Cigna Drug and Biologic Coverage Policy

Subject: Dimercaprol and Edetate Calcium Disodium

Effective Date: 2/15/2018
Next Review Date: 2/15/2019
Coverage Policy Number: 6019

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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.

Coverage Policy

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.

Cigna covers the respective Chelation Therapy agent as medically necessary for the associated condition(s) listed below:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Condition</th>
</tr>
</thead>
</table>
| Dimercaprol (BAL in Oil) | ANY of the following:  
- Arsenic, gold and mercury overload or toxicity confirmed by appropriate laboratory results (for example, blood, plasma, and/or urine) or clinical findings consistent with toxicity  
- Acute lead poisoning when used concomitantly with Edetate Calcium Disodium AND blood lead level greater than 44 μg/dL  
- Acute poisoning by mercury salts if therapy is begun no longer than 2 hours following ingestion |
| Edetate Calcium Disodium (Calcium EDTA) (Calcium Disodium Versenate) | Acute or chronic lead poisoning including lead encephalopathy AND blood lead level greater than 44 μg/dL |

NOTE: Due to pharmacological property differences and mechanisms of action, each chelation agent should only be used as indicated by the FDA or for the recognized off-label usage.
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 Chelation Therapy.

Cigna does not cover the use of dimercaprol (Bal in Oil) or edetate calcium disodium (Calcium EDTA) (Calcium Disodium Versenate) for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- Atherosclerotic vascular diseases
- Autism spectrum disorders
- Treatment of "mercury toxicity" from dental amalgam fillings

**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.

**FDA Recommended Dosing**

- **BAL in Oil**
  For mild arsenic or gold poisoning, 2.5 mg/kg of body weight four times daily for two days, two times on the third day, and once daily thereafter for ten days; for severe arsenic or gold poisoning, 3 mg/kg every four hours for two-days, four times on the third day, then twice daily thereafter for ten days. For mercury poisoning, 5 mg/kg initially, followed by 2.5 mg/kg one or two times daily for ten days. For acute lead encephalopathy, 4 mg/kg body weight is given alone in the first dose and thereafter at four-hour intervals in combination with Edetate Calcium Disodium Injection USP administered at a separate site. For less severe poisoning the dose can be reduced to 3 mg/kg after the first dose. Treatment is maintained for two to seven days depending on clinical response. Successful treatment depends on beginning injections at the earliest possible moment and on the use of adequate amounts at frequent intervals. Other supportive measures should always be used in conjunction with BAL in Oil (Dimercaprol Injection USP) therapy.

- **Calcium Disodium Versenate**
  Asymptomatic adults and pediatric patients whose blood lead level is <70 mcg/dl but >20 mcg/dl (World Health Organization recommended upper allowable level) dosing is 1000 mg/m²/day whether given intravenously or intramuscularly.

  For adults with lead nephropathy, the following dosing regimen has been suggested: 500 mg/m² every 24 hours for 5 days for patients with serum creatinine levels of 2-3 mg/dl, every 48 hours for 3 doses for patients with creatinine levels of 3-4 mg/dl, and once weekly for patients with creatinine levels above 4 mg/dl. These regimens may be repeated at one month intervals.
Calcium Disodium Versenate, used alone, may aggravate symptoms in patients with very high blood lead levels. When the blood lead level is > 70 mcg/dl or clinical symptoms consistent with lead poisoning are present, it is recommended that Calcium Disodium Versenate be used in conjunction with BAL (dimercaprol). Please consult published protocols and specialized references for dosage recommendations of combination therapy.

Therapy of lead poisoning in adults and pediatric patients with Calcium Disodium Versenate is continued over a period of five days. Therapy is then interrupted for 2 to 4 days to allow redistribution of the lead and to prevent severe depletion of zinc and other essential metals. Two courses of treatment are usually employed; however, it depends on severity of the lead toxicity and the patient's tolerance of the drug.

### Drug Availability

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Brand Name</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimercaprol</td>
<td>BAL in Oil</td>
<td>3 mL (100 mg/mL) ampules in a box of 10</td>
</tr>
<tr>
<td>Edetate Calcium Disodium</td>
<td>Calcium Disodium</td>
<td>2.5 ml ampule containing 200 mg of edetate calcium disodium per ml (500 mg per ampule), in boxes containing 10 ampules</td>
</tr>
<tr>
<td>(Calcium EDTA)</td>
<td>Versenate</td>
<td></td>
</tr>
</tbody>
</table>

### General Background

#### Pharmacology

Chelation therapy reduces the accumulation of essential heavy metals (e.g., iron and copper) or non-essential metals (e.g., lead and aluminum) in the body. Chelating agents bind with heavy metal ions and enhance the urinary and fecal excretion of these toxic metals. Chelation therapy is performed in cases of iron, lead, copper and aluminum overload and in some heavy metal toxicities.

The pharmacologic effects of edetate calcium disodium are due to the formation of chelates with divalent and trivalent metals. A stable chelate will form with any metal that has the ability to displace calcium from the molecule, a feature shared by lead, zinc, cadmium, manganese, iron and mercury. The amounts of manganese and iron mobilized are not significant. Copper is not mobilized and mercury is unavailable for chelation because it is too tightly bound to body ligands or it is stored in inaccessible body compartments. The excretion of calcium by the body is not increased following intravenous administration of edetate calcium disodium, but the excretion of zinc is considerably increased. (Graceway Pharmaceuticals, 2009)

Dimercaprol binds with metallic poisons (arsenic, gold, and mercury) and the complex is excreted. Dimercaprol is used in combination with Edetate Calcium Disodium Injection USP to promote the excretion of lead.

#### Guidelines associated with approved indications:

- **American Academy of Pediatrics Prevention of Childhood Lead Toxicity Guideline**

  The American Academy of Pediatrics policy statement regarding the Prevention of Childhood Lead Toxicity provides the following recommends for blood lead levels:

  **Lead level: Less than 5 μg/dL**

  Review laboratory results with the family (mean blood lead concentration for children between the ages 1 to 5 year old is less than 2 μg/dL [Note that approximately 2.5% have blood lead concentrations greater than or equal to 5 μg/dL]). In 6 to 12 months, repeat the blood lead concentration if the child is either at high risk or if the risk profile increases. For high risk children initially screened prior to being 12 months of age, consider retesting in 3 to 6 months (Note that as mobility increases, the lead exposure may also increase).

  **Lead Level: 5 to 14 μg/dL**

  Follow the steps above. To verify that the lead concentrations are not rising, retest venous blood lead concentration within the timeframe of 1 to 3 months. Provide nutrition counseling related to both calcium and iron and encourage iron rich foods (such as: cereals, meats). Screen for iron sufficiency with adequate lab testing (which includes: complete blood cell count, C-reactive protein, ferritin levels).

  **Lead Level: 15 to 44 μg/dL**

  ...
Follow the steps above. Confirm the blood lead concentration by repeating within a 1 week to 4 weeks timeframe. Consider abdominal radiography in those children who have either a history of pica for paint chips or have excessive mouthing behaviors. Also, gut decontamination may be considered if lead foreign bodies appear on radiography. Any treatment of blood lead concentrations within this blood lead level range should be provided in consult with an expert in the field.

**Lead Level: Greater than 44 μg/dL**
Follow the steps above. Within 48 hours, confirm the blood lead concentration with a repeat venous lead level. **Consider hospitalization or chelation therapy** (managed with the assistance of a provider with experience in this area).
(AAP, 2016)

- **Centers for Disease Control and Prevention (CDC) Prevention of Childhood Lead Toxicity and Advisory Committee on Childhood Lead Poisoning Prevention.**

The CDC revised the elevated blood lead level (BLL) definition for children in the United States from 10 mcg/dL to a reference value based on the 97.5 percentile of BLL distribution among children ages one to five years. The 2012 reference value is listed as 5 mcg/dL. This reference value is scheduled to be updated every four years. Blood lead screening remains necessary to identify children for whom primary prevention is unsuccessful.
(Centers for Disease Control and Prevention, 2016)

- **Department of Health and Human Services Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women**

Chelation therapy during pregnancy or early infancy may be warranted in situations where the maternal or neonatal blood lead are greater than or equal to 45 μg/dL and in consultation with a lead poisoning expert. Guidelines state that there is insufficient data with regards to the advisability of chelation for pregnant women with blood lead levels less than 45 ug/dl. Below are key recommendations per blood lead levels per the Department of Health and Human Services Guidelines:

**Women with prenatal blood lead levels greater than or equal to 5 μg/dL:**
Attempt to the determine source of lead exposure. Counsel the patient on avoiding further exposure. Provide advice for the individual on eating a balanced diet with adequate amounts of iron and calcium. Perform necessary blood lead testing that is in line with the recommended schedules.

**Women with prenatal blood lead levels of 10 to 14 μg/dL:**
Follow the steps above. Notify the Lead Poisoning Prevention Program in the local health department if blood lead levels are greater than or equal to 10 μg/dL.

**Women with prenatal blood lead levels of 15 to 44 μg/dL:**
Follow the steps above. Support assessment of risk within the environment and necessary lead source reduction. Notify the appropriate local or state health department.

**Women with prenatal blood lead levels greater than or equal to 45 μg/dL:**
Follow the steps above. In this blood level range, **treat as high-risk pregnancy and consult with a lead poisoning expert in lead on chelation and other treatment decisions.**

Blood lead levels greater than or equal to 70 μg/dL may result in significant maternal toxicity. Therapy with chelation should be considered, regardless of trimester at this blood lead level. Chelation therapy should also be considered in neonates and infants that are less than 6 months of age for a confirmed blood lead levels greater than or equal to 45 μg/dL.

(Department of Health and Human Services, 2010)

**Guidelines associated with Experimental, Investigational, or Unproven Uses**
- **American Academy of Family Physicians (AAFP)**
The AAFP endorses the 1983 American Medical Association (AMA) Diagnostic and Therapeutic Assessment of Chelation Therapy which states, “Chelation therapy with ethylenediaminetetraacetic acid or its sodium salt is not an established treatment for atherosclerotic vascular disease.” (AAFP, 2013)

- **American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)**
  A focused update of the 2012 guidelines for the diagnosis and management of patients with stable ischemic heart disease address the use of chelation therapy. While the 2012 guidelines recommend against use of chelation therapy to improve symptoms or decrease cardiovascular risk, the 2014 guidelines state that “the usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable ischemic heart disease.” (Fihn, 2014) This is a class IIb recommendation (i.e., procedure or treatment may be considered) based on level B evidence (i.e., limited populations evaluated; data derived from a single randomized trial or nonrandomized studies). (Fihn, 2014)

- **National Institute for Health and Care Excellence (NICE)**
  The National Institute for Health and Care Excellence (NICE) recommends against the use of chelation therapy for the management of autism in children, young people or to manage the core symptoms of adults with autism. (NICE: 2012, 2013)

**Experimental, Investigational, or Unproven Uses**

- **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).

**Note:** Edetate disodium

Edetate disodium (J3520) is not FDA approved for any condition; even when used for appropriately diagnosed metal intoxication.

### 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.

#### Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0470</td>
<td>Injection, dimercaprol, per 100 mg</td>
</tr>
<tr>
<td>J0600</td>
<td>Injection, edetate calcium disodium, up to 1,000 mg</td>
</tr>
</tbody>
</table>

#### Experimental/Investigational/Unproven/Not Covered:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3520</td>
<td>Edetate disodium, per 150 mg</td>
</tr>
<tr>
<td>M0300</td>
<td>IV chelation therapy (chemical endarterectomy)</td>
</tr>
</tbody>
</table>

### References


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