Drug and Biologic Coverage Policy

Effective Date 10/1/2023
Next Review Date… 10/1/2024
Coverage Policy Number IP0138

Dimercaprol and Edetate Calcium Disodium

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following products:

- **Dimercaprol (BAL in Oil)**
- **Edetate Calcium Disodium (Calcium EDTA) (Calcium Disodium Versenate)**

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Services for or in connection with an injury or illness arising out of, or in the course of, any employment for wage or profit are explicitly excluded under most Cigna benefit plans. Therefore, treatment of metal toxicity that occurs as a result of occupational exposure is generally not covered.

Dimercaprol (BAL in Oil) and Edetate Calcium Disodium (Calcium EDTA) (Calcium Disodium Versenate) are considered medically necessary when the following are met:

I. **Dimercaprol (BAL in Oil).** Individual meets **ONE** of the following criteria (1, 2, or 3):

1. **Arsenic, gold and mercury overload or toxicity.** Individual meets the following criteria (A):
   A. Confirmed by appropriate laboratory results (for example, blood, plasma, and/or urine) or clinical findings consistent with toxicity

2. **Acute lead poisoning.** Individual meets **BOTH** of the following criteria (A and B):
   A. Used concomitantly with Edetate Calcium Disodium
   B. Blood lead level greater than 44 µg/dL

3. **Acute poisoning by mercury salts.** Individual meets the following criteria (A):
   A. Therapy is begun no longer than 2 hours following ingestion

II. **Edetate Calcium Disodium (Calcium EDTA) (Calcium Disodium Versenate).** Individual meets the following criteria:

1. **Acute or chronic lead poisoning including lead encephalopathy.** Individual meets the following criteria (A):
   A. Blood lead level greater than 44 µg/dL

Due to pharmacological property differences and mechanisms of action, each chelation agent should only be used as indicated by the FDA.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Not applicable for continuation beyond initial approval duration.

Authorization Duration

Initial approval duration is up to 10 days

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven including the following (this list may not be all inclusive):

1. **Atherosclerotic vascular diseases**
2. **Autism spectrum disorders**
3. **Treatment of "mercury toxicity" from dental amalgam fillings**
4. **Other heavy metal poisoning**
   - Dimercaprol: poisoning caused by other heavy metals including antimony, bismuth, iron, cadmium or selenium
   - Edetate calcium disodium: poisoning caused by other heavy metals including aluminum, arsenic, cadmium, cobalt, manganese, mercury, plutonium or uranium

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed

above are met:

HCPCS Codes	Description
J0470	Injection, dimercaprol, per 100 mg
J0600	Injection, edetate calcium disodium, up to 1,000 mg

Background

FDA Approved Indications

BAL in Oil

BAL in Oil (Dimercaprol Injection USP) is indicated in the treatment of arsenic, gold and mercury poisoning. It is indicated in acute lead poisoning when used concomitantly with Edetate Calcium Disodium Injection USP.

Dimercaprol Injection USP is effective for use in acute poisoning by mercury salts if therapy is begun within one or two hours following ingestion. It is not very effective for chronic mercury poisoning.

Dimercaprol Injection USP is of questionable value in poisoning caused by other heavy metals such as antimony and bismuth. It should not be used in iron, cadmium, or selenium poisoning because the resulting dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.

Calcium Disodium Versenate

Edetate calcium disodium is indicated for the reduction of blood levels and depot stores of lead in lead poisoning (acute and chronic) and lead encephalopathy, in both pediatric populations and adults.

Chelation therapy should not replace effective measures to eliminate or reduce further exposure to lead.

Edetate Disodium

FDA has issued a public health advisory to alert patients and healthcare professionals about important safety information concerning the drug Edetate Disodium. There have been cases where children and adults have died when they were mistakenly given Edetate Disodium instead of Edetate Calcium Disodium (Calcium Disodium Versenate) or when Edetate Disodium was used for "chelation therapies" and other uses that are not approved by the FDA. As a result, FDA is reviewing the benefit/risk profile of Edetate Disodium to determine if the benefits for its intended use continue to outweigh the serious risks. (FDA, 2015)

Experimental, Investigational, or Unproven Uses

There is insufficient or non-supportive evidence for the use of dimercaprol or edetate calcium disodium for treatment of atherosclerotic vascular diseases, autism spectrum disorders, or treatment of “mercury toxicity” from dental amalgam fillings and other specific heavy metal poisoning.

Atherosclerotic Vascular Disease

Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been proposed as a noninvasive treatment alternative to established techniques of angioplasty and bypass surgery for atherosclerotic vascular disease. It is theorized that by removing iron and copper from the body, the generation of free radicals and propagation of lipid peroxidation are impaired and that low-density lipoproteins are lowered. (Miller, 2004; Villarruz, 2004)

The TACT trial, a double-blind, placebo-controlled trial sponsored by the National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine, was conducted to determine whether an EDTA-based chelation regimen reduces cardiovascular events (n = 1708). Patients age 50 years or older who had experienced a myocardial infarction (MI) at least six weeks prior, and had serum creatinine levels of 2.0 mg/dl or less were randomized to receive 40 infusions of a 500 ml chelation solution (3 g of disodium EDTA, 7 g of ascorbate, B vitamins, electrolytes, procaine and heparin) (n = 839) or placebo infusion (n = 869) and an oral vitamin mineral regimen or an oral placebo. Infusions were administered weekly for 30 weeks, followed by 10 infusions two to eight weeks apart. The primary endpoint was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or rehospitalization for angina. The median number of infusions received was 40; 76% of patients received at least 30 infusions, and 65% completed all 40 infusions. Thirty

percent (30%) of patients discontinued infusions (233 patients [28%] in the chelation group and 281 [32%] in the placebo group). The primary endpoint occurred in 222 (26%) of the chelation group and 261 (30%) of the placebo group (p = 035). The authors concluded that among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA compared with placebo modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. They further concluded that these results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for the treatment of patients who have had an MI. (Lamas, 2012)

A systematic review of seven articles from 1963 to 2005 assessed the potential use of EDTA chelation therapy for the treatment of cardiovascular disease. It is proposed that repeated administration of EDTA in combination with vitamins and minerals is a safe alternative treatment for atherosclerosis. The proposed action of EDTA is to reverse atherosclerosis and includes: calcium chelation to dissolve plaques, free radical scavenging action, reduction of iron stores, cell membrane stabilization, arterial dilation, improved arterial wall elasticity and increased production of nitric oxide. Their conclusion was that using EDTA as a treatment for cardiovascular disease is not supported by the literature. Most of the literature relied on uncontrolled evidence, thus indicating the need for a controlled trial. (Seely, 2005)

Autism Spectrum Disorders
Chelation has been proposed for treatment of autism spectrum disorders (ASD). The proposal is based on the theory that the chelating agent will remove mercury that is thought to be contained in the tissue after early childhood vaccinations in children with ASD. (Levy, 2005) While there have been several studies that have examined the relationship of mercury to ASD, no consistent associations have been identified. (Levy, 2005) There is insufficient evidence in the peer-reviewed literature regarding the efficacy of chelation therapy for treatment of ASD.

Treatment of "mercury toxicity" from dental amalgam fillings
Randomized studies (Bellinger 2006, DeRouen 2006) have been conducted on children to evaluate the safety of amalgam dental fillings. The first study, by Bellinger et al (2006), evaluated 534 children, between the ages of six to ten years, with no prior amalgam restorations and two or more posterior teeth with caries. These children were assigned randomly to receive either amalgam or resin composite fillings during a five year follow up period (n=267 for both groups). The authors of this study concluded no statistically significant differences were found in adverse neuropsychological or renal effects over the five year study duration in children that had caries restored using dental amalgam or resin composite materials (Bellinger, 2006). The second study, by DeRouen et al (2006), evaluated a total of 507 children, between the ages of eight and ten years, with at least one carious lesion on a permanent tooth and no previous amalgam exposure. This study concluded that children who received dental restorative treatment with amalgam did not have statistically significant differences in neurobehavioral assessments (or in nerve conduction velocity) when compared with children who received materials consisting of resin composite (DeRouen, 2006).

Other heavy metal poisoning
According the the FDA approved label for dimercaprol injection USP, this drug is of questionable value in poisoning caused by other heavy metals such as antimony and bismuth. It should not be used in iron, cadmium, or selenium poisoning because the resulting dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys. (Taylor Pharmaceuticals, 2017)

The place in therapy for use of edetate calcium disodium for treatment of toxicity from aluminum (Fulgenzi, 2015), arsenic (Mathew, 2010), cadmium (Gil, 2010; Bernhoft, 2013), cobalt (Smith, 2013), manganese, (Aschner, 2009) mercury (Sarikaya, 2010), plutonium (Konzen, 2016) or uranium (Smith 2013) has not been established. The available evidence is deficient, inconsistent, of low quality and does not adequately evaluate the benefits versus risks of its use.

References

1. American Academy of Family Physicians. Chelation therapy. November 13, 2013. Available at: http://www.aafp.org/about/policies/all/chelation-therapy.html.

a) American Board of Internal Medicine Foundation Choosing Wisely: Don't administer a chelating agent prior to testing urine for metals, a practice referred to as "provoked" urine testing. Washington, DC: American Board of Internal Medicine Foundation; 2013. Available at: http://www.choosingwisely.org/clinician-lists/american-college-academy-medical-toxicology-chelating-agents-prior-to-urine-test. Accessed January 4, 2019.
b) American Board of Internal Medicine Foundation Choosing Wisely: Don't order heavy metal screening tests to assess non-specific symptoms in the absence of excessive exposure to metals. Washington, DC: American Board of Internal Medicine Foundation; 2013. Available at: http://www.choosingwisely.org/clinician-lists/american-college-academy-medical-toxicology-heavy-metal-screening-tests. Accessed January 4, 2019.
c) American Board of Internal Medicine Foundation Choosing Wisely: Don't recommend chelation except for documented metal intoxication which has been diagnosed using validated tests in appropriate biological samples. Washington, DC: American Board of Internal Medicine Foundation; 2013. Available at: http://www.choosingwisely.org/clinician-lists/american-college-academy-medical-toxicology-chelation. Accessed January 4, 2019.

2. Aschner M, Erikson KM, Herrero Hernandez E, Hernandez EH, Tjalkens R. Manganese and its role in Parkinson's disease: from transport to neuropathology. Neuromolecular Medicine 2009;11(4):252-66.
3. Bellinger DC et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1775-83.
4. Bernhoft RA. Cadmium toxicity and treatment. Scientific World Journal 2013;2013:
5. Centers for Disease Control and Prevention. Low level lead exposure harms children: A renewed call for primary prevention. Report of the Advisory Committee on Childhood Lead Poisoning Prevention. www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf
6. DeRouen TA. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1784-92.
7. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2014; 130: 1749-67.
8. Fulgenzi A, De Giuseppe R, Bamonti F, Vietti D, Ferrero ME. Efficacy of chelation therapy to remove aluminium intoxication. Journal of Inorganic Biochemistry 2015;152:214-8.
9. Gil HW, Kang EJ, Lee KH, Yang JO, Lee EY, Hong SY. Effect of glutathione on the cadmium chelation of EDTA in a patient with cadmium intoxication. Human and Experimental Toxicology 2011;30(1):79-83.
10. Graceway Pharmaceuticals, LLC. Calcium Disodium Versenate (edetate calcium disodium injection,USP) [product information]. Bristol, TN: Graceway Pharmaceuticals, LLC. July 2013.
11. Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women. Adrienne S. Ettinger, ScD, MPH Centers for Disease Control and Prevention. November 2010 U.S. Department of Health and Human Services Atlanta, GA
12. Konzen K, Brey R, Miller S. Plutonium-DTPA model application with USTUR case 0269. Health Physics 2016;110(1):59-65.
13. Kosnett J et al. Recommendations for Medical Management of Adult Lead Exposure. Environmental Health Perspectives. 2007 March; Volume 115 Number 3.
14. Lamas GA, Goertz C, Boineau R, et al, TACT Investigators. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. JAMA. 2013 Mar 27; 309 (12):1241-50.
15. Levy SE, Hyman SL. Novel treatments for autistic spectrum disorders. Ment Retard Dev Disabil Res Rev. 2005; 11 (2): 131-42.
16. Mathew L, Vale A, Adcock JE. Arsenical peripheral neuropathy. Practical Neurology 2010;10(1):34-8.
17. Miller KL, Liebowitz RS, Newby LK. Complementary and alternative medicine in cardiovascular disease: a review of biologically based approaches. Am Heart J. 2004 Mar; 147 (3).
18. National Collaborating Centre for Mental Health. Autism in adults: diagnosis and management. London (UK): National Institute for Health and Care Excellence (NICE);2012 Jun. (Clinical guideline; no. 142)

19. National Collaborating Centre for Mental Health. Autism. The management and support of children and young people on the autism spectrum. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Aug. 36 p. (Clinical guideline; no. 170).
20. Prevention of Childhood Lead Toxicity. Council on Environmental Health. American Academy of Pediatrics. Pediatrics: Volume 138 , number 1 , July 2016 :e 20161493.
21. Sarikaya S, Karcioglu O, Ay D, Cetin A, Aktas C, Serinken M. Acute mercury poisoning: a case report. BMC Emergency Medicine 2010;10:7.
22. Seely D, Wu P, Mills E. EDTA chelation therapy for cardiovascular disease: a systematic review. BMC Cardiovasc Disord. 2005 Nov 1; 5: 32.
23. Smith SW. The role of chelation in the treatment of other metal poisonings. Journal of Medical Toxicology 2013;9(4):355-69
24. Taylor Pharmaceuticals. BAL in Oil Ampules (dimercaprol Injection USP) [product information]. Decatur, IL: Taylor Pharmaceuticals. April 2017.
25. U.S. Department of Health and Human Services Food and drug Administration (FDA). Information on Edetate Disodium (marketed as Endrate and generic products) 7/10/2015. Accessed 1/3/2019. Available at https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm113736.htm