Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Elemental Formula

Description/Background

Infants who cannot tolerate cow milk formulas, soy formula, breast milk or hydrolyzed formulas may require an elemental formula such as Neocate®, Neocate One Plus, Neocate® with DHA and ARA, PurAmino, Alfamino or EleCare. Diagnosis of cow's milk allergy can be difficult as it is based mostly on history and physical exam findings. The symptoms of cow's milk allergy manifest within the first few months of life, usually before the age of six months. Symptoms can vary from vomiting, diarrhea, irritability, blood in stool, failure to thrive, colicky abdominal pain, to life threatening anaphylaxis. The definitive treatment for all food allergies including cow's milk allergy is the strict elimination of the food from the diet[1].

Elemental/Amino Acid Formulas, Food supplements, specialized infant formulas, lactose-free foods, vitamins and/or minerals may be used to replace intolerable foods, for lactose intolerance, to supplement a deficient diet, or to provide alternative nutrition in the presence of such conditions as allergies, gastrointestinal disorders, hypoglycemia. Food supplements, lactose-free foods, specialized infant formulas, vitamins and/or minerals taken orally are not covered, even if they are required to maintain weight or strength and regardless of whether these are prescribed by a physician.

Elemental formulas are nutritionally complete, which means they contain all of the nutrients needed to maintain nutritional sustenance. They are unique in that the protein equivalent and fats (medium chain triglycerides) or MCTs are broken down to their simplest form, making them easier to digest.

The term "allergy" refers to a hypersensitivity reaction initiated by immunologic mechanisms. Three factors are needed to develop allergic disease: The appropriate genetic background, contact with the allergens(s), the environmental factors, such as timing, amount and frequency of exposure[2].

Protein hydrolysates are termed “partial” or “extensive,” depending on the degree of hydrolysis and ultrafiltration. Allergenicity decreases as the extent of hydrolysis and filtration increases. In the United States and Canada, formulas are considered hypoallergenic if they have demonstrated with 95% confidence that at least 90% of infants with documented cow’s milk allergy (CMA) will not react with defined symptoms to the formula under double blind, placebo-controlled conditions.[3]

- The partially hydrolyzed formulas (pHFs) available in the US, Good Start (pHF-W), partially hydrolyzed whey-based, Good Start Gentlease (partial casein/whey hydrolysate), and Total Comfort (partial casein/whey hydrolysate) are not considered hypoallergenic, as they contain significantly large peptides that can induce an allergic response in patients with cow milk allergy. In one study, pHF (PHF-W_ caused allergic reactions in approximately 50 percent of cow milk allergy infants[4].

- Three casein-based extensively hydrolyzed formulas (eHFs) are available in the US. Alimentum, Nutramigen, and Pregestimil are considered hypoallergenic because they contain peptides that are sufficiently small that at least 90% of children with cow milk allergy can tolerate the formula.[6]

- Amino acid-based formulas, such as Neocate, EleCare, and Puramino (formerly called NutramingenAA), are the formulas considered closest to being nonallergenic. They have been approved for use in children who still react to extensively hydrolyzed formulas (eHFs) and are an excellent source of nutrition for highly allergic children. Their disadvantages are high cost and low palatability.[5]

Convincing studies support the existence of a critical timing early in infancy during which the genetically predisposed atopic infant is at higher risk for becoming sensitized[3]. Thus, dietary interventions in the first year of life have been analyzed for their effects on the prevalence of allergic disease[7].

Infants at high risk for developing allergy: An infant can be defined as “high risk” for developing allergic disease if there is at lease one first degree relative (parent or sibling) with a documented allergic condition: atopic dermatitis (AD), asthma, allergic rhinitis (AR), or food allergy[3].This definition is based upon a consensus among several committees representing the American Academy of Pediatrics (AAP), the joint guidelines of the European Society for Pediatric Allergology and Clinical Immunology (ESPACI), and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[5]

Cow Milk Allergy: (Edwards, 2022)[7] Cow’s milk allergy is a common diagnosis in infants and children. It presents as an allergic reaction to the protein found in cow’s milk. Cow’s milk allergy manifests as a variety of symptoms and signs which commonly develop in infants and can regress by the age of 6. It can be a source of parental and family stress due to a milk-free diet and can lead to subsequent nutritional deficiency if not treated appropriately.
Hypoallergenic Formulas: These formulas are hydrolyzed via enzymes to break down the milk proteins. Depending on their processing level, products are classified as either partially or extensively hydrolyzed/elemental formulas. Recommendations are for extensively hydrolyzed formulas due to increased allergenicity and associated reactions in partially hydrolyzed formulas[9].

Soy-based formulas: As many as 50% of children affected by cow's milk protein intolerance also develop soy protein intolerance if fed with soy-based formulas. Therefore, soy-based formulas are not generally a viable option for the treatment of cow's milk protein intolerance.[10]

Nutritional formulas are products formulated to replace normal food products and are used for individuals with hereditary metabolic diseases or with a disorder of gross anatomy. Nutritional product formulas are specialized and/or nonspecialized infant formulas used for a specific medical condition. Over-the-counter products such as Ensure, Sustacal, Osmolite, and Boost are examples of formulas used for these conditions.

Standard infant formulas are foods that purport to be for special dietary use, solely as a food for infants, by reason of their simulation of human milk or their suitability as a complete or partial substitute for human milk.

Special medical foods are used for the treatment of inborn errors of metabolism (histidinemia, homocystinuria, maple syrup urine disease [MSUD], phenylketonuria [PKU], and tyrosinemia). The special oral formulas are designed to restrict intake of one or more amino acids. Some states now have mandates requiring coverage of these special medical foods. InsuranceCoverageAttachment.pdf (apfed.org)[18]

Most BCBS plans do not specifically include coverage of infant formulas when taken orally. In the absence of a specific inclusion or state mandate, specialized infant formulas are not covered.

BCBSM does not cover banked breast milk, food supplements, specialized infant formulas, vitamins and/or minerals taken orally.

Regulatory Status

Blended tube feeding via gastrostomy is not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation. Michigan is not a state mandated for insurance coverage for elemental formula State Insurance Mandates for Elemental Formula - Apfed.[17]

Medical Policy Statement

The safety and effectiveness of elemental formula for infants with cow's milk allergy have been established. Elemental formula is considered established when clinical criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions: When all of the following criteria are met:

1. An infant must demonstrate allergy to cow's milk formula **AND**

2. Must have a documented failed trial of soy based formula and a hydrolyzed formula, such as Alimentum, Nutramigen, Pregestimil, MJ3232A, or Good Start, by clinical documentation of one of the following:
   - Skin reaction such as eczema or atopic dermatitis **or**
   - Gastrointestinal (GI) disturbances including malabsorption, blood or mucous in the stool, diarrhea, colic, abdominal distention, or flatus **or**
   - Frequent upper or lower respiratory tract infections or bronchospasm **or**
   - Anaphylaxis

3. Removal of common allergens from the infant's or mother's diet (if breastfed) has failed to resolve the symptoms.

Infants who meet these criteria may have Neocate, Neocate one plus, Neocate with DHA and ARA, Elecare, PurAmino, Alfamino reimbursed up to 12 months of age. Most infants outgrow their allergies by this time. Thereafter, reassessment by the pediatrician must be documented to justify continuance beyond 12 months of age.

Exclusions:

All other formulas are considered investigational including:
- Elemental formula for adults
- Elemental diet for adults
- Elemental supplements
- Elemental formula for inborn errors of metabolism
- Donor Breast Milk

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

B4161*

*BO modifier should be used for billing as the formula is given orally

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Review of Evidence

Evidence reviews assess whether elemental formula is clinically useful. The first step in assessing if elemental formula is clinically useful is to formulate the clinical context and purpose of the elemental formula. Evidence reviews assess the evidence on whether elemental formula is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities

Sicherer and colleagues (2001)[11] Determined the hypoallergenicity and efficacy of a pediatric amino acid-based formula (AAF), EleCare, for children with cow's milk allergy (CMA) and multiple food allergies (MFA). Study design: Hypoallergenicity was determined by performing blinded oral food challenges in 31 consecutive children with documented CMA. Growth, tolerance, and biochemical response were evaluated during a nonrandomized feeding study with each child serving as his or her own control. Results: Thirty-one children (median age, 23.3 months; range, 6 months to 17.5 years) were recruited; 29 had MFA, 17 had acute reactions and cow's milk-specific IgE antibody, and 14 had allergic eosinophilic gastroenteritis. At study entry, 23 were receiving another AAF; 13 had not tolerated extensively hydrolyzed formula. Eighteen subjects with allergic eosinophilic gastroenteritis and/or MFA were followed up while receiving AAF for a median of 21 months (range, 7 to 40 months), with biochemical analysis performed at 4 months. No statistically significant differences were observed in the change in weight or height National Center for Health Statistics z scores from entry; the percent of expected growth exceeded 90%. There was a small decline in percent eosinophils and increase in hemoglobin, hematocrit, and serum ferritin level ($P < .05$). Except for small increases in plasma leucine and valine levels ($P <$ or $= .006$), the remaining biochemical markers were unchanged. In conclusion**:** The amino acid-based formula was hypoallergenic and effective in maintaining normal growth for children with cow's milk allergy and multiple food allergies.

Formula Selection for the High-Risk Infant

The quality of data are low and inconsistent with regard to the use of hypoallergenic formula for the prevention of allergic disease in high-risk infants. Some individual studies have suggested that using a hydrolyzed formula rather than a conventional cow’s milk formula for high-risk infants who cannot be exclusively breastfed for the first four to six month of life has a protective effect for prevention of eczema. However, a 2016, meta-analysis that examined use of conventional and hydrolyzed Cow Milk formulas in high-risk infants found limited efficacy with regard to prevention of atopic disease for most measures.[12] While a 2017 meta-analysis examining only the effect of a specific partial whey hydrolysate formula (pFH-W) formula

compared with cow milk formula found a decreased risk of eczema in high-risk infants at certain ages.[13] Amino acid- based formulas have not yet been studied in the primary prevention of allergy.

Formula versus Donor Breast Milk for Feeding Preterm or Low Birth Weight Infants

Quigley and colleagues (2018)[14] noted that when sufficient maternal breast milk is not available, alternative forms of EN for preterm or low birth weight (LBW) infants are donor breast milk or artificial formula. Donor breast milk may retain some of the non-nutritive benefits of maternal breast milk for preterm or LBW infants. However, feeding with artificial formula may ensure more consistent delivery of greater amounts of nutrients. Uncertainty exists about the balance of risks and benefits of feeding formula versus donor breast milk for preterm or LBW infants. In a Cochrane review, these investigators determined the effect of feeding with formula compared with donor breast milk on growth and development in preterm or LBW infants. They used the Cochrane Neonatal search strategy, including electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 6), Ovid Medline, Embase, and the Cumulative Index to Nursing and Allied Health Literature (until June 8, 2017), as well as conference proceedings and previous reviews. Randomized or quasi-randomized controlled trials (RCTs) comparing feeding with formula versus donor breast milk in preterm or LBW infants were selected for analysis. Two review authors assessed trial eligibility and risk of bias and extracted data independently. They analyzed treatment effects as described in the individual trials and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, and mean differences (MDs) for continuous data, with respective 95 % CIs. These researchers used a fixed-effect model in meta-analyses and explored potential causes of heterogeneity in subgroup analyses. They assessed the quality of evidence for the main comparison at the outcome level using "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methods. A total of 11 trials, in which 1,809 infants participated in total, fulfilled the inclusion criteria; 4 trials compared standard term formula versus donor breast milk; and 7 compared nutrient-enriched preterm formula versus donor breast milk. Only the 4 most recent trials used nutrient-fortified donor breast milk. The trials contain various weaknesses in methodological quality, specifically concerns about allocation concealment in 4 trials and lack of blinding in most of the trials. Formula-fed infants had higher in-hospital rates of weight gain (MD 2.51, 95 % CI: 1.93 to 3.08 g/kg/day), linear growth (MD 1.21, 95 % CI: 0.77 to 1.65 mm/week) and head growth (MD 0.85, 95 % CI: 0.47 to 1.23 mm/week). These researchers did not find evidence of an effect on long-term growth or neurodevelopment.

Formula feeding increased the risk of necrotizing enterocolitis (typical RR 1.87, 95 % CI: 1.23 to 2.85; RD 0.03, 95 % CI: 0.01 to 0.06).The GRADE quality of evidence was moderate for rates of weight gain, linear growth, and head growth (down-graded for high levels of heterogeneity) and was moderate for neurodevelopmental disability, all-cause mortality, and necrotizing enterocolitis (down-graded for imprecision).

The authors concluded that in preterm and LBW infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, resulted in higher rates of weight gain, linear growth, and head growth and a higher risk of developing necrotizing enterocolitis. The trial data did not show an effect on all-cause mortality, or on long-term growth or neurodevelopment.

Section Summary: Donor Breast Milk

The authors concluded that in preterm and low birth weight infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, resulted in higher rates of weight gain, linear growth, and head growth and a higher risk of developing necrotizing enterocolitis. The trial data did not show an effect on all-cause mortality, or on long-term growth or neurodevelopment.

Section Summary: Amino Acid Elemental Formula

In the above studies reviewed, the amino acid-based formulas were hypoallergenic and found effective in maintaining normal growth for children with cow's milk allergy and multiple food allergies.

Government Regulations
National:

BCBSM's policy on parenteral and enteral nutrition is similar to Medicare policy. Medicare provides reimbursement under the part-B prosthetic-device benefit for parenteral and enteral nutrition. Consistent with its policy of covering supplies necessary for use of prosthetics, Medicare will generally cover medically necessary supplies, equipment, and nutrients associated with parenteral and enteral nutrition if the coverage requirements for enteral or parenteral nutritional therapy are met under the prosthetic device benefit provision.

Local:

No LCD

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

SUPPLEMENTAL INFORMATION

Australasian Society of Clinical Immunology and Allergy (ASCIA): No longer recommends a (pHF) Partial hydrolyzed formula or (eHF) extensively hydrolyzed formula over a conventional Cow Milk formula for the prevention of atopic disease.[15]

Related Policies

Enteral Nutrition
Medical Formula for Inborn Errors of Metabolism
Metabolic Foods (Blue Cross Blue Shield of Michigan Policy)
Relizorb

References

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7. Greer FR, Sicherer SH, Curks AW, et al. The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Food. Pediatric 2019; 143
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12. Szajewska H, Horvath A. A partially hydrolyzed 100% whey formula and the risk of eczema and any allergy: an updated meta-analysis. World Allergy Organ J 2017; 10:27.
13. Boyle RJ, Ierodiakonous D, Khan T, et al. Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. BMJ 2016; 352:1974
14. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD002971. DOI: 10.1002/14651858.CD002971.pub5. Accessed 7/2/24
15. ASCIA Guidelines for allergy prevention in infants http://allergy.org.au/images/pcc/ASCIA_PCC_Guidelines_Allergy_Prevention_Infants_2016.pdf accessed 7/2/24
16. Food Allergy & Anaphylaxis Connection Team Government Relations | Statewide Insurance Coverage for Elemental Formula (foodallergyawareness.org) accessed 7/2/24
17. States with Insurance Coverage for Elemental Formula State Insurance Mandates for Elemental Formula - Apfed accessed 8/1/24
18. Special Medical Foods. InsuranceCoverageAttachment.pdf (apfed.org) accessed 8/1/24

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 7/2/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/23	6/13/23		Joint policy established (jf) Vendor Managed: NA Ref added 1,2,3,4,5,6,7,8,9,10,11,12,13,14
11/1/24	8/20/24		Routine Maintenance: (jf) Vendor managed: (NA) Ref added: 16,17,18 Added to the exclusions Donor Breast Milk • Update to the regulatory section that MI is not a state mandated state for insurance coverage for elemental formula. • Edit to MPS

Next Review Date: 2nd Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ELEMENTAL FORMULA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies.
BCNA (Medicare Advantage)	See Government Regulations Section of policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.