Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 07/01/2018</th>
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</thead>
<tbody>
<tr>
<td>Policy Number: 0226</td>
<td>Effective Date:</td>
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<td>Revision Date: 05/04/2018</td>
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<tr>
<td>Policy Name:</td>
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<tr>
<td>Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures</td>
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Type of Submission – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

CPB 0226 Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures

This CPB has been revised to state that hospitalization for initiation of a ketogenic diet is of unproven value for (i) adult super-refractory status epilepticus, and (ii) individuals with cancers.

Name of Authorized Individual (Please type or print): Dr. Bernard Lewin, M.D.

Signature of Authorized Individual: [Signature]
Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures

Policy

I. Aetna considers hospitalization for initiation of a ketogenic diet in the treatment of intractable seizures medically necessary when all of the following selection criteria are met:

A. Member has failed to respond to anticonvulsant medications (monotherapy and polytherapy) or is intolerant to anticonvulsant medications. There must have been an adequate trial of drug therapy (specifically, the correct anticonvulsant medications have been used in the correct dosage, the member has been carefully monitored for treatment effects and the
member has been compliant with drug therapy for at least 1 year); and

B. Member must be younger than 18 years old; and

C. Since strict adherence to this dietary regimen is tantamount to its effectiveness, parents/family members must be willing and dedicated to support compliance; and

D. There is reason to believe that the outpatient setting will not be effective in initiating the fasting and dehydration period required.

Aetna considers hospitalization for initiation of a ketogenic diet medically necessary in the treatment of members with glucose transporter protein type 1 deficiency or pyruvate dehydrogenase complex deficiency.

Aetna considers hospitalization for initiation of a ketogenic diet of unproven value for all other indications (e.g., adult super-refractory status epilepticus, and individuals with cancers; not an all-inclusive list)

**Note:** Most Aetna plans exclude coverage of dietary supplements; please check benefit plan descriptions for details. These plans do not cover any food supplements for the ketogenic diet.

II. Aetna considers hospitalization for initiation of the Atkins diet in the treatment of intractable seizures or other indications experimental and investigational because its effectiveness has not been established.
III. Aetna considers determination of variants in BAD, KCNJ11, and SLC2A1 to predict response to ketogenic dietary therapies for epilepsy experimental and investigational because of insufficient evidence of the effectiveness of this approach.

**Background**

The ketogenic diet, a diet that is very high in fats and extremely low in carbohydrates and 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 carbohydrate 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 will depend on the proposed initial starvation period, and generally should not exceed 3 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.

Than and colleagues (2005) stated that an early, dramatic response to the ketogenic diet is more likely in patients with predominant seizure types other than
complex partial. It may also be more likely to occur in children who have infantile spasms. In all other patient demographics and diet parameters, an equal likelihood of similar success was found. In a randomized controlled study (n = 48), Bergquist et al (2005) compared the effectiveness of a gradual ketogenic diet initiation with the standard ketogenic diet initiation preceded by a 24- to 48-hour fast. These investigators found that in children with intractable epilepsy, a gradual initiation results in fewer adverse events and is tolerated better overall while maintaining the effectiveness of the ketogenic diet.

In a randomized controlled study, Neal et al (2008) examined the effectiveness of the ketogenic diet in the treatment of childhood epilepsy. A total of 145 children aged between 2 and 16 years who had at least daily seizures (or more than 7 seizures per week) and had failed to respond to at least 2 anti-epileptic drugs, and who had not been treated previously with the ketogenic diet participated in this study. Children were seen at one of two hospital centers or a residential center for young people with epilepsy. Children were randomly assigned to receive a ketogenic diet, either immediately or after a 3-month delay, with no other changes to treatment (control group). Neither the family nor investigators was blinded to the group assignment. Early withdrawals were recorded, and seizure frequency on the diet was assessed after 3 months and compared with that of the controls. The primary endpoint was a reduction in seizures; analysis was intention-to-treat. Tolerability of the diet was assessed by questionnaire at 3 months. A total of 73 children were assigned to the ketogenic diet and 72 children to the control group. Data from 103 children were available for analysis: 54 on the ketogenic diet and 49 controls. Of those who did not complete the trial, 16 children did not receive their intervention, 16 did not provide adequate data, and 10 withdrew from the
treatment before the 3-month review, 6 because of intolerance. After 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the controls (62.0 % versus 136.9 %, 75 % decrease, 95 % confidence interval [CI]: 42.4 to 107.4 %; p < 0.0001). A total of 28 children (38 %) in the diet group had greater than 50 % seizure reduction compared with 4 (6 %) controls (p < 0.0001), and 5 children (7 %) in the diet group had greater than 90 % seizure reduction compared with no controls (p = 0.0582). There was no significant difference in the efficacy of the treatment between symptomatic generalized or symptomatic focal syndromes. The most frequent side effects reported at 3-month review were constipation, vomiting, lack of energy, and hunger. The authors concluded that these findings support the use of ketogenic diet in children with treatment-intractable epilepsy.

The Atkins diet, widely used for weight reduction, has recently been tried for the management of intractable seizures. The Atkins diet can induce a ketotic state, but has fewer protein and caloric restrictions than the traditional ketogenic diet. Kossoff et al (2003) reported the use on the Atkins diet in 6 patients (aged 7 to 52 years) for the treatment of intractable focal and multifocal epilepsy. Five patients maintained moderate to large ketosis for periods of 6 weeks to 24 months; 3 patients had seizure reduction and were able to reduce anti-epileptic drug (AEDs). This preliminary finding needs to be validated by more research.

Weber and colleagues (2009) evaluated the tolerability and efficacy of the modified Atkins diet given to children and adolescents with AED treatment resistant epilepsy. A total of 15 children with medically intractable epilepsy were enrolled in the study. Inclusion criteria were at least 1 seizure a week and a trial of at least 2 AEDs without obtaining seizure
freedom documented in a seizure calendar. At baseline subjects initiated a diet with carbohydrates restricted to make up 10 energy percent. If seizures were reduced by less than 50% after 7 to 14 days, carbohydrates were further restricted to 10 g per day. No change in AED treatment was allowed. The diet was well-tolerated. After 3 months, 6 out of the 15 children (40%) had a seizure reduction of more than 50%, which was seen in different epileptic syndromes and different age groups. The responders reported an increase in quality of life and cognition. At 12 months follow-up, 3 (20%) continued the diet with an unchanged marked seizure reduction. Results of this study confirmed the high tolerability and effect of the modified Atkins diet on seizure control in AED treatment resistant epilepsy. Moreover, the authors stated that further larger prospective studies are however needed to confirm these results.

Glucose is the brain's main source of energy. To pass the blood-brain barrier (BBB), glucose transporter protein type 1 (GLUT-1) is essential. Glucose transporter protein type 1 (GLUT-1) deficiency syndrome is caused by heterozygous mutations in the SLC2A1 gene, resulting in impaired glucose transport into the brain. It is characterized by a low glucose concentration in the cerebrospinal fluid (CSF; hypoglycorrhachia) in the absence of hypoglycemia, in combination with low-to-normal lactate in the CSF. The diagnosis is confirmed by genetic testing.

Rogovik and Goldman (2010) stated that the ketogenic diet can be considered an option for children with intractable epilepsy who use multiple anti-epileptic drugs. It is a treatment of choice for seizures associated with GLUT-1 deficiency syndrome (i.e., De Vivo disease) and pyruvate dehydrogenase (PDH) deficiency.
Ramm-Pettersen et al (2011) described the clinical consequences of mutations in the SLC2A1 gene, with special emphasis on GLUT-1 encephalopathy. This review was based on a non-systematic literature search in PubMed and the authors' experience within the field. Epileptic or epilepsy-like symptoms are usually the first sign in children with the GLUT-1 deficiency syndrome. Later on these children suffer delayed psychomotor development, microcephaly, ataxia, spasticity, or movement disorders; electroencephalographic abnormalities may develop. GLUT-1 deficiency syndrome should be suspected in children with epilepsy-like seizures and delayed development combined with a low content of glucose in spinal fluid. Treatment is a ketogenic diet, as ketone bodies pass the BBB using other transport proteins than GLUT-1. The authors concluded that GLUT-1 deficiency syndrome is a rare metabolic encephalopathy that is not well-known and probably under-diagnosed. An early diagnosis and early start of a ketogenic diet may give these children a normal or nearly normal life.

Graham (2012) stated that GLUT-1 deficiency syndrome often results in treatment-resistant infantile epilepsy with progressive developmental disabilities and a complex movement disorder. Recognizing GLUT-1 deficiency syndrome is important, since initiation of a ketogenic diet can reduce the frequency of seizures and the severity of the movement disorder.

Pong et al (2012) noted that GLUT-1 deficiency syndrome is defined by hypoglycorrhachia with normoglycemia, acquired microcephaly, episodic movements, and epilepsy refractory to standard AEDs. Gold standard treatment is the ketogenic diet, which provides ketones to treat neuroglycopenia. These investigators: (i) described epilepsy phenotypes in a large GLUT-1
deficiency syndrome cohort to facilitate diagnosis; and (ii) described cases in which non-ketogenic diet agents achieved seizure freedom to highlight potential adjunctive treatments. A retrospective review of 87 patients with GLUT-1 deficiency syndrome (45% female, age range of 3 months to 35 years, average diagnosis 6.5 years) from 1989 to 2010 was carried out. Seventy-eight (90%) of 87 patients had epilepsy, with average onset at 8 months. Seizures were mixed in 68% (53/78): generalized tonic-clonic (53%), absence (49%), complex partial (37%), myoclonic (27%), drop (26%), tonic (12%), simple partial (3%), and spasms (3%). These researchers described the first 2 cases of spasms in GLUT-1 deficiency syndrome.

Electrophysiologic abnormalities were highly variable over time; only 13 (17%) of 75 had exclusively normal findings. Ketogenic diet was used in 82% (64/78); 67% (41/61) were seizure-free and 68% of seizure-free patients (28/41) resolved in less than 1 week and 76% (31/41) in less than 1 month. Seven patients achieved seizure freedom with broad agents only. The authors conclude that GLUT-1 deficiency syndrome is a genetic metabolic encephalopathy with variable focal and multi-focal seizure types and electroencephalographic findings. Infants with seizures, spasms, or paroxysmal events should be tested for GLUT-1 deficiency syndrome. They stated that evidence is insufficient to recommend specific AEDs as alternatives to ketogenic diet. Early diagnosis and initiation of ketogenic diet and prevention of unnecessary AED trials in GLUT-1 deficiency syndrome are important goals for the treatment of children with epilepsy.
An UpToDate review on “The ketogenic diet” (Kossoff, 2012) stated that “GLUT1 deficiency syndrome is a genetic disorder characterized by impaired glucose transport across the blood brain barrier resulting in generalized epilepsy, developmental delay, and an associated movement disorder. A low cerebrospinal fluid glucose level suggests this diagnosis. The diagnosis can be confirmed in most cases with genetic testing (SLC2A1 mutation). The ketogenic diet is a first-line treatment for this disorder and provides ketones as an alternative energy source for the brain”.

Tzadok et al (2014) described a cohort of isolated and familial cases of GLUT-1 deficiency syndrome, emphasizing seizure semiology, electroencephalographic features, therapeutic response, and mutation pathogenicity. SLC2A1 mutations were detected in 3 sporadic and 4 familial cases. In addition, mutations were identified in 9 clinically unaffected family members in 2 families. The phenotypic spectrum of GLUT-1 deficiency is wider than previously recognized, with considerable intra-familial variation. Diagnosis requires either hypoglycorrachia followed by SLC2A1 sequencing or direct gene sequencing. A ketogenic diet should be the first line of treatment; carbonic anhydrase inhibitors (e.g., acetazolamide or zonisamide) can be effective for seizure control.

Inborn errors of the pyruvate dehydrogenase complex (PDHc) are associated with developmental delay, lactic acidosis, neuroanatomic defects, and early death. Pyruvate dehydrogenase complex deficiency is a clinically heterogeneous disorder, with most mutations located in the coding region of the X-linked alpha subunit of the first catalytic component, pyruvate dehydrogenase (E1). Treatment of E1 deficiency has included cofactor replacement, activation of PDC with dichloroacetate, as well as ketogenic diets.
Wexler et al (1997) described the outcome of ketogenic diet treatment in 7 boys with E1 deficiency. These patients were divided into 2 groups based on their mutations (R349H, 3 patients; and R234G, 4 patients, 2 sibling pairs). All 7 patients received ketogenic diets with varying degrees of carbohydrate restriction. Clinical outcome was compared within each group and between siblings as related to the intensity and duration of dietary intervention. Subjects who either had the diet initiated earlier in life or who were placed on greater carbohydrate restriction had increased longevity and improved mental development. Based on the improved outcomes of patients with identical mutations, it appears that a nearly carbohydrate-free diet initiated shortly after birth may be useful in the treatment of E1 deficiency.

Klepper et al (2004) stated that the ketogenic diet has been used for decades to treat intractable childhood epilepsies. It is also the treatment of choice for GLUT-1 deficiency syndrome and PDHc deficiency. Recent studies have once again confirmed the effectiveness of the diet, but the diet is hardly known in Europe and has never been quite accepted as an effective treatment of childhood epilepsy. These investigators reported retrospective data on 146 children treated with the ketogenic diet in Austria, Switzerland, and Germany. In 2000 and 2002, standardized questionnaires were sent to 13 neuropediatric departments to evaluate indications, effects and side effects. In children with refractory epilepsy (n = 111), 8 % became seizure-free on the diet. Seizure reduction of greater than 90 % was achieved in additional 9 % of patients; a seizure reduction of 50 to 90 % was attained in additional 14 % of patients. There was a great variability between epilepsy departments. All patients with GLUT-1 deficiency syndrome (n = 18) and PDHc deficiency (n = 15) showed clinical improvement. In GLUT-1 deficiency syndrome, complete seizure control was achieved in 94 % of
patients. Compliance was good in 82% of all patients regardless of the indication for the diet. The authors concluded that in contrast to the general restraint towards the ketogenic diet in Europe, these findings supported its effectiveness as the treatment of choice for GLUT-1 deficiency syndrome and PDHc deficiency. In children with refractory epilepsy, the ketogenic diet matched the effect of most anti-convulsants and was well-tolerated. These data and 2 work-shops resulted in recommendations for the use of the ketogenic diet in children as a basis for a general diagnostic and therapeutic standard to compare and improve the use of the ketogenic diet in Europe.

Prasad et al (2011) noted that the PDHc is a mitochondrial matrix multi-enzyme complex that provides the link between glycolysis and the tricarboxylic acid (TCA) cycle by catalyzing the conversion of pyruvate into acetyl-CoA. Pyruvate dehydrogenase complex deficiency is one of the commoner metabolic disorders of lactic acidosis presenting with neurological phenotypes that vary with age and gender. These researchers postulated mechanisms of epilepsy in the setting of PDHc deficiency using 2 illustrative cases (one with PDHc E1-alpha polypeptide (PDHA1) deficiency and the second one with PDHc E1-beta subunit (PDHB) deficiency (a rare subtype of PDHc deficiency)) and a selected review of published case series. Pyruvate dehydrogenase complex plays a critical role in the pathway of carbohydrate metabolism and energy production. In severe deficiency states, the resulting energy deficit impacts on brain development in-utero resulting in structural brain anomalies and epilepsy. Milder deficiency states present with variable manifestations that include cognitive delay, ataxia, and seizures. Epileptogenesis in PDHc deficiency is linked to energy failure, development of structural brain anomalies and
abnormal neurotransmitter metabolism. The use of the ketogenic diet bypasses the metabolic block, by providing a direct source of acetyl-CoA, leading to amelioration of some symptoms. Genetic counseling is essential as PDHA1 deficiency (commonest defect) is X-linked although females can be affected due to unfavorable lyonization, while PDHB and PDH phosphatase (PDP) deficiencies (much rarer defects) are of autosomal recessive inheritance.

El-Gharbawy et al (2011) reported the case of a male child with X-linked PDH deficiency presented with severe neonatal lactic acidosis. Poor compliance following initiation of the ketogenic diet justified modification to a less restrictive form that improved compliance. One year after starting the modified diet, the subject remained clinically stable, showing developmental progress.

An UpToDate review on “The ketogenic diet” (Kossoff, 2012) stated that “The ketogenic diet may also serve to provide an alternative energy source for the brain in PDH deficiency, a mitochondrial disease characterized by lactic acidosis, severe neurologic impairments, and occasionally, intractable epilepsy”.

**Determination of Variants in BAD and KCNJ11:**

Schoeler and colleagues (2015a) stated that in the absence of specific metabolic disorders, predictors of response to ketogenic dietary therapies (KDT) are unknown. These researchers examined if variants in established candidate genes KCNJ11 and BAD influence response to KDT. They sequenced KCNJ11 and BAD in individuals without previously-known glucose transporter type 1 deficiency syndrome or other metabolic disorders, who received KDT for epilepsy. Hospital records were used to obtain demographic and
clinical data. Two response phenotypes were used: greater than or equal to 50 % seizure reduction and seizure-freedom at 3-month follow-up. Case/control association tests were conducted with KCNJ11 and BAD variants with minor allele frequency (MAF) greater than 0.01, using PLINK. Response to KDT in individuals with variants with MAF less than 0.01 was evaluated. A total of 303 individuals had KCNJ11 and 246 individuals had BAD sequencing data and diet response data; 6 SNPs in KCNJ11 and 2 in BAD had MAF greater than 0.01. Eight variants in KCNJ11 and 7 in BAD (of which 3 were previously-unreported) had MAF less than 0.01. No significant results were obtained from association analyses, with either KDT response phenotype; p-values were similar when accounting for ethnicity using a stratified Cochran-Mantel-Haenszel test. There did not seem to be a consistent effect of rare variants on response to KDT, although the cohort size was too small to assess significance. The authors concluded that common variants in KCNJ11 and BAD did not predict response to KDT for epilepsy; they could exclude, with 80 % power, association from variants with a MAF of greater than 0.05 and effect size greater than 3. They stated that a larger sample size is needed to detect associations from rare variants or those with smaller effect sizes.

**Determination of Variants in SLC2A1:**

Schoeler and associates (2015b) examined if response to KDT was due to undiagnosed glucose transporter type 1 deficiency syndrome (GLUT1-DS). Targeted re-sequencing of the SLC2A1 gene was completed in individuals without previously known GLUT1-DS who received KDT for their epilepsy. Hospital records were used to obtain demographic and clinical data. Response to KDT at various follow-up points was defined as seizure reduction of at least 50 %. Seizure freedom
achieved at any follow-up point was also documented. Fisher's exact and gene-burden association tests were conducted using the PLINK/SEQ open-source genetics library. Of the 246 participants, 1 was shown to have a novel variant in SLC2A1 that was predicted to be deleterious. This individual was seizure-free on KDT. Rates of seizure freedom in cases without GLUT1-DS were below 8% at each follow-up point; 2 cases without SLC2A1 mutations were seizure-free at every follow-up point recorded. No significant results were obtained from Fisher's exact or gene-burden association tests. The authors concluded that a favorable response to KDT is not solely explained by mutations in SLC2A1; other genetic factors should be sought to identify those who are most likely to benefit from dietary treatment for epilepsy, particularly those who may achieve seizure freedom.

Ketogenic Diet for Adult Super-Refractory Status Epilepticus:

In a prospective, phase I/II multi-center study, Cervenka and colleagues (2017) examined the feasibility, safety, and efficacy of a KD for super-refractory status epilepticus (SRSE) in adults. Patients 18 to 80 years of age with SRSE treated with a KD treatment algorithm were eligible for inclusion into this trial. The primary outcome measure was significant urine and serum ketone body production as a biomarker of feasibility. Secondary measures included resolution of SRSE, disposition at discharge, KD-related side effects, and long-term outcomes. A total of 24 adults were screened for participation at 5 medical centers, and 15 were enrolled and treated with a classic KD via gastrostomy tube for SRSE. Median age was 47 years (interquartile
range [IQR] of 30 years), and 5 (33 %) were man. Median number of anti-seizure drugs used before KD was 8 (IQR 7), and median duration of SRSE before KD initiation was 10 days (IQR 7 days). Ketogenic diet treatment delays resulted from intravenous propofol use, ileus, and initial care received at a non-participating center. All patients achieved ketosis in a median of 2 days (IQR 1 day) on KD; 14 patients completed KD treatment, and SRSE resolved in 11 (79 %; 73 % of all patients enrolled). Side effects included metabolic acidosis, hyperlipidemia, constipation, hypoglycemia, hyponatremia, and weight loss; 5 patients (33 %) ultimately died. The authors concluded that KD is feasible in adults with SRSE and may be safe and effective; moreover, they stated that comparative safety and efficacy must be established with randomized placebo-controlled trials.

Ketogenic Diet for Individuals with Cancers:

Erickson and colleagues (2017) noted that the efficacy and benefits of KD have recently been gaining worldwide and remain a controversial topic in oncology. In a systematic, these researchers evaluated the clinical evidence on isocaloric KD dietary regimes and revealed that evidence supporting the effects of isocaloric KD on tumor development and progression as well as reduction in side effects of cancer therapy is missing. Furthermore, an array of potential side effects should be carefully considered before applying KD to cancer patients. The authors concluded that with regard to counseling cancer patients considering a KD, more robust and consistent clinical evidence is needed before the KD can be recommended for any single cancer
Maisch and associates (2018) stated that beside the classical anti-cancer treatment, patients often try to find proactive alternative therapies to fight their disease. Lifestyle changes such as introducing a KD is one of the most popular among them. The German Association of Urological Oncology presented a systematic review investigating the evidence of KD in cancer patients. These investigators performed a systematic literature research in the databases Medline, Livivo, and the Cochrane Library. Only clinical studies of tumor patients receiving chemotherapy while on a KD were included. The assessment of the results was performed according to the predefined primary end-points of overall survival (OS) and progression-free survival (PFS); and secondary end-points of quality of life (QOL) and reduction of adverse effects induced by cytostatics. A total of 9 studies met the inclusion criteria: 8 prospective and 1 retrospective study case series respectively cohort-studies, with a total of 107 patients. Currently there is no evidence of a therapeutic effect of a KD in patients with malignant tumors regarding the clinical outcome or QOL. The authors concluded that based on the current data, a KD cannot be recommended to cancer patients because prospective, randomized trials are missing.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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http://qawww.aetna.com/cpb/medical/data/200_299/0226_draft.html 06/13/2018
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<td>Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents</td>
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<td>Urine test or reagent strips or tablets (100 tablets or strips)</td>
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<td>Single vitamin/mineral/trace element, oral, per dose, not otherwise specified</td>
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<td>Multiple vitamins, with or without minerals and trace elements, oral, per dose, not otherwise specified</td>
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<td>E88.09</td>
<td>Other disorders of plasma-protein metabolism, not elsewhere classified [glucose transporter protein type 1 deficiency]</td>
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The above policy is based on the following references:


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0226 Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures

For the Pennsylvania Medical Assistance Plan, the use of Hospitalization for the Initiation of Ketogenic Diet may be considered for super refractory status epilepticus on a case by case basis.

www.aetnabetterhealth.com/pennsylvania  revised 05/04/2018