Chelation Therapy

Policy # 00014
Original Effective Date: 06/24/2002
Current Effective Date: 06/10/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider chelation therapy for treatment of individuals with relevant clinical findings suggestive of heavy metal toxicity and a probable exposure history when confirmed by laboratory testing[1] to be **eligible for coverage.****

Patient Selection Criteria

The use of chelation therapy for treatment of individuals with relevant clinical findings suggestive of heavy metal toxicity when confirmed by laboratory testing is considered **eligible for coverage**** in any of the following conditions:

- Individuals with disorders of iron metabolism (for example, primary or secondary hemochromatosis); **or**
- Lead overload in cases of acute or long-term lead exposure; **or**
- Individuals with disorders of copper metabolism (for example, Wilson's disease); **or**
- Arsenic, cadmium, copper, gold, iron, or mercury poisoning when long-term exposure and toxicity has been confirmed; **or**
- Aluminum overload in individuals on chronic hemodialysis.

[1]***Note:*** *Laboratory testing to confirm heavy metal toxicity should include blood or plasma specimens. In the case of suspected arsenic or mercury toxicity, it may be more appropriate to confirm diagnosis through a non-challenged urinalysis.*

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of chelation therapy for the treatment of all other conditions (e.g., Alzheimer disease, atherosclerosis, autism, diabetes, multiple sclerosis, arthritis) and when the patient selection criteria have not been met is considered to be **investigational.***

Policy Guidelines

A number of indications for chelation therapy have received U.S. Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care. These indications include:

- Extreme conditions of metal toxicity
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia
- Wilson disease (hepatolenticular degeneration)
- Lead poisoning
- Control of ventricular arrhythmias or heart block associated with digitalis toxicity
- Emergency treatment of hypercalcemia.

For the last 2 bullet points, most individuals should be treated with other modalities. Digitalis toxicity is currently treated in most individuals with Fab monoclonal antibodies. The FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1.

Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24-h urine: ≥50 µg/L urine or 100 µg/g creatinine

Metal	Toxic Levels (Normal Levels Where Indicated)
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or ≥15 µg/g creatinine
Chromium	No clear reference standard
Cobalt	Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)
Copper	Normative excretion: 25 µg/24 h (urine)
Iron	• Nontoxic: <300 µg/dL • Severe: >500 µg/dL
Lead	**Pediatric** • Symptoms or blood lead level ≥45 µg/dL (blood) • CDC level of concern: 3.5 µg/dL **Adult** • Symptoms or blood lead level ≥70 µg/dL • CDC level of concern: 10 µg/dL
Manganese	No clear reference standard
Mercury	Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[a]
Nickel	• Excessive exposure: ≥8 µg/L (blood) • Severe poisoning: ≥500 µg/L (8-h urine)
Selenium	• Mild toxicity: >1 mg/L (serum) • Serious toxicity: >2 mg/L

Metal	Toxic Levels (Normal Levels Where Indicated)
Silver	Asymptomatic workers have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)
Thallium	24-hour urine thallium >5 µg/L
Zinc	Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

Adapted from Adal (2018). CDC: Centers for Disease Control and Prevention.
[a] Hair analysis is useful to assess mercury exposure in epidemiologic studies. However, hair analysis in individual patients must be interpreted with consideration of the patient's history, signs, and symptoms, and possible alternative explanations. Measurement of blood and urine mercury levels can exclude exogenous contamination; therefore, blood or urine mercury levels may be more robust measures of exposure in individual patients.

Background/Overview

Chelation therapy, an established treatment for treating heavy metal toxicities, has been investigated for a variety of other applications including treatment of atherosclerosis, Alzheimer's disease, and autism.

Chelation therapy is an established treatment for the removal of metal toxins by converting them to a chemically inert form that can be excreted in the urine. Chelation therapy comprises intravenous or oral administration of chelating agents that remove metal ions such as lead, aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body. Specific chelating agents are used for particular heavy metal toxicities. For example, deferoxamine is used for individuals with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for individuals with lead poisoning. Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer disease, which is associated with the disequilibrium of cerebral metals. Unlike traditional systemic chelators that bind and remove metals from tissues systemically, MPACs have subtle effects on metal homeostasis and abnormal metal interactions. In

animal models of Alzheimer disease, MPACs promote the solubilization and clearance of β-amyloid by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. Therefore, MPACs interrupt 2 putative pathogenic processes of Alzheimer disease. However, no MPACs have received FDA approval for treating Alzheimer disease.

Chelation therapy also has been considered as a treatment for other indications, including atherosclerosis and autism spectrum disorder. For example, EDTA chelation therapy has been proposed in individuals with atherosclerosis as a method of decreasing obstruction in the arteries.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1953, EDTA (Versenate) was approved by the FDA for lowering blood lead levels among both pediatric and adult individuals with lead poisoning. In 1991, succimer (Chemet) was approved by the FDA for the treatment of lead poisoning in pediatric individuals only. The FDA approved disodium-EDTA for use in selected individuals with hypercalcemia and use in individuals with heart rhythm problems due to intoxication with digitalis. In 2008, the FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.

Several iron-chelating agents are FDA approved:

- In 1968, deferoxamine (Desferal®; Novartis)‡ was approved by the FDA for subcutaneous, intramuscular, or intravenous injections to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved by the FDA.
- In 2005, deferasirox (Exjade®; Novartis)‡ was approved by the FDA, is available as a tablet for oral suspension, and is indicated for the treatment of chronic iron overload due to blood transfusions in individuals age 2 years and older. Under the accelerated approval program, the FDA expanded the indications for deferasirox in 2013 to include treatment of individuals age 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia syndromes and specific liver iron concentration and serum ferritin levels. A generic version of deferasirox tablet for oral suspension has also been approved by the FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu®)‡ was approved by the FDA. All formulations of deferasirox carry a boxed warning because it may cause serious and fatal renal toxicity and failure, hepatic toxicity and failure, and gastrointestinal hemorrhage. As a

result, treatment with deferasirox requires close patient monitoring, including laboratory tests of renal and hepatic function.

- In 2011, the iron chelator deferiprone (Ferriprox®)‡ was approved by the FDA for treatment of individuals with transfusional overload due to thalassemia syndromes when another chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox®‡ carries a boxed warning because it can cause agranulocytosis, which can lead to serious infections and death. As a result, absolute neutrophil count should be monitored before and during treatment.

In a June 2014 warning to consumers, the FDA advised that FDA-approved chelating agents would be available by prescription only. There are no FDA approved over-the-counter chelation products.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Chelation therapy is an established treatment for the indications listed in the medically necessary policy statement, particularly for the treatment of metal toxicity and transfusional hemosiderosis. Thus, literature searches have focused on the use of chelation therapy for other conditions including, but not limited to, atherosclerosis, autism, Alzheimer's disease, multiple sclerosis, and diabetes.

Atherosclerosis

In 2002, a Cochrane review was published evaluating studies on EDTA chelation therapy for treating individuals with atherosclerotic cardiovascular disease. Five placebo-controlled randomized-controlled trials (RCTs) were identified, none of which reported mortality, non-fatal events, and cerebrovascular vascular events. Four of the 5 studies (total n=250) found no significant benefits of EDTA chelation therapy on outcomes reported including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study, which included only 10 individuals, was apparently stopped early due to benefit, but relevant outcome data were not available. The Cochrane reviewers concluded that there was insufficient evidence to draw

conclusions of the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were needed.

Among the published RCTs, Knudtson and colleagues randomized 84 individuals with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo, 3 hours per treatment twice weekly for 15 weeks, and once per month for an additional 3 months. The main outcome measures included change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the two groups. Another double-blind, randomized controlled study of EDTA chelation or placebo showed no change in short- or long-term improvement in vasomotor response to EDTA when compared to placebo. Two small randomized trials have also reported no benefit of chelation therapy as a treatment of peripheral arterial disease.

Section summary: Several RCTs have been published on chelation therapy for treating atherosclerosis; these have generally reported intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs that report health outcomes are needed to establish the efficacy of this treatment.

Autism Spectrum Disorder
Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard and colleagues hypothesized a link between environmental mercury and autism. This theory was rejected by Nelson and Bauman, who found that many of the characteristics of mercury poisoning such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children. In 2007, a systematic review by Ng and colleagues concluded that there was no association between mercury poisoning and autism.

Rossignol (2009) published a systematic review of novel and emerging treatments for autism and identified no controlled studies. Rossignol (2009) stated that case series had suggested a potential role for chelation in treating some autistic people with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

Section summary: There is a lack of controlled studies on the effect of chelation therapy on health outcomes in individuals with autism.

Alzheimer's Disease

A Cochrane review (2008) evaluated metal protein attenuating compounds for treating Alzheimer disease. Reviewers identified a placebo-controlled randomized trial. This study by Ritchie et al (2003) assessed individuals treated with PBT1, a metal protein attenuating compound also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier. The U.S. Food and Drug Administration (FDA) withdrew clioquinol for oral use from the market in 1970 because of its association with subacute myelo-optic neuropathy. Ritchie et al (2013) administered oral clioquinol to 16 Alzheimer disease individuals in doses increasing to 375 mg twice daily and compared this group with 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer Disease Assessment Scale–Cognitive. One patient in the treatment group developed impaired visual acuity and color vision during weeks 31 to 36 of treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. Updates of this Cochrane review (2012 and 2014) included trials through January 2012. Only the Lannfelt et al (2008) trial (discussed next) was identified.

Further study of PBT1 was abandoned in favor of a successor compound, PBT2. Lannfelt et al (2008) completed a double-blind, placebo-controlled randomized trial of 78 Alzheimer disease individuals who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29). There was no statistically significant difference in Alzheimer Disease Assessment Scale–Cognitive or Mini-Mental Status Examination scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis, transient ischemic event) were reported in the placebo arm.

Diabetes

A trial by Cooper et al (2009) in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 individuals with type 2 diabetes. Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area in the active treatment group (-10.6 g/m^2) than in the placebo group (-0.1 g/m^2; p=.01). The trial was limited by small sample size and high dropout rate.

Escolar et al (2014) published results of a prespecified subgroup analysis of diabetic individuals in TACT. In this trial (also discussed above), there was a statistically significant interaction between

treatment (EDTA or placebo) and presence of diabetes. Among 538 (31% of the trial sample) self-reported diabetic individuals, those randomized to EDTA had a 39% reduced risk of the primary composite outcome (ie, death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years) compared with placebo (HR=0.61; 95% CI, 0.45 to 0.83; p=.02); among 1170 nondiabetic individuals, risk of the primary outcome did not differ statistically between treatment groups (HR=0.96; 95% CI, 0.77 to 1.20; p=.73). For the subsequent subgroup analysis, the definition of diabetes was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose of 126 mg/dL or more at trial entry. Of 1708 individuals in TACT, 633 (37%) had diabetes by this definition: 322 were randomized to EDTA and 311 to placebo. Compared with all other trial participants, this subgroup of diabetic individuals had higher body mass index, fasting blood glucose, and prevalence of heart failure, stroke, hypertension, peripheral artery disease, and hypercholesterolemia. Within this subgroup, baseline characteristics were similar between treatment groups. With approximately 5 years of follow-up, the primary composite endpoint occurred in 25% of the EDTA group and 38% of the placebo group (adjusted HR=0.59; 99.4% CI, 0.39 to 0.88; p=.002). In adjusted analysis of the individual components of the primary endpoint, there were no statistically significant differences between treatment groups. Thirty-six adverse events attributable to the study drug led to trial withdrawal (16 in the EDTA group versus 20 in the placebo group).

Several additional post-hoc analyses of TACT examined outcomes in individuals with diabetes. Ujueta et al (2020) reported outcomes in 162 post-myocardial infarction individuals with diabetes mellitus and peripheral artery disease. The analysis showed that chelation therapy was associated with a significant reduction in the composite primary endpoint compared with placebo (HR=0.52; 95% CI, 0.30 to 0.92; p=.0069). Escolar et al (2020) performed a sub-analysis of diabetes mellitus individuals included in TACT (n=633) to determine the association between glucose lowering therapy and outcomes. Chelation therapy was associated with a lower frequency of the primary outcome compared with placebo in individuals on insulin (n=162; 26% vs. 48%; HR, 0.42, 95% CI, 0.25 to 0.74), but not in individuals on oral glucose-lowering therapy or no glucose-lowering therapy. As previously mentioned, the TACT2 is further examining EDTA in this patient population.

Diabetic nephropathy
Chen et al (2012) conducted a single-blind RCT assessing the effects of chelation therapy on the progression of diabetic nephropathy in Chinese individuals with high-normal lead levels. Fifty individuals with diabetes, high-normal body lead burden (80 to 6000 μg), and serum creatinine of

3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 µg/dL in the treatment group and 7.1 µg/dL in the control group; baseline mean body lead burden was 151 µg in the treatment group and 142 µg in the control group. According to the U.S. Occupational and Health Safety Administration, the maximum acceptable blood lead level in adults is 40 µg/dL. Individuals were randomized to 3 months of calcium disodium EDTA or to placebo. During 24 months of treatment follow-up, individuals in the chelation group received additional chelation treatments as needed (ie, for serum creatinine level above pretreatment levels or body lead burden >60 µg), and individuals in the placebo group continued to receive placebo medication. All individuals completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate. Mean yearly rate of decrease in estimated glomerular filtration rate was 5.6 mL/min/173 m^2 in the chelation group and 9.2 mL/min/173 m^2 in the control group, a statistically significant difference (p=.04). The secondary endpoint was the number of individuals in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) individuals in the treatment group and 17 (68%) in the control group attained the secondary endpoint, a statistically significant difference (p=.02). There were no reported adverse events of chelation therapy during the trial.

Myocardial infarction (MI)

The largest RCT included in the meta-analyses is the multicenter, 2´2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT), which was published by Lamas et al in 2013. TACT included 1708 individuals, age 50 years or older, who had a history of myocardial infarction at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Individuals were randomized to 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Individuals also received oral high-dose vitamin plus mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. The primary endpoint was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years. The threshold for statistical significance was adjusted for multiple interim analyses to a p-value of.036. A total of 361 (43%) individuals in the chelation group and 464 (57%) individuals in the placebo group discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary endpoint was 33% (95% CI, 29% to 37%) in the chelation group and 39% (95% CI, 35% to 42%) in the control group, a statistically significant difference (p=.035). The most common individual clinical endpoint was coronary revascularization, which occurred in 130 (16%) of 839 individuals in the chelation group and 157 (18%) of 869 individuals in the control group (p=.08). The next most frequent endpoint was death, which occurred in 87 (10%) individuals in the chelation

group and 93 (11%) individuals in the placebo group (p=.64). No individual component of the primary outcome differed statistically between groups; however, the trial was not powered to detect differences in individual components. Four severe adverse events definitely or possibly related to study therapy occurred, 2 each in the treatment and control groups, including 1 death in each. Quality of life outcomes (reported in 2014) did not differ between groups at 2-year follow-up.

A 2014 follow-up publication reported results for the 4 treatment groups in the 2´2 factorial design (double-active group [disodium-EDTA infusions with oral high-dose vitamins; n=421 individuals], active infusions with placebo vitamins [n=418 individuals], placebo infusions with active vitamins [n=432 individuals], or double placebo [n=437 individuals]). The proportion of individuals who discontinued treatment, withdrew consent, or were lost to follow-up per treatment group were not reported. Five-year Kaplan-Meier estimates for the primary composite endpoint were 32%, 34%, 37%, and 40%, respectively. The reduction in primary endpoint by double-active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74; 95% CI, 0.57 to 0.95). In 633 individuals with diabetes (»36% of each treatment group), the primary endpoint reduction in the double-active group compared with the double placebo group was more pronounced (HR=0.49; 95% CI, 0.33 to 0.75). A post-hoc analysis showed that chelation was associated with a lower risk of the primary endpoint compared with placebo in individuals with post anterior myocardial infarction (n=674; HR, 0.63; 95% CI, 0.47 to 0.86; p=.003); however, this effect was not seen in post non-anterior myocardial infarction.

The trial was limited by the high number of withdrawals, with differential withdrawals between groups. The primary endpoint included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary endpoint barely met the significance threshold; if more individuals had remained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the original (2013) publication, 60% of individuals were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in the selection of a population not generalizable to that seen in general clinical care. Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings. This secondary analysis had the same limitations as the parent study previously described (ie, high and differential withdrawal, heterogeneous composite endpoint). Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

The TACT2 study replicated the design of the original TACT study evaluating 40 weekly infusions of EDTA-based chelation in individuals with prior myocardial infarction and diabetes. Enrollment was complete in December 2020 and treatment was complete in December 2021. Subjects are now being followed for up to 5 years for a composite primary endpoint of all-cause mortality, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Results are anticipated in 2024.

A Cochrane review of several RCTs of chelation therapy did not show sufficient evidence to draw conclusions about the efficacy of EDTA chelation therapy compared to placebo. A 2022 systematic review included similar RCTs and numerous observational trials but did not perform meta-analysis on clinical outcomes. Additional RCTs reporting health outcomes would be needed to establish treatment efficacy. The largest of the RCTs included in systematic reviews has significant limitations, including a high dropout rate with differential dropout between groups, but reported that cardiovascular events were reduced in individuals treated with chelation therapy. This effect was greater among individuals with diabetes and post-anterior myocardial infarction. However, this trial was not of high-quality and, therefore, results might have been biased.

Other potential indications
No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for MS or arthritis were identified.

Iron chelation therapy is being investigated for Parkinson's disease and endotoxemia. Devos et al (2022) conducted a phase 2, randomized, double-blind, 36-week trial in 372 individuals with newly diagnosed Parkinson's disease. Individuals randomized to iron chelation with deferiprone had worse outcomes than those treated with placebo, with 22% of deferiprone-treated individuals requiring initiation of dopaminergic therapy versus 2.7% of those treated with placebo. In addition, scores on the Unified Parkinson's Disease Rating Scale were worse with deferiprone, worsening by 15.6 points from baseline compared with 6.3 points in the placebo group (difference, 9.3 points; 95% CI, 6.3 to 12.2; $p<.001$).

Summary
Chelation therapy is an established treatment for the medically necessary indications listed in the policy statement, such as treatment of metal toxicity and transfusional hemosiderosis. There is insufficient evidence that chelation therapy improves health outcomes for individuals with other

conditions including, but not limited to, atherosclerosis, autism, Alzheimer's disease, diabetes and arthritis. Thus, chelation therapy for these other applications is considered investigational.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association and American College of Cardiology

In 2016, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a joint guideline on the management of patients with lower extremity peripheral artery disease, which stated that chelation therapy (eg, ethylenediaminetetraacetic acid) is not beneficial for the treatment of claudication.

In 2014, the ACC and AHA published a focused update of the guideline for the management of stable ischemic heart disease, in conjunction with the American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. This update included a revised recommendation on chelation therapy stating that the "usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable IHD." Compared to the original publication of this guideline in 2012, the recommendation was upgraded from a class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies). A 2023 guideline from these organizations on managing chronic coronary disease provided comments about chelation therapy but no formal recommendations.

American Heart Association

In 2023, the AHA published a scientific statement about the cardiovascular risk of contaminant metals. The authors cited the TACT trial findings of a reduced relative risk of cardiovascular events among patients who received chelation therapy, but also noted that TACT did not evaluate metal

levels. Results of the TACT2 trial (which finished in 2023), are awaited to provide objective data on the metal level lowering effects of chelation therapy.

American Academy of Pediatrics
In 2019, the American Academy of Pediatrics published guidance for the management of children with autism spectrum disorder. The guidance cautioned against the use of chelation therapy due to safety concerns and lack of supporting efficacy data.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicare have issued 2 national coverage determinations on chelation therapy relevant to this evidence review. Section 20.21 states:

"The application of chelation therapy using ethylenediamine-tetra-acetic acid (EDTA) for the treatment and prevention of atherosclerosis is controversial. There is no widely accepted rationale to explain the beneficial effects attributed to this therapy. Its safety is questioned, and its clinical effectiveness has never been established by well designed, controlled clinical trials. It is not widely accepted and practiced by American physicians. EDTA chelation therapy for atherosclerosis is considered experimental. For these reasons, EDTA chelation therapy for the treatment or prevention of atherosclerosis is not covered.

Some practitioners refer to this therapy as chemoendarterectomy and may also show a diagnosis other than atherosclerosis, such as arteriosclerosis or calcinosis. Claims employing such variant terms should also be denied under this section."

Section 20.22 states:
"The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA [U.S. Food and Drug Administration] as an approved use is not covered. Any such use of EDTA is considered experimental."

These national coverage determinations are long-standing; effective dates of these versions have not been posted.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05111821	Long-term Iron Chelation in the Prevention of Secondary Remote Degeneration After Stroke	100	Jun 2024
Unpublished			
NCT02733185	Trial to Assess Chelation Therapy 2	1000	Jun 2023

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 06/24/2002
Current Effective Date: 06/10/2024

06/20/2002	Medical Policy Committee review. Format revision. No substance change to policy.
06/24/2002	Managed Care Advisory Council approval
07/14/2005	Medical Director review
07/19/2005	Medical Policy Committee review. Format revision. Rationale/Source added. Patient selection criteria defined and: “Heavy metal toxicity, or iron or lead poisoning when toxic levels are not documented by blood levels” added to investigational statement.
08/24/2005	Managed Care Advisory Council approval
07/07/2006	Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval. No changes to policy guidelines.

Chelation Therapy

Policy # 00014
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10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee approval
10/14/2009	Medical Policy Implementation Committee approval. Added that when patient selection criteria are not met, or if chelation therapy is used for non-FDA approved indications, to deny investigational.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Autism and Alzheimer's disease added to investigational indications.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2013	Coding revised
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. "Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non transfusion dependent thalassemia (NDTD)" was added as eligible for coverage. Investigational statements clarified.
10/02/2014	Medical Policy Committee review
10/15/2014	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage. Note added.
12/06/2018	Medical Policy Committee review

Chelation Therapy

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12/19/2018	Medical Policy Implementation Committee approval. No change to coverage.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/30/2021	Coding update
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility completely rewritten. Added Policy Guidelines.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross

Chelation Therapy

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Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0470, J0600, J0895, J3520, M0300, S9355 Delete code effective 06/12/2023: J3490
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.