# Medical Policy

BlueCross BlueShield of Kansas
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## Title: Chelation Therapy for Off-Label Uses

**Professional**
Original Effective Date: October 29, 2009
Revision Date(s): November 19, 2012; March 31, 2014, August 19, 2016; April 11, 2018
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**Institutional**
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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With Alzheimer disease, | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With cardiovascular disease | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |

| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With autism spectrum disorder | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With diabetes | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With multiple sclerosis | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With arthritis | Interventions of interest are:<br>• Chelation therapy | Comparators of interest are:<br>• Standard medical care | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Morbid events<br>• Functional outcomes<br>• Health status measures<br>• Quality of life<br>• Treatment-related morbidity |

## DESCRIPTION

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

### Objective

The objective of this evidence review is to determine whether chelation therapy is an effective treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

### Background

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 (see Appendix Table 1). Specific chelating agents are used for particular

heavy metal toxicities. For example, desferroxamine (not approved by the Food and Drug Administration [FDA]) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning (Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.[1])

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer's 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's disease, they promote the solubilization and clearance of β-amyloid by binding its metal-ion complex, and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt 2 putative pathogenic processes of Alzheimer's disease. However, no MPACs have received FDA approval for the treatment of Alzheimer's disease.

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

## Regulatory Status

In 1953, EDTA (Versenate) was approved by the FDA for lowering blood lead levels among both pediatric and adult patients with lead poisoning. In 1991, succimer (Chemet) was approved by FDA for the treatment of lead poisoning in pediatric patients only. The FDA approved disodium-EDTA for use in selected patients with hypercalcemia and use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.[2]

Several iron chelating agents are FDA approved:

- In 1968, deferoxamine (Desferal®; Novartis) was approved by 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 FDA.
- In 2005, deferasirox (Exjade®; Novartis) was approved by FDA, is available as a tablet for oral suspension, and is indicated for the treatment of chronic iron overload due to blood transfusions in patients ages 2 years and older. Under the accelerated approval program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients 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 FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu™) was approved by FDA. All formulations of deferasirox carry a black box 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 FDA for treatment of patients with transfusional overload due to thalassemia syndromes when another chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox® carries a black box 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, FDA advised that FDA-approved chelating agents would be available by prescription only.[3] There are no FDA-approved over-the-counter chelation products.

## POLICY

Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration) are considered **experimental / investigational,** including, but not limited to:

1. Alzheimer's disease
2. arthritis (includes rheumatoid arthritis)
3. atherosclerosis (eg, coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
4. autism
5. diabetes
6. multiple sclerosis

Policy Guidelines

1. A number of indications for chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:
   a. extreme conditions of metal toxicity
   b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)
   c. Wilson disease (hepatolenticular degeneration)
   d. lead poisoning
   e. control of ventricular arrhythmias or heart block associated with digitalis toxicity
   f. emergency treatment of hypercalcemia

2. For items 1 e and 1 f, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. 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.
3. Suggested toxic or normal levels of select heavy metals are listed in Appendix Table

## RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through December 11, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

Chelation therapy is an established treatment for metal toxicity and transfusional hemosiderosis. These uses are not discussed herein. Literature searches have focused on the use of chelation therapy for off-label conditions including, but not limited to, Alzheimer disease, atherosclerosis, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

### Alzheimer Disease

A Cochrane review (2008) evaluated metal protein attenuating compounds for treating Alzheimer disease.[4] Reviewers identified a placebo-controlled randomized trial. This study by Ritchie et al (2003) assessed patients treated with PBT1, a metal protein attenuating compound also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier.[5] The Food and Drug Administration withdrew clioquinol for oral use from the market in 1970 because of its association with subacute myelo-optic neuropathy. Ritchie administered oral clioquinol to 16 Alzheimer disease patients 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. The update of this Cochrane review (2012) included trials through December 2011.[6] Only the Lannfelt 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 patients who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29).[7] 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.

**Section Summary: Alzheimer Disease**
There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published RCTs did not find that chelation was superior to placebo for improving health outcomes.

## Cardiovascular Disease

### Atherosclerosis

Villarruz et al (2002) published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease.[8] Five placebo-controlled randomized trials were identified, none of which reported mortality, nonfatal events, or cerebrovascular events. Four (n=250 patients) of the 5 studies found no significant benefit of EDTA chelation therapy on reported outcomes, including direct or indirect measures of disease severity and subjective measures of improvement. The fifth study (N=10 patients) was stopped early due to benefit, but relevant outcome data were unavailable. Cochrane reviewers found that the evidence was insufficient to support conclusions about the efficacy of chelation therapy for treating atherosclerosis. Additional RCTs reporting health outcomes like mortality and cerebrovascular events were suggested.

Among published RCTs, Knudtson et al (2002) randomized 84 patients with coronary artery disease and a positive treadmill test to EDTA chelation therapy or placebo.[9] Treatment was administered for 3 hours twice weekly for 15 weeks and then monthly for 3 months. Outcome measures included a change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the 2 groups. Another double-blind, placebo-controlled randomized trial (2003) of EDTA chelation showed no difference between groups in short- or long-term improvement in vasomotor response.[10] Two small RCTs from the 1990s also reported no benefit of chelation therapy as a treatment for peripheral arterial disease.[11,12]

#### *Section Summary: Atherosclerosis*

Several RCTs of chelation therapy for treating atherosclerosis generally have reported on intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs reporting health outcomes would be needed to establish treatment efficacy.

### Myocardial Infarction

Lamas et al (2013) published results of the multicenter, 2×2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT).[13] TACT included 1708 patients, ages 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. Patients were randomized to 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Patients 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 end point 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 0.036. A total of 361 (43%) patients in the chelation group and 464 (57%) patients in the placebo group discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary end point was 33% (95% confidence interval [CI], 29% to 37%) in the chelation group and 39% (95% CI, 35% to 42%) in the control group, a statistically significant difference (p=0.035). The most common individual clinical end point was coronary revascularization, which occurred in 130 (16%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=0.08). The next most frequent end point was death, which occurred in 87 (10%) patients in the chelation group and 93 (11%) patients in the placebo group (p=0.64). 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, two 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.[14]

Another 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 patients], active infusions with placebo vitamins [n=418 patients], placebo infusions with active vitamins [n=432 patients], double placebo [n=437 patients]).[15] The proportions of patients 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 end point were 32%, 34%, 37%, and 40%, respectively. The reduction in primary end point 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 patients with diabetes (≈36% of each treatment group), the primary end point 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).

The trial was limited by the high number of withdrawals, with differential withdrawals between groups. The primary end point included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary end point barely met the significance threshold; if more patients 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 patients 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.[16] Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings.[17] This secondary analysis had the same limitations as the parent study previously described (ie, high and differential withdrawal, heterogeneous composite end point). Additionally, because

diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

### *Section Summary: Myocardial Infarction*

One RCT with limitations, including high dropout rate with differential dropout between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes. However, this trial was not of high-quality and, therefore, results might have been biased. More high-quality trials are needed to corroborate whether chelation therapy improves outcomes in patients with prior myocardial infarction.

## Autism spectrum disorder

Based on symptoms similarities between mercury poisoning and autism spectrum disorder, Bernard et al (2001) hypothesized a link between environmental mercury and autism.[18] This theory was rejected by Nelson and Bauman (2003), who found that many characteristics of mercury poisoning, such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children.[19] A meta-analysis by Ng et al (2007) concluded that there was no association between mercury poisoning and autism.[20]

Rossignol (2009) published a systematic review of novel and emerging treatments for autism and identified no controlled studies.[21] Rossignol 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: Autism Spectrum Disorder

There is a lack of controlled studies on how chelation therapy effects health outcomes in patients with autism.

## Diabetes

### Cardiovascular Disease in Patients With 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 patients with type 2 diabetes.[22] 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=0.01). 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 patients in TACT.[23] 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 patients, 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=0.02); among 1170 nondiabetic patients, risk of the primary outcome did not differ statistically between treatment groups (HR=0.96; 95% CI, 0.77 to 1.20; p=0.73).[13] 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 patients 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 patients 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 end point 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=0.002). In adjusted analysis of the individual components of the primary end point, 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 vs 20 in the placebo group).

### 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 patients with high-normal lead levels.[24] Fifty patients with diabetes, high-normal body lead burden (80-6000 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.[25] Patients were randomized to 3 months of calcium disodium EDTA or to placebo. During 24 months of treatment follow-up, patients 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 patients in the placebo group continued to receive placebo medication. All patients 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=0.04). The secondary end point was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) patients in the treatment group and 17 (68%) in the control group attained the secondary end point, a statistically significant difference (p=0.02). There were no reported adverse events of chelation therapy during the trial.

### Section Summary: Diabetes

Two small RCTs with limitations represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small, single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients that report health outcomes (eg, cardiovascular events, end-stage renal disease, mortality) are needed.

## Other Potential Indications: MuLTiple Sclerosis and arthritis

No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for other conditions (eg, multiple sclerosis, arthritis) were identified. Iron chelation therapy is being investigated for Parkinson disease[26,27] and endotoxemia.[28]

## Summary of Evidence

For individuals who have Alzheimer disease, or cardiovascular disease, or autism spectrum disorder, or diabetes, or multiple sclerosis, or arthritis who receive chelation therapy, the evidence includes a small number of RCTs and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of

life, and treatment-related morbidity. One RCT (the Trial to Assess Chelation Therapy) reported that chelation therapy reduced cardiovascular events in patients with previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations (eg, high dropout rates) and, therefore, conclusions are not definitive. For other conditions, the available RCTs did not report improvements in health outcomes with chelation therapy and, as evidence, the case series are inadequate to determine efficacy. The evidence is insufficient to determine the effect of the technology on health outcomes.

## Practice Guidelines and Position Statements

### American College of Physicians et al

The American College of Physicians, American College of Cardiology Foundation, American Heart Association (AHA), and 3 other medical associations published joint clinical practice guidelines (2012) on the management of stable ischemic heart disease (IHD).[29] The guidelines recommended that "chelation therapy should not be used with the intent of improving symptoms or reducing cardiovascular risk in patients with stable IHD. (Grade: strong recommendation; low-quality evidence)." However, citing the Trial to Assess Chelation Therapy,[13] a 2014 focused update of these guidelines 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."[30] The recommendation was upgraded from 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).

The American College of Physician's clinical practice guidelines (2004) stated that chelation "should *not* be used to prevent myocardial infarction or death or to reduce symptoms in patients with symptomatic chronic stable angina. (Level of evidence B: Based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.)"[31]

### American College of Cardiology et al

In 2005, the American College of Cardiology, AHA, and other medical societies stated that chelation "is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses)."[32] In 2013, the American College of Cardiology Foundation and AHA compiled previous American College of Cardiology/AHA and American College of Cardiology Foundation/AHA recommendations issued in 2005[32] and 2011[33] on the management of peripheral artery disease.[34] The recommendation against chelation therapy remained unchanged.

### Canadian Cardiovascular Society

The evidence-based, consensus guidelines (2014) from the Canadian Cardiovascular Society included a conditional recommendation (based on moderate-quality evidence) that chelation therapy should not be used to attempt to improve angina or exercise tolerance in patients with stable IHD.[35]

### National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence issued guidance reports (2013) on autism in children and young people,[36] and autism in adults which was updated in 2016.[37] Both

documents specifically recommended against the use of chelation therapy for the management of autism.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### 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** | | | |
| NCT02728843[a] | Study of Parkinson's Early Stage With Deferiprone (SKY) | 140 | July 2018 |
| NCT02175225 | Study of Deferoxamine Mesylate in Intracerebral Hemorrhage | 294 | Aug 2018 |
| NCT02655315 | Conservative Iron Chelation as a Disease-modifying Strategy in Parkinson's Disease (FAIRPARKII) | 338 | Dec 2018 |
| NCT02733185 | Trial to Assess Chelation Therapy 2 (TACT2) | 1200 | Aug 2021 |
| **Unpublished** | | | |
| NCT02367248 | Safety and Effectiveness Study of Deferoxamine and Xingnaojing Injection in Intracerebral Hemorrhage | 180 | Dec 2016 (unknown) |
| NCT01741532[a] | A Randomized, Double-blind, Placebo-controlled Trial of Deferiprone in Patients With Pantothenate Kinase-associated Neurodegeneration (PKAN) | 89 | Jan 2017 (completed) |

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

## CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

CPT/HCPCS

| | |
|---|---|
| 96365 | Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour |
| 96366 | Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure) |
| 96374 | Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug |
| J0470 | Injection, dimercaprol, per 100 mg |
| J0600 | Injection, edetate calcium disodium, up to 1,000 mg |
| J0895 | Injection, deferoxamine mesylate, 500 mg |
| J3520 | Edetate disodium, per 150 mg |
| M0300 | IV chelation therapy (chemical endarterectomy) |

S9355 Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

## Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

| **REVISIONS** | |
|---|---|
| 11-19-2012 | Policy added to the bcbsks.com web site. |
| | Effective for Institutional providers 12-19-2012. |
| 03-31-2014 | Description section updated |
| | In Policy section:<br>▪ Added to A 4 "and due to nontransfusion-dependent thalassemia (NDTD)" to read, "4. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NDTD)"<br>▪ Added to B 1 "secondary prevention in patients with myocardial infarction" to read, "1. atherosclerosis (i.e., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)" |
| | Rationale section updated |
| | In Coding section:<br>▪ Removed ICD-9 Diagnoses Codes: 427.9, 440.0-440.9<br>▪ Added ICD-10 Diagnoses Codes |
| | References updated |
| 08-19-2016 | Published 07-20-2016. Effective 08-19-2016 |
| | Policy title changed to "Chelation Therapy for Off-Label Uses" from "Chelation Therapy" |
| | Description section updated |
| | In Policy section:<br>▪ Removed the following from the Policy language and restated the FDA approved indications in Policy Guidelines:<br>"Chelation therapy may be considered medically necessary in the treatment of each of the following conditions:<br>1. extreme conditions of metal toxicity<br>2. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT) (NDTD)<br>3. Wilson's disease (hepatolenticular degeneration)<br>4. lead poisoning<br>5. control of ventricular arrhythmias or heart block associated with digitalis toxicity<br>6. emergency treatment of hypercalcemia"<br>▪ In policy statement removed "Other" and added "Off-label" and "(see Policy Guidelines section for uses approved by the Food and Drug Administration)" to read "Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration) are considered experimental / investigational, including, but not limited to:"<br>▪ Removed Off-label indication "hypoglycemia"<br>▪ Added Policy Guidelines to read:<br>" 1. A number of indications for chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:<br>a. extreme conditions of metal toxicity |

| REVISIONS | |
|---|---|
| | b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)<br>c. Wilson disease (hepatolenticular degeneration)<br>d. lead poisoning<br>e. control of ventricular arrhythmias or heart block associated with digitalis toxicity<br>f. emergency treatment of hypercalcemia<br>2. For items 1 e and 1 f, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.<br>3. Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1." |
| | Rationale section updated |
| | In Coding section:<br>▪ CPT Code Correction: Replaced 96375 with 96374<br>▪ Removed ICD codes and replaced with the phrase "Experimental / Investigational for all diagnoses related to this medical policy." |
| | References updated |
| | Added "Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals" |
| 04-11-2018 | Description section updated |
| | Revision section updated |
| | References updated |
| | Appendix updated |

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## APPENDIX

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 |
| 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<br>• Severe: >500 µg/dL |
| Lead | **Pediatric**<br>• Symptoms or blood lead level ≥45 µg/dL (blood)<br>• CDC level of concern: 5 µg/dL[40]<br>• **Adult**<br>• Symptoms or blood lead level ≥70 µg/dL<br>• CDC level of concern: 10 µg/dL[41] |
| Manganese | No clear reference standard |
| Mercury | Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[42,a] |
| Nickel | • Excessive exposure: ≥8 µg/L (blood)<br>• Severe poisoning: ≥500 µg/L (8-h urine) |
| Selenium | • Mild toxicity: >1 mg/L (serum)<br>• Serious toxicity: >2 mg/L |
| 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[43] |
| Zinc | Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells) |

Adapted from Adal (2018).[44]
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.[45]