keveyis. Because of the specialized skills required for evaluation and diagnosis of patients treated with Keveyis, as well as the monitoring required for adverse events and long-term efficacy, approval requires Keveyis to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for
1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**
Coverage of Keveyis is recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **Hypokalemic Periodic Paralysis (HypoPP) and Related Variants.**
   A) **Initial Therapy.** Approve for 2 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
   i. Patient has a confirmed diagnosis of primary hypokalemic periodic paralysis by meeting at least ONE of the following (a, b, or c):
      a) Patient has had a serum potassium concentration of less than 3.5 mEq/L during a paralytic attack; OR
      b) Patient has a family history of the condition; OR
      c) Patient has a genetically confirmed skeletal muscle calcium or sodium channel mutation; AND
   ii. The prescribing physician has excluded other reasons for acquired hypokalemia (e.g., renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic or laxative abuse); AND
   iii. Patient has had improvements in paralysis attack symptoms with potassium intake; AND
   iv. Patient has tried oral acetazolamide therapy (e.g., Diamox tablets, Diamox Sequels extended-release capsules, generics); AND
   v. According to the prescribing physician, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND
   vi. Keveyis is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist).
   B) **Patients Continuing Therapy.** Approve for 1 year if the patient has responded to Keveyis (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescribing physician.

   The normal serum potassium concentration ranges from 3.5 to 5.0 mEq/L, although there may be slight fluctuations in the normal range depending on the laboratory.\(^4\) Generally, serum potassium concentration < 3.5 mEq/L is considered hypokalemia.

2. **Hyperkalemic Periodic Paralysis (HyperPP) and Related Variants.**
   A) **Initial Therapy.** Approve for 2 months if the patient meets the following criteria (i, ii, iii, iv and v):
   i. Patient has a confirmed diagnosis of primary hyperkalemic periodic paralysis by meeting at least ONE of the following criteria (a, b, c, or d):
      a) Patient has had an increase from baseline in serum potassium concentration of greater than or equal to 1.5 mEq/L during a paralytic attack; OR
      b) Patient has had a serum potassium concentration during a paralytic attack of greater than 5.0 mEq/L; OR
      c) Patient has a family history of the condition; OR
      d) Patient has a genetically confirmed skeletal muscle sodium channel mutation; AND
ii. The prescribing physician has excluded other reasons for acquired hyperkalemia (e.g., drug abuse, renal and adrenal dysfunction); AND

iii. Patient has tried oral acetazolamide therapy (e.g., Diamox tablets, Diamox Sequels extended-release capsules, generics); AND

iv. According to the prescribing physician, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND

v. Keveyis is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist).

B) Patients Continuing Therapy. Approve for 1 year if the patient has responded to Keveyis (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescribing physician.

Hyperkalemia can be caused by a variety of other conditions such as renal dysfunction, so it is important to exclude other known causes of hyperkalemia to confirm diagnosis of HyperPP. The normal serum potassium concentration ranges from 3.5 to 5.0 mEq/L, although there may be slight fluctuations in the normal range depending on the laboratory. Generally, serum potassium concentration > 5.0 mEq/L or 5.5 mEq/L is considered hyperkalemia.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Keveyis has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES
**HISTORY**

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes*</th>
<th>TAC Approval Date</th>
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<tbody>
<tr>
<td>New Policy</td>
<td>--</td>
<td>11/18/2015</td>
</tr>
<tr>
<td>Annual revision</td>
<td>No criteria changes</td>
<td>11/16/2016</td>
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<tr>
<td>DEU revision</td>
<td>Added published randomized study as a new reference. Deleted line under Efficacy Data that noted only one study was published.</td>
<td>4/27/2017</td>
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<tr>
<td>Annual revision</td>
<td>No criteria changes</td>
<td>11/29/2017</td>
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<tr>
<td>Annual revision</td>
<td><strong>Hypokalemic Periodic Paralysis (HypoPP) and Related Variants:</strong> Criterion added that the prescribing physician has excluded other causes of acquired hypokalemia.</td>
<td>12/19/2018</td>
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TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: [http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx](http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx).