Clinical Policy Title: Ketone monitoring devices for ketogenic diet in epilepsy

Clinical Policy Number: 09.01.11

Effective Date: July 1, 2016
Initial Review Date: February 17, 2016
Most Recent Review Date: March 15, 2017
Next Review Date: March 2018

Policy contains:
- Ketone monitoring device.
- Ketogenic diet in epilepsy.

Related policies:
None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of ketone monitoring devices for monitoring members with epilepsy prescribed ketogenic diets to be investigational and, therefore, not medically necessary.

Limitations:

None.

Alternative covered services:

Urine test kits to test for ketones in members on the ketogenic diet for epilepsy.

Background
About 5.1 million Americans have a history of epilepsy, and 2.9 million have active epilepsy (CDC, 2016). The ketogenic diet is a special high-fat, low-carbohydrate diet in use since the 1920s (Rogovik, 2010) that helps to control seizures in some people with epilepsy. It is prescribed by a physician and carefully monitored by a dietitian. It is stricter with calorie, fluid, and protein measurement and occasional restriction than the modified Atkins diet, which is also used today. The diet is a potential option for treating epilepsy, as 1/3 of people with the disease are resistant to medication (Dhamija, 2013).

Ketogenic means that a producer of ketones in the body (keto = ketone, genic = producing). Ketones are organic compounds formed when the body uses fat for its source of energy. Usually the body uses carbohydrates (such as sugar, bread, and pasta) for its fuel, but because the ketogenic diet is very low in carbohydrates, fats become the primary fuel instead. Ketones are not dangerous. They can be detected in the urine, blood, and breath. Ketones are one of the more likely mechanisms of action of the diet, with higher ketone levels often leading to improved seizure control. However, there are many other theories for why the diet will work. There are probably multiple mechanisms by which the ketogenic diet suppresses seizures (Bough, 2007).

The ketogenic diet, a diet that is very high in fats, extremely low in carbohydrates, and adequate in protein has been used for the treatment of uncontrolled seizures. The traditional ketogenic diet entails an initial fasting and dehydration period, during which patients receive no food, and fluid intake is limited until ketones are present in the urine. Thereafter, a diet high in fat and low in carbohydrates and protein is introduced. Strict compliance with this unpalatable dietary regimen has been shown to have anti-convulsant effects, particularly in children. Hospitalization may be necessary during an initial starvation period to induce marked ketosis and weight loss. The length of hospital stay depends on the proposed initial starvation period and generally should not exceed three days.

According to an evidence-based guideline on diagnosis and management of epilepsy from the National Institute for Clinical Excellence (NICE, 2004), the ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy. The guidelines state, however, that the ketogenic diet should not be recommended for adults with epilepsy.

There are several ketone monitoring devices on the market, which are mainly used for managing diabetes:

- FreeStyle® Optium Neo, which has a choice of tools designed to help people who use insulin.
- Precision Xtra® system and Precision Xtra blood ketone test strips.
- Ketonix® breath ketone monitor, which is a reusable breath ketone analyzer that measures the level of breath ketones. Measurements indicate the acetone in a user’s breath, which is produced from the breakdown of acetoacetate in the person’s blood, and are highly accurate and reliable.
- Nova Max® Plus glucose and ketone monitoring system.
- Walgreens TRUEresult® system.
Searches

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on January 31, 2017. Search terms were “ketogenic diet” and “ketone monitoring.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

A 26-member panel of the Charlie Foundation comprised of pediatric epileptologists and dietitians from nine nations produced a consensus statement on manuscript of the ketogenic diet (Kossoff, 2009). Two physicians from Children’s Hospital of Philadelphia developed a treatment algorithm for treating epilepsy, including the ketogenic diet (Abend, 2008). The guideline includes monitoring the patient’s condition and treatment, but no specific mention of ketone monitoring was made (Kossoff, 2008).

A more recent guideline mentions ketogenic diet as one of the means of treating children with epilepsy for patients who are pharmacologically resistant (Tolaymat, 2015). Another recent guideline states recommendations for treating infants with seizures using the ketogenic diet (van der Louw, 2016).

Currently, randomized controlled trials (RCTs) on the effects of ketogenic diets are limited. One meta-analysis of 19 studies (n = 1084) of children (average age, 5.8) with epilepsy found the pooled odds ratio for those on the diet with a 50 percent or greater reduction in seizures was 2.25 (Henderson, 2006).

An RCT of 103 children ages 2 – 16 with daily seizures and failure to respond to two or more antiepileptic drugs for three months placed on the ketogenic diet had baseline seizures of 62 percent, compared to 137 percent in the control group. Those with epilepsy reported 38 percent (n = 28) of those on the diet had at least a 50 percent seizure reduction, compared to just six percent (n = 4) of those in
the control group (Neal, 2008). In a comparison of 125 children on a ketogenic diet vs. a classical diet, there were no significant differences between the percent of baseline seizures at 3, 6, and 12 months (Neal, 2009).

A systematic review found 32 percent of epileptic adults treated with ketogenic diets achieved at least a 50 percent reduction in seizures, not different from the 29 percent placed on a modified Atkins diet. The proportions achieving at least a 90 percent reduction were 9 and 5 percent, a significant difference. However, even though the effects are long term, they might not outlast treatment. Diets are well tolerated, but 51 percent and 42 percent of the ketogenic and modified Atkins diet patients discontinued them before study completion because of their restrictiveness (Klein, 2014). Another systematic review of 14 studies found the diet reduced seizures more than 50 percent in 33 percent of children (Keene, 2006).

A recent Cochrane review of seven RCTs of 427 children and adolescents found relatively similar results between persons with epilepsy on ketogenic diets and modified Atkins diets, but cautioned that more research is necessary to confirm these findings (Martin, 2016).

Ketone monitoring in urine and blood for compliance with the ketogenic diet may be performed at least daily, at any time. One study suggests that ketonuria is most reliably measured in the early morning and after dinner, as stable ketosis is highest at these times (Urbain, 2016).

Despite some positive results, some issues on efficacy of the ketogenic diet remain unaddressed. These include necessity of initial fast, duration of diet, fluid restriction, use of medium- vs. long-chain triglyceride fatty acid foods in the diet, need for carnitine supplements, long-term adverse effects, and interactions with antiseizure drugs (Rogovik, 2010).

Policy updates:

This version of the policy contains three additional practice guidelines/other, along with eight peer-reviewed references.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolaymat A (2014)</td>
<td>Key points:</td>
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<tr>
<td></td>
<td>- Epilepsy is a relatively common neurologic disorder in children, with important implications for development, parents, and society. Correct diagnosis starts with an accurate and complete history that consequently leads to a directed diagnostic workup.</td>
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<td></td>
<td>- Outlines a diagnostic and management approach to pediatric seizures and epilepsy syndromes. Correctly diagnosing epilepsy or nonepileptic imitators allows the health care provider to prescribe appropriately.</td>
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<td>- Alternative options for pharmacologically resistant patients, such as ketogenic diet, vagal nerve stimulation, and surgery are discussed. Most children favorably respond,</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<td>but early identification of medication failure is important to ensure optimal neurodevelopment.</td>
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<tr>
<td>Klein (2014)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Comparison of ketogenic diet and modified Atkins diet</td>
<td>• Review studies of ketogenic (KD) and modified Atkins diet (MAD) for refractory epilepsy.</td>
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<tr>
<td></td>
<td>• Achievement of &gt; 50% seizure reduction comparable (32% KD, 29% MAD).</td>
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<tr>
<td></td>
<td>• Achievement of &gt; 90% seizure reduction greater for KD (9% vs. 5%).</td>
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<td>• Effects take place quickly, with few side effects.</td>
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<td>• Many stop the diet before study completion (51% for KD, 42% for MAD).</td>
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<tr>
<td>Neal (2008)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Seizure changes in children who have failed to respond to antiepileptic drugs</td>
<td>• RCT of 145 children ages 2 – 16 with (at least daily) seizures who had failed at least two trials of antiepileptic drugs, comparing ketogenic diet to no change in treatment.</td>
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<td></td>
<td>• In three months, average % baseline seizures was lower in the diet group (62% vs. 137%).</td>
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<td>• Greater proportion in diet group had &gt; 50% reduction in seizures (38% vs. 6%).</td>
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<td>Henderson CB et al. (2006)</td>
<td><strong>Key points:</strong></td>
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<td></td>
<td>• The ketogenic diet (KD) is a medical nutrition therapy (MNT) for the treatment of epilepsy. As such, it can affect the outcome of an individual’s health and chronic medical condition. The components of MNT which have been established by the American Dietetic Association as core guidelines for nutrition care include a diet history, assessment, diet therapy, and a follow-up plan of care (American Dietetic Association, 2002). We have utilized these guidelines in designing our approach to KD therapy in our pediatric population. Many of the practices described here have been adopted from our practical experience.</td>
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**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Blood ketone test or reagent strip</td>
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