

Drug Evaluation: dichlorphenamide (Keveyis®) tablets

Date of Review: March 2018

Generic Name: dichlorphenamide

End Date of Literature Search: 01/03/18

Brand Name (Manufacturer): Keveyis (Taro Pharmaceuticals)

Dossier Received: No, dossier pending at time of request

Research Questions:

1. Does dichlorphenamide have superior efficacy compared to placebo or is it more effective than currently available medications (e.g. acetazolamide) for the treatment of hyperkalemic and hypokalemic periodic paralyses (HyperPP and HypoPP, respectively)?
2. Is dichlorphenamide safe for the treatment of HyperPP and HypoPP and what is the relative safety compared to current treatments?
3. Are there subpopulations (i.e. age, gender, ethnicity, disease duration, or severity) for which dichlorphenamide is more effective or associated with more harms?

Conclusions:

- Evidence for dichlorphenamide includes 2 poor quality randomized control trials (RCTs) with high risk for performance, detection, attrition and reporting bias.^{1,2} In addition, data were limited by small overall sample sizes for HypoPP (n=44 and 42) and HyperPP (n=21 and 31).^{1,2} These flaws in study design substantially limit interpretation of study results and may bias results in favor of treatment.^{1,2} It is difficult to draw any meaningful conclusions regarding efficacy and safety of dichlorphenamide based on these flawed studies.
- For patients with HyperPP, there is insufficient evidence that dichlorphenamide is more effective than placebo in reducing weekly paralytic attack rates or severity weighted attack rates over 9 weeks.^{1,2} Statistical significance for weekly paralytic attack rate and severity weighted attack rate was inconsistent between studies.^{1,2} In addition, there was no significant difference in the 36-Item Short Form Survey (SF-36) mental or physical components of quality of life for patients with HyperPP, and in some cases, placebo was non-significantly better than dichlorphenamide.¹
- For patients with HypoPP, there is insufficient evidence that dichlorphenamide is more effective than placebo in reducing weekly paralytic attack rates (mean difference [MD] 0.9 ± 1.4 , $p=0.02$; median difference -2.2 , 95% confidence interval [CI] -6.8 to -0.4 , $p=0.02$), preventing acute disease worsening (ARR 26.5%, number needed to treat [NNT] 5), or reducing the severity weighted attack rate (MD 1.1 ± 1.5 ; median difference -5.2 , 95% CI -25.2 to -1.2 , $p=0.02$) over a 9-week treatment period.^{1,2} Though results achieved statistical significance, data are limited by high risk for performance bias, high attrition rates, use of per-protocol analyses, poorly reported data, and broad exclusion criteria limiting applicability to the Oregon Health Plan (OHP) population.
- There is insufficient evidence that dichlorphenamide improves quality of life compared to placebo in patients with HypoPP over 9 weeks. The mean difference in the SF-36 physical component scores was 7.29 points (95% CI 2.26-12.32, $p=0.006$) with dichlorphenamide compared to placebo over a 9-week period (scale range 0-100).¹ There was no significant difference between groups for the mental component score, and both groups showed a numerical decline in quality of life. The clinical significance of this change is unclear, and results are significantly limited by high risk of bias in studies which affect interpretation of these results. The overall change in quality of life score (including physical, mental, and emotional components) was not reported.¹

- There is insufficient evidence to evaluate safety of dichlorphenamide. Numerous side effects were substantially more common in the dichlorphenamide group compared to the placebo group including paresthesia (number needed to harm [NNH] 3). Dichlorphenamide had numerically higher rates of discontinuation due to adverse events (statistical difference not reported).^{1,2} Dichlorphenamide labeling includes warnings for increased risk of falls, hypersensitivity, concomitant use of aspirin, hypokalemia and metabolic acidosis.³ In addition, the following serious adverse events were reported post approval: cardiac failure, amnesia, convulsion, fetal death, hallucination, pancytopenia, psychotic disorder, nephrolithiasis, renal tubular necrosis, stupor, tremor, and syncope.⁴ Though cause and effect have not clearly been established, the severity of these adverse effects is concerning.
- There is insufficient evidence to ascertain whether dichlorphenamide would provide more benefits or risks to selected subpopulations including children and patients with mild or severe disease.^{1,2} There is insufficient evidence to compare dichlorphenamide to other medications used for periodic paralysis such as acetazolamide at this time. Acetazolamide labeling includes similar adverse effects, but there have been no trials directly comparing the safety or efficacy of acetazolamide to dichlorphenamide.^{5,6,7}

Recommendations:

- Recommend implementation of prior authorization (PA) criteria for dichlorphenamide (**Appendix 2**).
- The Committee also referred funding of dichlorphenamide to the Health Evidence Review Commission (HERC) for prioritization consideration.

Background:

Primary periodic paralyses are genetic neuromuscular disorders characterized by flaccid limb paralysis due to channel abnormalities in skeletal muscle tissue.⁸⁻¹³ Genetic mutations in the SCN4A and CACNA1S genes affect sodium and calcium channels respectively.⁷ These channel defects allow for the dysregulation of potassium fluctuations in skeletal muscles.⁷ HypoPP is more common, with a prevalence of 1 in 100,000 compared to 1 in 200,000 for HyperPP.¹⁰⁻¹³ Based on the Oregon Medicaid population, there may be 10 people with HypoPP and 5 people with HyperPP. HyperPP affects both genders equally whereas HypoPP is 3 to 4 times more clinically prevalent in men.⁸⁻¹³ Age of onset is typically younger than 10 years old for both conditions, but may start later in HypoPP.^{7,10,12} Episodes generally occur more often at younger ages and decrease in frequency as age increases.^{7,10,12}

Episodes of HyperPP may last minutes to hours and episodes of HypoPP may last several hours. Some patients experience episodes which may last for a day or more.⁸⁻¹³ The episodes of paralysis are related to the serum level of potassium, with either hyperkalemia or hypokalemia acting as the precipitating factor.⁸⁻¹³ Other activities or actions that affect potassium levels such as a high carbohydrate diet, rest after exercise, fasting, and stress can also precipitate paralytic attacks.⁸⁻¹³ Medications which affect potassium levels such as steroids, insulin, and diuretics may also trigger attacks.⁸⁻¹³ Some people may experience few attacks in their lifetime or require no treatment, but some may experience frequent attacks which cause a sharp decrease in quality of life.⁸⁻¹³ Long-term consequences include myopathies, possibility of arrhythmias due to potassium fluctuations, and permanent muscle weakness.^{7-9,11,13} Data from several small studies indicate patients with either form of periodic paralysis are likely to experience myopathies and weakness during middle age when the attacks start to become less frequent.^{7-9,11,13} As many as 80% of patients with HyperPP over the age of 40 may develop permanent muscle weakness and 33% may develop progressive myopathies.⁷ There does not appear to be a correlation between attack frequency and development of myopathies.^{7-9,11,13} Myopathies from HypoPP and Hyper PP tend to affect the muscles of the pelvic girdle and the extremities.^{7-9,11,13}

Symptoms of HyperPP and HypoPP are typically not life-threatening and differ from Andersen-Tawil Syndrome (ATS), a more severe form of the disease which is associated with complications in other tissues besides skeletal muscle.^{7,8-13} ATS is caused by a defect in the KCNJ2 gene which is responsible for creating the KIR 2.1 potassium channel and affects cardiac, skeletal, and facial muscles.⁷ It causes a triad of features: cardiac arrhythmias, flaccid muscle weakness, and skeletal

malformations (including a short stature, low set ears, clinodactyly, hypo or micrognathia, and hypo or hypertelorism).⁷ Paramyotonia congenita is another similar condition which differs from HypoPP and HyperPP in that it can cause periodic paralysis with muscle tension instead of muscle weakness.¹⁴

Diagnosis of HypoPP and HyperPP is first based on genetic testing to determine the presence of mutations in the SCNA4 and CACNA1S genes.⁷ However, not all patients have an identifiable mutation, in which case diagnosis is based on clinical tests and characteristics.⁷ A positive family history of either condition, confirmed hypo- or hyperkalemia during an attack, typical episode triggers, and a positive long-exercise test are indicative of these conditions.⁷ The long exercise test determines muscle action potential over numerous time points after performing isometric exercises in specific muscles to induce a paralytic episode.⁷ A drop of >40% in the compound muscle action potential (CMAP) after the long exercise test indicates the presence of these conditions.⁷

Currently, there is no guideline-based standard of care for these conditions.⁷⁻⁹ There are also no guidelines for when to start treatment, if any treatment should be used in a preventative capacity, or for treatment of any permanent muscle weakness that may occur.⁷⁻⁹ Lifestyle and diet modifications to avoid potassium shifts are recommended, but may not prevent attacks from occurring altogether.⁷ Dichlorphenamide is the first FDA-approved medication for HypoPP and HyperPP.⁷ Medications which have historically been used to treat HypoPP include oral potassium and spironolactone.⁷⁻⁹ Medications occasionally used for HyperPP include inhaled beta agonists and thiazide diuretics.⁷⁻⁹ These treatment suggestions are based on case reports.⁷⁻¹³ Acetazolamide is a carbonic anhydrase inhibitor that has been used to treat both paralysis types, introducing the idea that another carbonic anhydrase inhibitor, dichlorphenamide, may also work.⁷⁻⁹ Evidence regarding acetazolamide's efficacy is poor, as it is based primarily on case reports and single blind studies in two patients.⁷⁻¹³ One small RCT (n=8) found that acetazolamide provided a statistically significant improvement in muscle strength, but did not evaluate attack frequency or quality of life.¹⁵ An uncontrolled retrospective analysis of 14 HypoPP patients in the United Kingdom taking acetazolamide demonstrated that only 57% of the patients experienced treatment benefit (i.e. decrease in attack rate or severity).¹⁶ The exact rate or frequency of attacks was not reported.¹⁶ Case reports of acetazolamide indicate that patients with specific mutations (such as CACNA1S mutations) are more likely to respond to acetazolamide.¹⁶ However, additional controlled trials need to be conducted to establish efficacy. The exact mechanism of action of these medications for the treatment of periodic paralysis is unknown, but several theories have recently emerged.⁷⁻⁹ Carbonic anhydrase inhibitors cause kaliuresis, increase bicarbonate excretion, and a non-anion gap acidosis.⁷ This action may lead to increased opening of the calcium dependent potassium channels in skeletal muscle and reduce susceptibility to paralytic attacks.⁷

The main goals of therapy are to reduce attack frequency and severity and increased quality of life. The minimal clinically important differences (MCID) have not been described for periodic paralysis and these outcomes.⁷⁻⁹ Quality of life was assessed in one of the studies using the SF-36 version 2 assessment, a validated tool to measure patient perceptions regarding their physical, mental, and emotional standing.^{1,2,17} The SF-36 version 2 is used for a variety of chronic conditions, and the estimated score used to establish a MCID varies depending on the condition. In patients with rheumatoid arthritis, changes of 4.4 points in the physical component score and 3.1 points in the mental component score have been suggested as a MCID.¹⁸ For patients with chronic obstructive pulmonary disorder, asthma, or heart disease, a score change of 6-8.5 points has been considered as a clinically meaningful improvement.¹⁹ The MCID for the SF-36 has not been established in patients with HyperPP and HypoPP. Each of the 36 questions are scored from 0-100 based on the chosen response.¹⁷ The scores are averaged by group (physical, mental, or emotional).¹⁷ The final outcome for each group falls on the scale between 0 and 100, with 100 being the best patient satisfaction.¹⁷ In clinical trials, means and medians were used to document attack rates from weeks 2-9 during treatment phases.^{1,2} The patient-reported attack severity was also assessed using numerical scales with ranges from 1-4 or 1-10, with 4 and 10 respectively being the most severe.^{1,2} Scores were reported as the average over the last 8 weeks of treatment.^{1,2} Intolerable increases in attack frequency or severity requiring withdrawal were also examined in the HypoPP groups to assess worsening of the condition.^{1,2}

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The FDA approved dichlorphenamide under the orphan drug designation for the treatment of HyperPP and HypoPP.^{3,4} This approval was based on two poor quality studies (HYP-HOP and Study 2), each consisting of two sub-studies of patients with HyperPP and HypoPP.³ Both studies were phase 3, multicenter, placebo-controlled, RCT.^{1,2} One of the studies had a crossover design with 4 phases (run-in period, 2 treatment phases, and an active washout period).² The other trial had one treatment phase.¹ Overall bias was high due to potential unblinding and high attrition rates in both studies (**Table 2**).^{1,2} The studies have limited applicability to the entire population with these conditions because patients with severe (>3 attacks/day) or very mild (<1 attack/week) disease, as well as chronic kidney, liver, heart, thyroid, and lung diseases were excluded.^{1,2} Only one study included participants younger than 18 years of age.² Additionally, dichlorphenamide was not studied in patients with other neuromuscular diseases, certain glaucoma variations, or in patients taking concomitant beta blockers, calcium channel blockers, or diuretics.^{1,2} The primary outcome in most instances was median attack rate per week or improvement of mean attack rate per week.^{1,2} The HypoPP arm in Study 2 used a primary endpoint of acute worsening necessitating withdrawal from the study as the primary outcome. This outcome was chosen because a high percentage of patients (approximately 65%) were receiving treatment with dichlorphenamide or acetazolamide prior to the studies, which could lead to worsening symptoms if randomized to placebo.² This was expected given the availability of these medications as off-label treatment, but it limits applicability to treatment naïve patients and increases risk of selection bias. Important secondary outcomes were the severity weighted attack rate and SF-36 mental and physical component score changes from baseline.^{1,2} Currently, there are no established minimal clinically important difference thresholds for these outcomes in HyperPP and HypoPP.⁷⁻⁹ Patients who were treatment naïve received 50mg of dichlorphenamide twice daily, but doses for treatment-experienced patients varied based on their current dose of acetazolamide (ACZ) or dichlorphenamide.^{1,2} Treatment phases were 9 weeks in duration.^{1,2}

The HYP-HOP study compared dichlorphenamide to placebo for patients with HyperPP (n=44) and HypoPP (n=21).¹ Patients were included if they had genetically definite, clinically definite, or clinically probable HypoPP or HyperPP.¹ Genetically definite was defined as a documented genetic mutation associated with HypoPP or HyperPP with either two attacks of tetraparesis or one attack with a positive family history. Clinically definite included patients who fit the aforementioned attack parameters and typical clinical features of either condition in addition to documented hypo- or hyperkalemia during an episode or a positive family history for either condition. Clinically probable was defined as meeting the previously mentioned attack rate parameters and typical clinical features.¹ The mean dose of dichlorphenamide in the HyperPP arm was 77.1 ± 31.0 mg/day and 93.75 mg/day in the HypoPP arm.¹ The primary outcome of median weekly attack rate was significantly lower with dichlorphenamide compared to placebo in the HypoPP arm (0.3 vs 2.4 for placebo, treatment effect [TE] -2.2, 95% CI -6.8 to -0.4, p=0.02).¹ The difference was not significant in the HyperPP arm.¹ The overall changes in median attack rates per week from baseline were low, with the largest difference in the HyperPP group which decreased from a median of 2 attacks per week to 0.9 attacks per week.¹ The median severity-weighted attack rate was significantly lower with dichlorphenamide compared to placebo for the HypoPP (0.6 vs 5.7 for placebo, TE -5.2, 95% CI -25.2 to -1.2, p=0.02) but not the HyperPP arm (1.0 vs 5.7 for placebo, TE -4.9, 95% CI NA to 1.2, p=0.03) due to the CI in the HyperPP group crossing the null.¹ Changes in quality of life, as assessed by SF-36 scores, were not consistent between sub-studies, were generally below thresholds set for other conditions, and in some cases placebo had improvement while dichlorphenamide showed worsening.^{1,18,19} Acute worsening evaluated in the HypoPP arm was defined as an intolerable increase in attack frequency or severity requiring withdrawal from the study.¹ Five participants (21%) in the placebo group and none in the dichlorphenamide arm reached this endpoint (ARR 21%, NNT 5).¹

Study 2 used a crossover study design to compare dichlorphenamide to placebo and included both a Potassium Sensitive Periodic Paralysis (PSPP) group and a HypoPP group.² The PSPP group included both patients with HyperPP and Paramyotonia congenita, and it is unclear if there were differences in response rates

between these populations as no data was provided regarding the number of HyperPP patients in the PSPP group.² Participants aged 10-75 years were eligible for enrollment (mean age 37-38 years).² Diagnostic criteria used for the HypoPP arm include a typical clinical profile, normal serum thyroxine level, and documented hypokalemia during an attack in the patient or one of their family members. Diagnostic criteria for the PSPP arm include presence of a mutation in the α subunit of the sodium channel and a positive potassium challenge in the patient or a family member (without the presence of a sodium channel mutation on skeletal muscle).² The primary outcomes were mean improvement in attack rates per week for the PSPP group and intolerable increase in frequency or severity of attacks necessitating withdrawal from the study for the HypoPP group.² The primary analysis for HypoPP patients included only participants who completed both treatment phases.² Eleven participants (32.4%) reached the endpoint of disease worsening in the placebo phase versus 2 participants (5.8%) in the dichlorphenamide phase ($p=0.02$, NNT 4).² The mean attack rate per week in the PSPP sub-study showed a statistically significant reduction with dichlorphenamide compared to placebo (MD 2.3 ± 2.9 , $p=0.006$).² The mean improvement in attack rate per week in the HypoPP arm also showed a statistically significant reduction compared to placebo (MD 0.9 ± 1.4 , $p=0.02$).² While the results for reduction of attacks per week between dichlorphenamide and placebo were significant, the improvement from baseline was different between the sub-studies, indicating there may be more benefit in the PSPP group.² The secondary endpoint for both sub-studies was mean improvement in the severity weighted attack rate.² The HypoPP (MD 1.1 ± 1.5) and PSPP (MD 4.6 ± 5.7) sub-studies showed a significant decrease in the dichlorphenamide group compared to placebo ($p=0.01$ and $p=0.003$, respectively).² Overall, dichlorphenamide demonstrated some effect on attack frequency and severity compared to placebo for patients with HypoPP and HyperPP.^{1,2} However, the sample size was small due to the rarity of disease, and analysis based on an even smaller per protocol population in study 2 severely limits interpretation of these results.^{1,2} Attrition was high in both studies. Risk of performance and detection bias was high due to broken blinding in all sub-studies.^{1,2} This is particularly concerning given the subjective nature of patient-reported outcomes including attack severity and quality of life. Additionally, the observed reduction in attack rate and severity does not appear to correlate with a consistently increased quality of life as assessed by the SF-36 scale.^{1,2,7-9} Reporting bias was high in study 2 due to inconsistencies in reported data and lack of data for individual groups.² Since it was approved under the orphan drug designation, it is not required to assess efficacy in the pediatric population.⁴ Further studies would need to be conducted in this population before using it in children at time of diagnosis. Additional studies comparing dichlorphenamide to acetazolamide or other therapies would also be warranted to determine if other options are effective. Due to poor quality of the studies and substantial bias, the lack of internal validity may have skewed the outcomes in favor of the treatment groups. Therefore, conclusions regarding efficacy based on these trials may be unreliable.

Clinical Safety:

The FDA safety analysis included 21 patients with HyperPP and 44 patients with HypoPP from the HYP-HOP study.³ The most common side effects seen in greater than 5% of patients and more common in the dichlorphenamide group compared to placebo include paresthesia, cognitive disorder, dysgeusia, and confusional state (**Table 1**).³ The NNH for paresthesia in the dichlorphenamide group compared to placebo over a 9-week period was 3 in the HypoPP arm of the HYP-HOP trial.¹ Compared to placebo, both the HypoPP (TE -13.1 mmHg) and HyperPP (TE -9.4 mmHg) arms showed a significant decrease of mean systolic blood pressures in the dichlorphenamide groups.¹ Only the HypoPP arm showed a significant decrease in diastolic blood pressures for dichlorphenamide compared to placebo (TE -7.4 mmHg).¹ Withdrawal due to adverse events occurred for one patient (4.2%) with HypoPP and 2 patients (16.7%) with HyperPP compared to placebo.¹

Data regarding serious adverse events in patients with HyperPP and HypoPP was limited. Serious adverse events reported in trials included rash requiring hospitalization and a fractured humerus, each of which only occurred in one patient.¹ The 52-week safety data included 53 patients, 8 of whom developed new renal calculi and 2 patients had an increase in the number or size of pre-existing calculi.¹ Statistical differences between groups were not reported.¹ Additionally, labeling for dichlorphenamide includes warnings for hypersensitivity/anaphylaxis, hypokalemia, metabolic acidosis, concomitant use of aspirin, and risk of falls.³ Baseline and periodic monitoring of serum potassium and bicarbonate is recommended.³ The exact rate of these adverse events is unclear, though risk of falls

may be higher in the elderly population and with higher doses.³ Additional adverse events reported in the post-approval period include the following: cardiac failure, amnesia, convulsion, fetal death, hallucination, pancytopenia, psychotic disorder, nephrolithiasis, renal tubular necrosis, stupor, tremor, and syncope.⁴ Though cause and effect have not clearly been established, the severity of these adverse effects is concerning.

Table 1. Adverse Reactions occurring in more than 5% of patients and greater in the dichlorphenamide group than the placebo group.³

Adverse Reaction	Dichlorphenamide (%) n=36	Placebo (%) n=29
Paresthesia	44	14
Cognitive disorder	14	7
Dysgeusia	14	0
Confusional state	11	0
Headache	8	7
Hypoesthesia	8	0
Lethargy	8	0
Fatigue	8	0
Muscle spasms	8	0
Rash	8	0
Dizziness	6	0
Diarrhea	6	3
Nausea	6	0
Malaise	6	0
Weight decrease	6	0
Arthralgia	6	3
Muscle twitching	6	0
Dyspnea	6	0
Pharyngolaryngeal pain	6	0
Pruritis	6	0

In comparison to dichlorphenamide, acetazolamide has similar side effects including metabolic acidosis, potentially increased risk of falls in the elderly, malaise, paresthesia, and cognitive disturbances.^{5,6} However, no trials provide direct comparative evidence regarding safety or rates of side effects.⁶ Hematologic side effects such as agranulocytosis and thrombocytopenia may occur with both medications.^{5,6,20,21}

The FDA is requiring the manufacturer to conduct a post-marketing trial to assess the pharmacokinetic profile of dichlorphenamide and identify additional cytochrome P450 drug-drug interactions.⁴ Though FDA documents indicate these studies may have been completed in 2016, results are not yet published.⁴ Overall, there is little evidence of poor quality to adequately support and assess the safety profile of dichlorphenamide. Trials included few patients and were limited to 9 weeks. It is unclear if the benefits of long-term treatment with dichlorphenamide outweigh the potential risks associated with therapy.

Pharmacology and Pharmacokinetic Properties: Currently unknown.^{3,20,21}

		<p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Evidence of ATS, respiratory muscle weakness, or cardiac arrhythmias during attacks Renal, hepatic, thyroid, lung, or heart disease Chronic, non-congestive acute-angle glaucoma Any other neuromuscular disease History of worsening symptoms with ACZ Concurrent use of other medications altering potassium levels 		<p>*NA: 2/9 placebo participants experienced acute worsening, assigned arbitrarily large attack rate for analysis</p> <p>Treatment effect for median outcomes calculated as the median of the bootstrap distribution of the treatment group differences in median response (DCP - placebo); mean differences used for mean outcomes</p>				<p>Applicability:</p> <p><u>Patient:</u> Broad exclusion criteria. Studied in adults likely not newly diagnosed. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HyperPP generally equally prevalent in both genders). Small sample size studied.</p> <p><u>Intervention:</u> 50mg BID is accepted starting dose for treatment naive patients or at a dose comparable to current therapy with titration based on symptoms. Mean dose of DCP was 77.1 ± 31.0 mg/day</p> <p><u>Comparator:</u> Placebo appropriate to determine efficacy. Lifestyle changes (e.g. diet, exercise) not monitored. Lack of comparison to acetazolamide limits conclusions regarding place in therapy.</p> <p><u>Outcomes:</u> Clinically relevant outcomes evaluated. Power not met, but statistically significant differences found in some outcomes. Significant differences between DCP and placebo for reduction in severity-weighted attack rates. Only randomized over 9-week period. Large differences between side effect rates.</p> <p><u>Setting:</u> Hospitals in the United States, United Kingdom, and Italy. 62% of participants were from the United States. Patients were admitted to the hospital for 3 days at treatment initiation which may not happen in practice.</p>
<p>1. Sansone et al.¹</p> <p>HYP-HOP NCT00494507</p> <p>Phase 3</p> <p>DB, PC, RCT, MC, PG</p> <p>Evaluated two separate populations, one studying participants with HyperPP (see above) and the other studying HypoPP</p>	<p>1. DCP 50mg BID, 20% of current ACZ home dose as DCP, or current home dose of DCP</p> <p>2. Placebo BID</p> <p>Randomization ratio not used</p> <p>9 weeks</p> <p>52 week uncontrolled study period followed the DB, PC controlled 9 week study</p>	<p>Demographics:</p> <ul style="list-style-type: none"> Mean age: 44 years Male gender: 73% Treatment naive: 28% Median attack rate per week: DCP 1.1 placebo 1.8 Mental SF-36 mean scores (0-100): DCP 52.1 placebo 48.5 Physical SF-36 mean scores (0-100): DCP 39.2 placebo 42.1 <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Genetically confirmed, clinically confirmed, or clinically probable HypoPP 	<p>ITT:</p> <p>1. 24 2. 20</p> <p>Attrition:</p> <p>1. 8.3% 2. 5%</p>	<p>Primary Endpoint:</p> <p>Assessed during weeks 2-9</p> <p>Median attack rate per week</p> <p>1. 0.3 2. 2.4</p> <p>TE: -2.2, (95% CI, -6.8 to -0.4); p=0.02</p> <p>Secondary Endpoint:</p> <p>Assessed during weeks 2-9</p> <p>Median severity-weighted attack rate (scale of 1-10)</p> <p>1. 0.6 2. 5.7</p> <p>TE: -5.2 (95% CI, -25.2 to -1.2) P= 0.02</p>	<p>NA</p> <p>NA</p>	<p>Outcome:</p> <p>Paresthesia</p> <p>1. 9 (38%) 2. 1 (5%) P= 0.01</p> <p>Cognitive disorder</p> <p>1. 5 (21%) 2. 2 (10%) P-value NR</p> <p>Serious adverse event</p> <p>1. 1 (4.2%) 2. 0 (0%) P-value NR</p>	<p>33%/3</p> <p>NA</p> <p>NA</p>	<p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> LOW. See HYP-HOP.</p> <p><u>Performance Bias:</u> HIGH. See HYP-HOP. Baseline attack rates lower in the HypoPP arm compared to HyperPP.</p> <p><u>Detection Bias:</u> HIGH. See HYP-HOP.</p> <p><u>Attrition Bias:</u> HIGH. See HYP-HOP. There was a 7% difference in diary entry median compliance between treatment groups.</p> <p><u>Reporting Bias:</u> UNCLEAR. See HYP-HOP.</p> <p>Applicability:</p> <p><u>Patient:</u> See HYP-HOP. Gender differences appropriate (HypoPP 3-4 times more common in men).</p> <p><u>Intervention:</u> See HYP-HOP. Mean dose of DCP was 93.75 mg/day. Potassium supplementation commonly used during HypoPP attacks.</p> <p><u>Comparator:</u> See HYP-HOP.</p> <p><u>Outcomes:</u> See HYP-HOP. P-values indicate statistical differences between DCP and placebo for median attack rates and severity weighted attack rates.</p> <p><u>Setting:</u> See HYP-HOP. 55% of participants from the United States.</p>

(presented here)	Patients allowed to take potassium supplements during acute attacks of HypoPP	<ul style="list-style-type: none"> • See HYP-HOP <u>Key Exclusion Criteria:</u> <ul style="list-style-type: none"> • See HYP-HOP • Known mutation in the α subunit of the mutated sodium channel (more commonly associated with HyperPP) 		<p>Mean Improvement in SF-36 scores from baseline</p> <p>1. Mental -0.96; Physical 4.68 2. Mental -6.52; Physical -2.61 MD Mental: 5.56 (95% CI -0.69 to 11.81); p=0.08 MD Physical: 7.29 (95% CI 2.26 to 12.32); p=0.006</p> <p>Intolerable increase in attack rate or severity necessitating withdrawal from phase</p> <p>1. 0 (0%) 2. 5 (21%) p-value 0.01</p> <p>Treatment effect: see above</p>	NA; NA	<p>Study withdrawal due to adverse event</p> <p>1. 1 (4.2%) 2. 0 (0%) P-value NR</p> <p>95% CI NR</p>	NA	
<p>2. Tawil et al.² NCT00004802</p> <p>Phase 3</p> <p>DB, PC, MC, crossover, RCT</p> <p>Analysis consists of two separate populations: participants with HypoPP (presented here) and the other studying PSPP (HyperPP and Paramyotonia Congenita with periodic paralysis; see below)</p>	<p>1. DCP 50 mg BID, 20% of ACZ home dose as DCP, or current home dose of DCP</p> <p>2. Placebo BID</p> <p>Randomization ratio not used</p> <p>4 phase trial</p> <ul style="list-style-type: none"> • <i>Phase I:</i> run-in period to assess journaling ability • <i>Phase II:</i> 9 week trial, all pre-study medications for PP stopped • <i>Phase III:</i> 9-week active washout 	<p><u>Demographics:</u></p> <ul style="list-style-type: none"> • Mean age: 38 years • Male gender: 76% • Treatment naïve: 43% • Mean attack rate/week: 2.5 <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> • 10-75 years old • >1 distinct episode/week but <3 episodes daily • Positive clinical profile meeting diagnostic criteria of HypoPP <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> • Pregnancy or no contraceptive use • History of thyroid, heart, respiratory, hepatic, or heart disease • History of worsening symptoms with ACZ 	<p><u>ITT:</u> 42</p> <p><u>PerP:</u> Primary Analysis 34</p> <p>Secondary Analysis 17</p> <p><u>Attrition:</u> Dropout during placebo phases versus DCP phases 1. 5 2. 1</p> <p>Dropout during any time 8 (19%)</p>	<p><u>Primary Endpoint:</u> Assessed weeks 2-8 during Phase II and IV</p> <p>Intolerable increase in attack rate or severity necessitating withdrawal from phase*</p> <p>1. 2 (5.9%) 2. 11 (32.4%) P= 0.02</p> <p><u>Secondary Endpoints:</u> Assessed weeks 2-8 during Phases II and IV</p> <p>Mean improvement in attack rate per week</p> <p>1. NR 2. NR MD 0.9 \pm 1.4 P= 0.02</p> <p>Mean improvement in severity weighted attack rate (scale of 1-4)</p> <p>1. NR 2. NR MD 1.1 \pm 1.5 P= 0.01</p>	26.5% /4	<p><u>Outcome:</u> Paresthesia</p> <p>1. 16 (42%) 2. 0</p> <p><u>Outcome:</u> Cognitive disorder</p> <p>1. 8 (21%) 2. 0</p> <p><u>Outcome:</u> Study withdrawal due to adverse event</p> <p>1. 2 (4.8%) 2. NR</p> <p>P-value and 95% CI NR</p>	NA	<p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> LOW. Used computer generated randomization plan with blocking and stratification. Sealed opaque envelopes used. Baseline characteristics not reported between groups though all patients received placebo and DCP.</p> <p><u>Performance Bias:</u> HIGH. Adequate blinding procedures. Medications identical in appearance. Blinding likely broken due to adverse events and subjective symptom improvement.</p> <p><u>Detection Bias:</u> HIGH. Blinding almost entirely broken due to presumed efficacy and side effects of DCP. Unclear if power met, but differences between groups were statistically significant.</p> <p><u>Attrition Bias:</u> HIGH. Not all data clearly described or available. Only 55% of patients completed all 4 phases of the HypoPP study. Did not use ITT; primary analysis only included data from 34 patients (81%) with HypoPP who had complete data from all phases. Attack rates only reported for 17 participants (23%) with HypoPP who had complete data.</p> <p><u>Reporting Bias:</u> HIGH. No protocol or supplementary material available, outcomes specified a priori. Attack rates only reported as a mean difference between treatment and placebo. There were inconsistencies in reported data, and attack rate was not reported for individual groups. Unclear how severity weighted attack rate was calculated.</p>

	<ul style="list-style-type: none"> Phase IV: 9-week crossover trial, all pre-study medications for PP stopped <p>Patients allowed to take potassium supplements during acute attacks of HypoPP</p>	<ul style="list-style-type: none"> History of life-threatening respiratory muscle weakness or cardiac arrhythmias Concurrent use of other medications altering potassium levels or affecting the heart 						<p>Applicability: <u>Patient:</u> Pediatric patients allowed to participate. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HypoPP 3-4 times more common in men). Few patients studied. <u>Intervention:</u> 50mg BID is accepted starting dose, titration can occur. Consistent dose not used. Potassium supplementation commonly used during HypoPP attacks. <u>Comparator:</u> Placebo used, diet and exercise not recorded but mimicked home routine during hospitalization <u>Outcomes:</u> Clinically relevant outcomes evaluated. Only used 9-week randomized treatment periods. Large differences between side effect rates. <u>Setting:</u> MC in United States and Canada from 1992 to 1995. Patients were admitted to the hospital for 3 days at treatment initiation to monitor for acute worsening with weekly follow-up which may not happen in practice.</p>
<p>2. Tawil et al.² NCT00004802</p> <p>Phase 3</p> <p>DB, PC, MC, crossover, RCT</p> <p>Analysis consists of two separate populations: participants with HypoPP (see above) and the other studying PSPP (HyperPP and Paramytonia Congenita with periodic paralysis; presented here)</p>	<p>1. DCP 50 mg BID, 20% of ACZ home dose as DCP, or current home dose of DCP</p> <p>2. Placebo BID</p> <p>Randomization ratio not used</p> <p>4 phase trial</p> <ul style="list-style-type: none"> Phase I: run-in period to assess journaling ability Phase II: 9 week trial, all pre-study medications for PP stopped Phase III: 9-week active washout 	<p>Demographics:</p> <ul style="list-style-type: none"> Mean age: 37 years Male gender: 58% Treatment naïve: 35% Mean attack rate/week: 3.8 <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> 10-75 years old >1 distinct episode/week but <3 episodes daily Positive clinical profile meeting diagnostic criteria of PSPP <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Pregnancy or no contraceptive use History of thyroid, heart, respiratory, hepatic, or heart disease History of worsening symptoms with ACZ 	<p>ITT: 31</p> <p>PerP: 16</p> <p>Attrition: Dropout during placebo phases versus DCP phases 1. 3 2. 2</p> <p>Dropout during any time 16 (51.6%)</p>	<p>Primary Endpoint: Assessed weeks 2-8 during Phase II and IV Mean improvement in attack rate per week 1. NR 2. NR MD 2.3 ± 2.9 P= 0.006</p> <p>Secondary Endpoints: Assessed weeks 2-8 during Phases II and IV Mean improvement in severity weighted attack rate (scale of 1-4) 1. NR 2. NR MD 4.6 ± 5.7 P= 0.003</p>	NA	<p>Outcome: Paresthesia 1. 11 (35%) 2. 2 (8%)</p> <p>Outcome: Cognitive disorder 1. 7 (24%) 2. 1 (3%)</p> <p>Outcome: Study withdrawal due to adverse event 1. 1 (3.2%) 2. NR</p> <p>P-values and 95% CI NR</p>	<p>NA</p> <p>NA</p> <p>NA</p>	<p>Risk of Bias (low/high/unclear): <u>Selection Bias:</u> LOW. See Tawil, et al. <u>Performance Bias:</u> HIGH. See Tawil, et al. <u>Detection Bias:</u> HIGH. See Tawil, et al. <u>Attrition Bias:</u> HIGH. Not all data clearly described or available. >50% attrition in PSPP sub-study. Did not use ITT; subjects used for analysis were those with complete attack rate data for both treatment phases. <u>Reporting Bias:</u> HIGH. See Tawil, et al.</p> <p>Applicability: <u>Patient:</u> Paramytonia congenita and HyperPP combined, impossible to distinguish efficacy for each condition. Pediatric patients allowed to participate. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HyperPP generally equally prevalent in both genders). Few patients studied. <u>Intervention:</u> 50 mg BID is accepted starting dose, titration can occur. Consistent dose not used. <u>Comparator:</u> Placebo used, diet and exercise not recorded but mimicked home routine during hospitalization. <u>Outcomes:</u> Clinically relevant outcomes evaluated. Only used 9-week randomized treatment periods. Large differences between side effect rates. <u>Setting:</u> MC in United States and Canada from 1992 to 1995. Patients were admitted to the hospital for 3 days at treatment initiation to monitor for acute worsening with weekly follow-up which may not happen in practice.</p>

	<ul style="list-style-type: none"> • <i>Phase IV</i>: 9-week crossover trial, all pre-study medications for PP stopped 	<ul style="list-style-type: none"> • History of life-threatening respiratory muscle weakness or cardiac arrhythmias • Concurrent use of other medications altering potassium levels or affecting the heart 						
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Abbreviations [alphabetical order]: ACZ = acetazolamide; ARR = absolute risk reduction; ATS = Andersen-Tawil Syndrome; BID = twice daily; CI = confidence interval; DB = double blind; DCP = dichlorphenamide; HyperPP = hyperkalemic periodic paralysis; HypoPP = hyperkalemic periodic paralysis; ITT = intention to treat; MC = multicenter; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PG = parallel group; PP = periodic paralysis; PerP = per protocol; PSPP = potassium sensitive periodic paralysis; RCT = randomized controlled trial; SF-36 = short form-36; TE = treatment effect.

- 20) Dichlorphenamide In: Lexi-Drugs. *Lexicomp Online [online database]*. Hudson, Ohio: Wolters Kluwer Health; December 4, 2017. Available at: <http://online.lexi.com.liboff.ohsu.edu/lco/action/search?q=dichlorphenamide&t=name&va=>. Accessed January 3, 2017.
- 21) Dichlorphenamide In: Drugdex. *Micromedex 2.0 [on-Line database]*. 2017. Greenwood Village, Colorado: Truven Health Analytics; October 10, 2017. Available at: http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/CS/493027/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/C27AB0/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegrateratedSearch?SearchTerm=dichlorphenamide&UserSearchTerm=dichlorphenamide&SearchFilter=filterNone&navitem=searchGlobal#. Accessed January 3, 2017.

Appendix 1: Prescribing Information Highlights³

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 Taro at 1-866-923-4914, 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: 8/2015

Appendix 2: Proposed Prior Authorization Criteria

Dichlorphenamide

Goal(s):

- Encourage appropriate use of dichlorphenamide for Hyperkalemic and Hypokalemic Periodic Paralysis.

Length of Authorization:

- Up to 3 months for the first authorization and first renewal. Up to 6 months for renewals thereafter.

Requires PA:

Dichlorphenamide

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP funded condition AND is the requested treatment funded by the OHP for that condition? Note: Treatments referenced on an unfunded line of the prioritized list (http://www.oregon.gov/oha/HPA/CSIHERC/Pages/Prioritized-List.aspx) are not funded by the OHP.	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Is the request for continuation of dichlorphenamide treatment previously approved by Fee-For-Service?	Yes: Go to Renewal Criteria	No: Go to #4

Approval Criteria		
4. Is the requested treatment for Andersen-Tawil Syndrome or Paramyotonia congenita?	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: Dichlorphenamide is only approved for Hyperkalemic and Hypokalemic Periodic Paralyzes.</p>	No: Go to #5
5. Is the request for treatment of Hyperkalemic or Hypokalemic Periodic Paralysis based on genetic testing or clinical presentation?	Yes: Go to #6	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: Dichlorphenamide is not indicated for other forms of periodic paralysis.</p>
6. Does the patient have an average baseline attack rate of ≥ 1 attack per week?	<p>Yes: Go to #7</p> <p>Document baseline attack rate.</p>	No: Pass to RPh. Deny; medical appropriateness.
7. Has the patient previously tried and failed acetazolamide?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness.
8. Has the patient previously experienced disease worsening upon treatment with acetazolamide?	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: Dichlorphenamide was not studied in this population due to potential for similar disease worsening effects.</p>	No: Go to #9

Approval Criteria		
<p>9. Have potential precipitating factors (including lifestyle and recent medication changes) been evaluated for with documentation of continued attack rate or severity upon changes to therapy or lifestyle modifications?</p> <p>Note: Medications which affect potassium levels include, but are not limited to, oral potassium, steroids, insulin, and diuretics.</p>	<p>Yes: Go to #10</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: Lifestyle and medication changes are generally regarded as first line therapy.</p>
<p>10. Is the patient currently taking ≥ 1000mg of aspirin daily?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: Concurrent use of ≥ 1000mg aspirin daily with dichlorphenamide is contraindicated.</p>	<p>No: Go to #11</p>
<p>11. Is the patient ≥ 18 years old?</p>	<p>Yes: Go to #12</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Note: There is insufficient evidence of safety and efficacy in the pediatric population.</p>
<p>12. Have baseline serum potassium and bicarbonate been documented as >3.5 mmol/L and >22 mmol/L respectively?</p>	<p>Yes: Approve for up to 3 months.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

Renewal Criteria		
<p>1. Has the weekly average attack rate decreased from baseline?</p>	<p>Yes: Go to #2</p> <p>Document attack rate.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

Renewal Criteria

2. Have the serum potassium and bicarbonate been measured and documented as >3.5 mmol/L and >22 mmol/L respectively since the last approval?

Yes: Approve for 3 months at first renewal and up to 6 months for renewals thereafter.

No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 3/18 (EH)

Implementation: 4/16/18