Subject: Ketogenic Diet Induction for Treatment of Intractable Seizures in the Hospital Setting		Original Effective Date: 6/19/2019
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Contents

DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina clinical policy document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [24-26]

Ketogenic dietary therapies (KDTs) are established, effective nonpharmacologic treatments for intractable childhood epilepsy. There are currently 4 major ketogenic diet therapies (KDTs): the classic KD, the modified Atkins diet (MAD), the medium chain triglyceride diet (MCT), and the low glycemic index treatment (LGIT). The classic ketogenic diet is a high-fat, low-protein, low-carbohydrate diet which has been used for the

treatment of uncontrolled seizures for many years and produces metabolic changes (ketosis) often associated with the starvation state. The diet is usually started with a brief fasting period and changes in plasma ketones, insulin, glucose, glucagon, and free fatty acids can occur within hours of initiation. The ketogenic diet is quite restrictive, requiring the cooperation of the individual, family and an appropriately trained dietician. The diet may be initiated in the inpatient or outpatient setting. In the inpatient setting, children are admitted to the hospital and fasted for one to two days. Then, daily calorie intake and/or the ketogenic diet ratio is gradually increased until the full ketogenic diet for home use is achieved. The purpose for hospitalization is to monitor for potential acute complications such as hypoglycemia, excessive ketosis, emesis, diarrhea and/or dehydration; educate parents/caregivers around how to manage the diet at home and how to treat potential complications; and ensure parents/caregivers can safely manage the diet at home. The proposed length of hospital stay will depend on the patient's tolerance and safety, but generally should not exceed 3-4 days. However, there is no evidence that inpatient initiation of the ketogenic diet was superior to outpatient initiation.

POSITION STATEMENT RECOMMENDATION [24-26]

1. Inpatient hospitalization for initiation of a ketogenic diet is considered NOT medically necessary in **children and adolescents who are <18 years of age** for the treatment of drug resistant epilepsy, intractable seizures and/or any other diagnosis due to insufficient peer reviewed medical literature. Generally, the initiation of a ketogenic diet may be safely performed in the Outpatient/Observation or home setting and it is not medically necessary to fully admit to the inpatient hospital setting.
2. Inpatient hospitalization for initiation of a ketogenic diet is considered experimental, investigational and unproven in **adults who are >18 years of age** for the treatment of drug resistant epilepsy, intractable seizures and/or any other diagnosis due to insufficient peer reviewed medical literature.

SUMMARY OF MEDICAL EVIDENCE [2-21]

Inpatient Hospitalization Ketogenic Diet

There are no randomized, controlled trials in the peer reviewed medical literature or evidence based professional society guidelines that outline medically necessary eligibility for inpatient hospitalization, concurrent review and discharge in patients for the initiation of a ketogenic diet for any diagnosis. The literature consists of retrospective studies and case series that do not compare inpatient vs. outpatient services. Additional research using double-blind, placebo-controlled designs is needed to further define patient selection criteria, efficacy, and safety of inpatient vs. outpatient initiation of the ketogenic diet.

Lin et al, (2017) conducted a retrospective study of children with intractable epilepsy electively admitted for ketogenic diet initiation. Charts were reviewed for adverse effects during the admission period and then examined for seizure reduction and compliance at three months. A rating scale (1 to 4) was created for severity of any adverse events. A total of 158 children were included, with the mean age 4.6 years. Potentially attributable adverse effects occurred in 126 (80%) children, most commonly emesis, food refusal, and hypoglycemia. Seventy-three (46%) children received some form of intervention by the medical team, most commonly the administration of juice (24%). Younger age was correlated with an increased likelihood of moderate to severe adverse effects during admission, often repeated hypoglycemia (3.6 versus 4.9 years, P = 0.04). Fasting was more likely to result in lethargy and a single blood glucose in the 30 to 40 mg/dL range, but

it was not correlated with emesis, repeated hypoglycemia, or higher adverse effect scores. There was no statistically significant correlation between the severity of adverse effects and the three-month seizure reduction. The authors concluded that mild easily treated adverse effects occurred in most children admitted for the ketogenic diet. Younger children were at greater risk for significant difficulties and should be monitored closely. Because fasting led to more lethargy and hypoglycemia, it may be prudent to avoid this in younger children. [12]

In 2004, Vaisleib et al. conducted a case series of 37 individuals who underwent outpatient induction of the ketogenic diet, whose outcomes were compared retrospectively to those who underwent inpatient dietary induction. The mean age of the individuals was 6.6 years, with a range of 1.8 to 14 years. The authors reported that there was no evidence that inpatient initiation of the ketogenic diet was superior to outpatient initiation.

Ketogenic Diet for Drug resistant Epilepsy

There is evidence in the peer reviewed medical literature indicating that ketogenic diets can significantly reduce seizure frequency in a sizable percentage of pediatric patients with epilepsy who have failed or cannot tolerate AED treatment. There is a paucity evidence regarding the efficacy of ketogenic diets in adult patients. Therefore, the ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy but should not be recommended for adults with epilepsy.

A recent Cochrane publication by Martin et al, (2018) assessed the effects of ketogenic diets (KDs) for drug resistant epilepsy by reviewing the evidence from randomised controlled trials (RCTs). 11 RCTs that generated 15 publications were identified. All trials applied an intention-to-treat analysis with varied randomization methods. The 11 studies recruited 778 patients; 712 children and adolescents and 66 adults. A meta-analysis was not conducted due to the heterogeneity of the studies and the quality of the evidence was low to very low. Reported rates of seizure freedom reached as high as 55% in a classical 4:1 KD group after three months and reported rates of seizure reduction reached as high as 85% in a classical 4:1 KD group after three months (GRADE rating low).One trial found no significant difference between the fasting-onset and gradual-onset KD for rates of seizure freedom, and reported a greater rate of seizure reduction in the gradual-onset KD group. Studies assessing the efficacy of the MAD reported seizure freedom rates of up to 25% and seizure reduction rates of up to 60% in children. One study used a simplified MAD (sMAD) and reported seizure freedom rates of 15% and seizure reduction rates of 56% in children. One study utilized a MAD in adults and reported seizure reduction rates of 35%, but no patients became seizure free. Adverse effects of the dietary interventions were experienced in all studies. The most commonly reported adverse effects were gastrointestinal syndromes. It was common that adverse effects were the reason for participants dropping out of trials. Other reasons for dropout included lack of efficacy and non-acceptance of the diet. Although there was some evidence for greater antiepileptic efficacy for a classical 4:1 KD over lower ratios, the classical 4:1 KD was consistently associated with more adverse effects. One study assessed the effect of dietary interventions on quality of life, cognition and behavioral functioning, reporting participants in the KD group to be more active, more productive and less anxious after four months, compared to the control group. However, no significant difference was found in quality-adjusted life years (QALYs) between the KD group and control group at four or 16 months (GRADE rating very low). The authors concluded that the RCTs discussed in this review show promising results for the use of KDs in epilepsy. However, the limited number of studies, small sample sizes and the limited studies in adults, resulted in a low to very low overall quality of evidence. There were adverse effects within all of the

studies and for all KD variations, such as short-term gastrointestinal-related disturbances and increased cholesterol. However, study periods were short, therefore the long-term risks associated with these adverse effects is unknown. Attrition rates remained a problem with all KDs and across all studies; reasons for this being lack of observed efficacy and dietary tolerance. Only one study reported the use of KDs in adults with epilepsy; therefore further research would be of benefit. Other more palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but this assumption requires more investigation. For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, KDs remain a valid option; however, further research is required. [14]

Professional Society Guidelines

According to the National Institute for Clinical Excellence (NICE) guideline on epilepsies, children and young people with epilepsy whose seizures have not responded to appropriate antiepileptic drugs (AEDs) should be referred to a tertiary pediatric epilepsy specialist for consideration of the use of a ketogenic diet. [22]

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
99499	Unlisted evaluation and management service [when specified as services related to ketogenic diet]

HCPCS	Description
	N/A

ICD-10	Description: [For dates of service on or after 10/01/2015]
G40.009, G40.019, G40.109, G40.119, G40.209, G40.219, G40.309, G40.319, G40.A09, G40.A19, G40.B09, G40.B19, G40.409, G40.419, G40.509, G40.802, G40.804, G40.812, G40.814, G40.822, G40.824, G40.909, G40.919	Epilepsy and recurrent seizures, without status epilepticus

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REVIEW/REVISION HISTORY

6/19/2019: New Policy
6/17/2020 & 2/8/21: Policy reviewed, no changes. References updated.