Molina Clinical Policy
Ketogenic Diet Induction for Treatment of Intractable Seizures in the Hospital Setting: Policy No. 344

Last Approval: 02/12/2025
Next Review Due By: February 2026

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Seizures are defined as paroxysmal disorders of the central nervous system characterized by abnormal cerebral neuronal discharge, with or without loss of consciousness. Most seizures can be categorized as either focal or generalized according to whether the onset of electrical activity involves both sides or a focal region of the brain. Seizures and corresponding seizure disorders have a multitude of causes often originating from genetic, idiopathic, and/or metabolic origins. Anti-epileptic medications are the first line of defense in treating seizures, however, many cases remain uncontrolled even in the setting of a rigorous drug regimen.

Ketogenic diet is an effective non-pharmacologic treatment to control intractable seizures in the pediatric population. The ketogenic diet is a high fat diet, adequate protein, and low carbohydrate diet that results in a state of ketosis of the body. Side effects of a ketogenic diet may include constipation, reflux, weight changes, kidney stones, and mood changes. A ketogenic diet can be effective for all seizure types and epilepsy syndromes for effective treatment of intractable seizures, the patient must be strict in their adherence to the diet and should be followed by an interdisciplinary team to monitor their health status, developmental milestones, seizure frequency and management, metabolic lab values, and growth curves. Additional dietary modification options that have shown promise in reducing seizure frequency are the medium-chain triglyceride diet, modified-Atkins diet, and low glycemic index treatment (Kossoff 2023).

Historically pediatric patients beginning the classic ketogenic diet were monitored for 3-5 days during an inpatient hospital admission. The younger a patient is, the higher the risk of complications during initiation of a ketogenic diet, however, the diet can most often be safely started under observation, or in the outpatient setting. The location, resources needed, and whether fasting is necessary varies per the individual patient's situation.

COVERAGE POLICY

1. Inpatient hospitalization solely 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. Initiation may be safely performed under an observational stay, outpatient setting, or home setting.

2. Inpatient hospitalization solely 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.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Randomized Controlled Trials

Li et al. (2023) conducted a randomized controlled trial comparing the safety and efficacy of inpatient versus outpatient initiation of the ketogenic diet in pediatric patients. Patients met inclusion criteria if they were 16 years old or younger, had tried at least two anti-epileptic medications, had at least three countable seizures per week, and the parents were motivated and capable of adhering to the ketogenic diet. A total of 190 patients were included and randomized into outpatient (78) and inpatient (112) initiation groups. The inpatient group were admitted and closely monitored for the first week of initiation. The outpatient group included a 1-day case admission for baseline measurements and parental education with the rest of initiation monitoring in the outpatient setting. The medical team monitored all patients regularly to look out for side effects, to ensure nutritional needs were being met, and to assess the diet's effect on seizure control. The length of the ketogenic diet treatment was 12 months long, and the family recorded data on the patient's diet, adverse events, and seizures. The primary clinical outcome was a ≥ 50% reduction in seizure frequency after initiation of the ketogenic diet assessed at 1, 3, 6, and 12 months. The inpatient group had a rate of seizure reduction ≥50% of 25.41, 43.09, 49.35, and 65.75% at 1 month (n=181), 3 months (n = 181), 6 months (n = 152), and 12 months (n = 72) respectively. The outpatient group had a rate of seizure reduction ≥50% of 31.94, 51.39, 56.25, and 69.70%, at 1, 3, 6, and 12 months, respectively. Compared with 12 months, the rate of seizure reduction ≥50% was lower at 1, 3, and 6 months. There were no significant differences in height, weight, BMI, and BMI Z-score between the inpatient and outpatient groups over the 12-month period. Adverse events were reported by 31 patients (43.05%) in the outpatient group, and 46 patients (42.20%) in the inpatient group, with no statistical differences (p = 0.909) in the incidence of adverse events between the two groups. The most common adverse events were diarrhea [outpatient group, 6 (19.35%); inpatient group, 9 (20.93%)], anorexia [outpatient group, 7 (22.58%); inpatient group, 8 (18.60%)], constipation [outpatient group, 3 (9.68%); inpatient group, 8 (18.60%)], slow growth [outpatient group, 4 (12.90%); inpatient group, 5 (11.63%)], and sleep disorder [outpatient group, 4 (12.90%); inpatient group, 4 (4.65%)]. The authors concluded that outpatient initiation of the ketogenic diet was safe and effective in patients with refractory epilepsy.

Systematic Reviews and Meta-Analyses

Devi et al. (2023) conducted a systematic review and meta-analysis on the short-term efficacy and safety of dietary therapies for childhood drug resistant epilepsy. The review analyzed randomized controlled trials that investigated the ketogenic diet, medium chain triglyceride diet, modified Atkins diet, and low glycemic index therapy. Cochrane risk-of-bias tool was used to assess study quality. Effect sizes were calculated as odds ratio with 95% CI using random-effects model. The primary outcomes analyzed were short-term (≤3 months) 50% or higher, and 90% or higher reduction in seizure frequency. Twelve RCTs were included in the analysis for a total of 907 patients. The review revealed all dietary interventions were more efficacious than care as usual for 50% or higher seizure reduction (low glycemic index therapy: odds ratio [OR], 24.7 [95% CI, 5.3-115.4]; modified Atkins diet: OR, 11.3 [95% CI, 5.1-25.1]; ketogenic diet: OR, 8.6 [95% CI, 3.7-20.0]), while ketogenic diet (OR, 6.5 [95% CI, 2.3-18.0]) and modified Atkins diet (OR, 5.1 [95% CI, 2.2-12.0]) were better than care as usual for seizure reduction of 90% or higher. The ketogenic diet (OR, 8.6 [95% CI, 1.8-40.6]) and modified Atkins diet (OR, 6.5 [95% CI, 1.4-31.2]) had a significantly higher discontinue/noncompliance rate due to higher adverse events and difficulty with strict dietary adherence when compared to compliance with care as usual. The authors concluded that all dietary therapies were effective in seizure reduction, with the modified Atkins diet having both a high probability of 50% or higher seizure reduction, in addition to lower noncompliance rates the ketogenic diet. Direct head-to-head comparison studies are needed to confirm these findings.

Sourbron et al. (2022) reviewed the medical literature on the efficacy and tolerability of ketogenic diet and the Modified Atkins Diet (MAD) in children and adolescents with refractory epilepsy. Five randomized controlled trials were analyzed from seven publications; this included a total of 472 total children and adolescents ≤ age 18. Seizure reduction was reported in 35-56% of intervention group participants compared to 6-18% among the control group. The most reported side effect was mild gastrointestinal issues. The authors concluded that dietary interventions are beneficial for children and adolescents with refractory epilepsy who do not meet criteria for epilepsy surgery. The need for additional studies that are multi-center and long-term was also noted to evaluate potential biomarkers and side effects.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Ruiz-Herrero et al. (2021) conducted a retrospective, descriptive, and observational study on the use of ketogenic diets in children under the age of two. Forty-two children treated between 2000-2018 were analyzed; 40 children started a classic ketogenic diet with four patients transferred to a Modified Atkins Diet. At follow-up, 79% of infants remained on a ketogenic diet at 3 months; at six months 57% remained on the diet, 38% at 12 months and 17% at 24 months. A reduction in seizures of ≥50% (when compared to baseline) was found in in 50%, 45%, 38% and 17% at 3, 6, 12 and 24 months, respectively. Seizure control was excellent with a reduction of >90% in 33% (at 3 months), 31% (at 6 months), 26% (at 12 months) and 12% (at 24 months). The mean length of a ketogenic diet was 390 days (16 days to 4.9 years). Early adverse effects occurred in 40% of infants during month one; the most common were asymptomatic hypoglycemia and gastrointestinal issues. Hypercalciuria and dyslipidemia were reported as late-onset side effects. The classic ketogenic diet is the most accepted diet in infants.

Mir et al. (2020) conducted a retrospective chart review on the incidence of potentially serious adverse events during hospital-based ketogenic diet initiation among children with drug-resistant epilepsy. A total of 66 children were analyzed over the course of their inpatient hospital stay for the initiation of the classic ketogenic diet. The mean age at the initiation of the ketogenic diet was 48.0 ± 38.4 months, mean weight was 14.6 ± 6.3 kg, and median number of anticonvulsant medications used at the time of diet initiation was three. Adverse events occurred in 28.7% of patients, specifically hypoglycemia (20%), hypoactivity (6.1%), somnolence (3%), and vomiting (7.6%). The groups' urine ketone levels on all 5 days were compared, and a statistically significant difference was found on day 3 ($P = 0.026$). A statistically significant difference in the serum bicarbonate levels ($P = 0.038$) was found between the patients taking topiramate and those not taking it. The authors concluded that adverse event rates during initiation were low and easily managed with basic medical intervention; however, children less than 3 years old and underweight at the time of initiation were found to have higher risk for adverse events. Hypoglycemia was the most common adverse event, and patients taking topiramate needed closer monitoring of serum bicarbonate levels than their counterparts. In conclusion, carefully selected patients may initiate the ketogenic diet in the outpatient setting with close monitoring if parents are prepared with education and resources to treat adverse events.

Van der Louw et al. (2019) conducted a retrospective observational non-inferiority study evaluating the induction of a ketogenic diet in children with intractable epilepsy in the outpatient setting. Due to inpatient hospitalizations being a costly intervention, the study aimed at comparing the safety, efficacy, and cost effectiveness outpatient versus inpatient ketogenic diet induction. The team retrospectively reviewed the charts of 105 patients who underwent ketogenic diet induction between 2001 -2017 and were under the age of 18 years old. The main outcomes were evaluating effectiveness defined as at least a 50% reduction in seizures, safety defined as measuring the number of emergency department visits and complications, and economic impact defined as total cost of treatment. Of those that underwent diet initiation inpatient, 43 patients, at three months the ketogenic diet was effective in 63% of patients versus 61% in the 62 patients who underwent diet initiation outpatient. Safety metrics revealed ketogenic diet induction was considered safe in 36% of the outpatient group versus 29% in the inpatient group. Both the effectiveness and safety outcomes revealed the non-inferiority of inducing a ketogenic diet in the outpatient setting. Last, calculated in euros, the cost of outpatient induction was € 2901 per patient, versus € 8195 per patient in the inpatient setting; thus leading to the conclusion that outpatient induction of the ketogenic diet in patients with intractable epilepsy is safe, effective, and cost effective.

National and Specialty Organizations

The **International Ketogenic Diet Study Group (IKDSG)** published updated guidelines in 2018 *Optimal clinical management of children receiving dietary therapies for epilepsy* which reevaluated best practices originally published in 2008. The IKDSG recommends ketogenic diets for children after two antiseizure drugs have failed. The guidelines state initiation is often started during an inpatient admission but can also safely be initiated in the outpatient setting depending on a variety of factors such as familial compliance and resources. The guidelines emphasize flexibility in the initiation process based on family situation/ needs, patient's age, and whether fasting is necessary. In addition, the IKDSG guidelines include information on the management of children on a ketogenic diet with respect to frequency of follow up visits, nutrition, laboratory results, side effects, and discontinuation when appropriate. Updates made in 2018 focus on the decrease in use of fasting at initiation of a ketogenic diet, evidence to support alternative diets Modified Atkins Diet and Low Glycemic Index Treatment, utilizing a non-fasting classic ketogenic diet for children under age 2, implementing a one-month follow-up visit, and further explanations of ideal scenarios to implement a ketogenic diet. (Kossoff et al. 2018).

The **National Institute for Clinical Excellence (NICE)** (2022) published a clinical guideline titled *Epilepsies in Children, Young People, and Adults.* The guideline covers the diagnosis and management of epilepsy in the population in the primary and secondary care settings; guidance is also given on referral to tertiary services. A section is included on ketogenic diet which provides an overview of benefits, inpatient versus outpatient initiation management is not stipulated.

The *International Recommendations for the Management of Adults Treated with Ketogenic Diet Therapies* was published by Cervenka et al. (2021) and addressed selection of patients, contraindications and potential adverse events associated with ketogenic diet therapies, initiation guidelines, supplementation, monitoring, and discontinuation. The panel of experts recommends initiation of ketogenic diets via outpatient management; however, the authors did note that approximately 40% of ketogenic diets are initiated inpatient as a treatment due to an admission for refractory or super refractory status epilepticus. Therefore, the sole initiation of a ketogenic diet does not require inpatient admission, as inpatient admission is most appropriate for the concurrent treatment of severe uncontrolled epilepsy.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

02/12/2025	Policy reviewed. No changes to coverage criteria.
02/14/2024	Policy reviewed. No changes to coverage criteria, updated overview, and summary of medical evidence. IRO Peer Reviewed on January 9, 2024, by a practicing physician board certified in Neurology and Vascular Neurology.
02/08/2023	Policy reviewed, no changes to criteria.
02/09/2022	Policy reviewed; no changes to coverage criteria; updated Overview, Summary of Medical Evidence and Reference sections.
02/08/2021	Policy reviewed, no changes to criteria, references updated.
06/17/2020	Policy reviewed, no changes to criteria, references updated.
06/19/2019	New policy. IRO Peer reviewed March 29, 2019, by an Advanced Medical Reviews (AMR) practicing, board-certified physician in Neurology and Sleep Medicine.

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