Chelation Therapy

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Replaces 8.01.02

Chelation therapy may be considered medically necessary, when toxic levels are documented by standard testing methods, as a treatment for the following conditions:

- Chronic iron overload due to blood transfusions (transfusional hemosiderosis)
- Chronic iron overload due to non-transfusion-dependent thalassemia (NTDT)
- Digitalis toxicity with ventricular arrhythmias or heart block
- Extreme conditions of metal toxicity (see Table 1 for select heavy metals)
- Hypercalcemia emergency treatment
- Lead poisoning
- Wilson's disease (hepatolenticular degeneration)

Off-label uses of chelation therapy that are considered investigational, include, but are not limited to:

- Alzheimer disease
- Arthritis (includes rheumatoid arthritis)
- Atherosclerosis (eg, coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
- Autism
- Diabetes
- Multiple sclerosis
- Other indications not listed as medically necessary above

Related Policies

None

Policy Guidelines

For the two conditions listed below, generally other treatments are used in place of chelation therapy:

- Control of ventricular arrhythmias or heart block associated with digitalis toxicity (eg, currently treated, in most patients, with digoxin immune fragment antigen-binding [Fab] monoclonal antibodies).
Emergency treatment of hypercalcemia using IV hydration and other pharmacologic agents is individualized based on the root cause.\(^{(45)}\)

**Note:** FDA removed the approval for NaEDTA (sodium EDTA) as chelation therapy in 2008 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.

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### Table 1. Toxic or Normal Concentrations of Heavy Metals (1-3,5)
Reference standards for bismuth, chromium, and manganese were not identified and are not included in Table 1.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Toxic Levels (Normal levels where indicated)</th>
</tr>
</thead>
</table>
| Arsenic | 24-h urine:  
≥50 µg/L urine or  
100 µg/g creatinine |
| Cadmium | Proteinuria and/or ≥15 µg/g creatinine |
| Cobalt  | Normal excretion:  
0.1-1.2 µg/L (serum)  
0.1-2.2 µg/L (urine) |
| Copper  | Normal excretion:  
25 µg/24 h (urine) |
| Iron    | Nontoxic: <300 µg/dL  
Severe: >500 µg/dL |
| Lead    | **Pediatric**  
Blood lead level ≥45 µg/dL  
**Adult**  
Blood lead level ≥40 µg/dL |
| Mercury | Background exposure normal limits: 1-8 µg/L (whole blood);  
4-5 µg/L (urine)\(^{(4)}\),\(^{a}\) |
| 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 |
| Silver  | Asymptomatic workers have mean levels of 11 µg/L (serum) and  
2.6 µg/L (spot urine) |
| Thallium | >3 µg/L (blood) \(^{(1)}\)  
>5 µg/L (24-hour urine) \(^{(5)}\) |
| Zinc    | Normal range:  
0.6-1.1 mg/L (plasma),  
10-14 mg/L (red cells) |

\(^{a}\) 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.\(^{(6)}\)

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### Coding

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<th>HCPCS</th>
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<tr>
<td>J0470</td>
<td>Dimercaprol injection, per 100 mg</td>
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<tr>
<td>J0600</td>
<td>Edetate calcium disodium, up to 1000mg</td>
</tr>
<tr>
<td>J0895</td>
<td>Injection, deferoxamine mesylate, 500 mg</td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J3520</td>
<td>Edetate disodium, per 150 mg</td>
</tr>
<tr>
<td>M0300</td>
<td>Chelation therapy (Chemical endarterectomy)</td>
</tr>
<tr>
<td>S9355</td>
<td>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</td>
</tr>
</tbody>
</table>
Background

Chelation therapy is an established treatment for the removing metal toxins from the body by converting them to a chemically inert form that can be excreted in the urine. Therapy involves 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 Table 1.)

Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not FDA-approved) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (Ca-EDTA) is used for patients with lead poisoning. Note that 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, they promote the solubilization and clearance of beta amyloid by binding its metal-ion complex, and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt two putative pathogenic processes of Alzheimer disease. However, no MPACs have received FDA approval for the treatment of Alzheimer disease.

Chelation therapy also has 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

- Calcium-EDTA (Versenate) is FDA approved for lowering blood lead levels for both pediatric and adult patients with lead poisoning.
- Succimer is approved for the treatment of lead poisoning in pediatric patients only.
- Disodium-EDTA (Endrate® or Edetate Disodium) was formerly approved for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with the drug, digitalis. However, in 2008, 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:

- Deferoxamine for subcutaneous, intramuscular, or intravenous injections was approved to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia.
- Deferasirox, approved in 2005, is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients aged 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 NTDT.
- Deferiprone (Ferriprox®), an iron chelator was approved in 2011 for treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form for oral use.

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

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Benefit Application

N/A

Rationale

This policy was created in 2016 with a literature search using MEDLINE focusing on the use of chelation therapy for off-label conditions.

Alzheimer Disease

A 2008 Cochrane Review evaluated metal protein attenuating compounds (MPAC) for treating Alzheimer disease.(10) The review identified one placebo-controlled randomized controlled trial (RCT). This study, by Richie et al., was published in 2003. Patients were treated with PBT1, an MPAC also known as clioquinol, an anti-fungal medication that crosses the blood-brain barrier.(11) FDA withdrew clioquinol for oral use in 1970 because of its association with subacute myelo-optic neuropathy. Richie et al 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 (ADAS-Cog). One patient in the treatment group developed impairments in visual acuity and color vision during weeks 31 to 36 during treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. A 2012 update of this review included trials through December 2011. Only the Lannfelt et al. trial discussed next was identified.(12)

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt et al. (2008) completed a double-blind, placebo-controlled RCT of 78 Alzheimer disease patients who were treated for 12 weeks with 50 mg PBT2 (n=20), 250 mg PBT2 (n=29), or placebo (n=29).(13) There was no statistically significant difference in ADAS-Cog 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 and transient ischemic event) were reported, both by patients receiving placebo.

Ongoing investigations in chelation therapy for the treatment of Alzheimer disease and other neurodegenerative diseases include linking a carbohydrate moiety to drug molecules to enhance drug delivery across the blood-brain barrier; this strategy may solve the potential problem of premature and indiscriminate metal binding. In addition, multi-function drugs that not only bind metal but also have significant antioxidant capacity are in development.(14)

Section Summary

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 the treatment was superior to placebo for improving health outcomes.

Atherosclerosis

In 2002, Villarruz et al. published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease.(15) Five randomized placebo-controlled trials were identified, none of which reported mortality, nonfatal events, or cerebrovascular vascular events. Four of the 5 studies (total n=250) found no significant benefit of EDTA chelation therapy on reported outcomes, including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study, which included only 10 patients, was apparently stopped early due to benefit, but relevant outcome data were unavailable. The Cochrane reviewers concluded that evidence was insufficient to draw conclusions about the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were needed.

Among published RCTs, Knudtson et al. (2002) randomized 84 patients with coronary artery disease and a
positive treadmill test to receive EDTA chelation therapy or placebo. Treatment was administered for 3 hours twice weekly for 15 weeks and then monthly for 3 months. Outcome measures included 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 RCT of EDTA chelation showed no difference between groups in short- or long-term improvement in vasomotor response. Two small RCTs from the 1990s also reported no benefit of chelation therapy as a treatment for peripheral arterial disease.

**Section Summary**

Several RCTs of chelation therapy for treating atherosclerosis generally have 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.

**Myocardial Infarction**

In 2013, Lamas et al. published results of the multicenter, 2x2 factorial, randomized, double-blind Trial to Assess Chelation Therapy (TACT). The trial included 1,708 patients, age 50 years or older, who had a history of myocardial infarction (MI) at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to receive 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Patients also received either oral high-dose vitamin and mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. 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 patients in the chelation group (43%) and 464 patients in the placebo group (57%) discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary endpoint were 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 (log-rank test, \( p=0.035 \)). The most common individual clinical endpoint was coronary revascularization, which occurred in 130 (15%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (\( p=0.08 \)). The next most frequent endpoint was death, which occurred in 87 patients (10%) in the chelation group and 93 patients (11%) in the placebo group (\( p=0.64 \)). No individual component of the primary outcome differed statistically between groups; however, the study was not powered to detect differences in individual components. Four severe adverse events that were definitely or possibly related to study therapy occurred. There were 2 events each in the treatment and control groups, including 1 death in each group. Quality-of-life outcomes (reported in 2014) did not differ between groups with 2 years of follow-up. A subsequent publication in 2014 reported results of the 4 treatment groups in the 2x2 factorial design (double active group [disodium EDTA infusions with oral high-dose vitamins], n=421 patients randomized), active infusions with placebo vitamins [n=418], placebo infusions with active vitamins [n=432], and double placebo [n=437]). The proportion of patients who discontinued treatment, withdrew consent, or were lost to follow-up per treatment group was 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 of double active compared with double placebo was more pronounced (HR=0.49 [95% CI: 0.33 to 0.75]).

The study is 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 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 a population that is not generalizable to that seen in general clinical care. Editorialists commenting on the subsequent (2014) publication suggested that further research is warranted to replicate the findings.

Escolar et al. (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. In TACT, there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes: Among 538 self-reported diabetic patients (31% of the trial sample), those randomized to EDTA had a 39% reduced risk of the primary composite outcome compared with placebo (HR=0.61; 95% CI: 0.45 to 0.83; log rank test, \( p=0.02 \)); among 1,170 nondiabetic patients, risk of the primary outcome did not differ statistically.
between treatment groups (HR=0.96; 95% CI: 0.77 to 1.20; log rank test, p=0.73).(20) For the subsequent subgroup analysis, the definition of diabetes mellitus was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose 126 mg/dL or more at trial entry. Of 1708 patients in TACT, 633 (37%) had diabetes mellitus 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 (HR=0.59; 99.4% CI [adjusted for multiple subgroups], 0.39 to 0.88; log -rank test, p=0.002). In adjusted analysis of the individual components of the primary end point, there were no statistically significant differences between treatment groups. There were 36 adverse events attributable to study drug that led to trial withdrawal, 16 in the EDTA group and 20 in the placebo group.

This sub-study has the same limitations as the parent study previously described, namely, high and differential withdrawal and 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

One RCT with limitations, including high dropout with differential drop-out between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes mellitus. However, this was not a high-quality trial and, therefore, results may be biased. Further trials of high quality are needed to corroborate whether chelation therapy improves outcomes in patients with prior MI.

Autism

Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard et al. (2001) hypothesized a link between environmental mercury and autism.(26) 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.(27) A 2007 systematic review by Ng et al concluded that there was no association between mercury poisoning and autism.(28)

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and identified no controlled studies.(29) The author stated that case series 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 patients with autism.

Diabetes

Cardiovascular Disease in Patients with Diabetes

A 2009 trial by Cooper et al. in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes.(30) 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 compared with the placebo group (-10.6 g/m2 vs. -0.1 g/m2, p=0.01). The study was limited by the small sample size and high drop-out rate.

Diabetic Nephropathy

Chen et al. (2012) in China conducted a single-blind RCT of chelation therapy effects on the progression of diabetic nephropathy in patients with high-normal lead levels.(31) Fifty patients with diabetes, high-normal body lead burden (80-6000 µg), and serum creatinine 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, and 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, maximum acceptable blood lead level in adults is 40 µg/dL. (32) Patients were randomized to 3 months of calcium disodium EDTA or placebo. During 24 months of treatment, 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 (eGFR). Mean (SD) yearly rate of decrease in eGFR was 5.6 (5.0) mL/min/173 m² in the chelation group and 9.2 (3.6) mL/min/173 m² in the control group, a statistically significant difference (p=0.04). Secondary end point was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine patients (36%) 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 effects of chelation therapy during the 27-month trial period.

Section Summary
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 such as cardiovascular events, end-stage renal disease, and mortality are needed.

Other Potential Indications
No RCTs or other controlled trials that evaluated safety and efficacy of chelation therapy for other conditions, such as multiple sclerosis or arthritis, were identified. Iron chelation therapy is being investigated for Parkinson disease (33,34) and endotoxemia. (35)

Summary of Evidence
Chelation therapy is an established treatment for metal toxicities and transfusional hemosiderosis. The evidence for chelation therapy in individuals who have Alzheimer disease, cardiovascular disease, arthritis, autism, diabetes, or multiple sclerosis consists of a small number of RCTs and case series. Relevant outcomes include symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One randomized controlled trial, the Trial to Assess Chelation Therapy (TACT), reported that chelation therapy reduced cardiovascular events in patients with a previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this study had significant limitations, including high dropout rates, and therefore the conclusions are not definitive. For other conditions, the available RCTs do not report improvements in health outcomes with chelation therapy and the case series are not adequate evidence to determine efficacy. The evidence is insufficient to determine the effect of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently incomplete and unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
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<tr>
<td>NCT01741532a</td>
<td>A Randomized, Double-blind, Placebo-controlled Trial of Deferiprone in Patients With Pantothenate Kinase-associated Neurodegeneration (PKAN)</td>
<td>89</td>
<td>Dec 2016</td>
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<tr>
<td>NCT02175225</td>
<td>Study of Deferoxamine Mesylate in Intracerebral Hemorrhage</td>
<td>294</td>
<td>Aug 2018</td>
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<tr>
<td>NCT02367248</td>
<td>PKAN Safety and Effectiveness Study of Deferoxamine and Xingnaojing Injection in Intracerebral Hemorrhage</td>
<td>180</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT02733185</td>
<td>Trial to Assess Chelation Therapy 2 (TACT2)</td>
<td>1200</td>
<td>Aug 2021</td>
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</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

**American College of Physicians et al.**
In 2012, the American College of Physicians (ACP), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, and Society of Thoracic Surgeons published a clinical practice guideline on management of stable ischemic heart disease (IHD).\(^{36}\) 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,\(^{20}\) a 2014 focused update of this guideline 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."\(^{37}\) 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).

**American College of Cardiology (ACC)**
In 2005, the American College of Cardiology 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.)"\(^{38}\) In 2013, ACCF and AHA compiled previous ACC/AHA and ACCF/AHA recommendations issued in 2005\(^{38}\) and 2011\(^{39}\) on the management of peripheral artery disease.\(^{40}\) The recommendation against chelation therapy remained unchanged.

**American College of Physicians (ACP)**
A 2004 clinical practice guideline from ACP\(^{41}\) 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.)"

**Canadian Cardiovascular Society (CCS)**
Evidence-based, consensus guidelines from the Canadian Cardiovascular Society in 2014 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 ischemic heart disease.\(^{42}\)

**National Institute for Health and Care Excellence (NICE)**
The National Institute for Health and Care Excellence issued clinical guidance on autism in children and young people in 2013\(^{43}\) and autism in adults in 2012.\(^{44}\) Both documents specifically recommend against the use of chelation therapy for the management of autism.

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

**Medicare National Coverage**
Medicare publication 100-3, NCD Manual Section 20.21, "Chelation Therapy for the Treatment of Atherosclerosis," and NCD Manual Section 20.22, "EDTA Chelation Therapy for the Treatment of Atherosclerosis" made the following determinations:\(^{45}\):

- 20.21: "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.”

- 20.22: “The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA as an approved use is not covered. Any such use of EDTA is considered experimental.”

These are long-standing national coverage decisions (NCD); effective dates of these versions have not been posted.

References

17. Anderson TJ, Hubacek J, Wyse DG, et al. Effect of chelation therapy on endothelial function in patients...


24. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: When evidence conflicts with beliefs. Am Heart J. Jul 2014;168(1):4-5. PMID 24952853


Appendix

N/A

History

<table>
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<th>Date</th>
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<tr>
<td>04/01/16</td>
<td>New policy, replaces deleted policy 8.01.02. Approved March 8, 2016. Chelation therapy for FDA approved indications may be considered medically necessary when criteria are met. All other indications are considered investigational.</td>
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<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. No change to policy statements. No references added.</td>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.
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Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

يحيى هذا الإشعار للمعلومات. قد يحيى هذا الإشعار معلومات مهمة مخصصة بطبيك أو يحيى هذا الإشعار معلومات عن متطلباتك الصحية في هذا الإشعار. طالما أنك جاهز لإثبات أنك تحتوي على مستنداتك الصحية والمعلومات في هذا الطلب. يحتوي ذلك المستند على هذه المعلومات والمساءلة بناءًا على ترتيب أو ترتيبات محترمة وذلك كي تكون لديك كل المعلومات المطلوبة.

Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要信息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

 предусوم كانن-secondary SCHOOL Association


Français (French):


Kreyòl ayisyen (Creole):


Deutsche (German):


Hmoob (Hmong):


Ilokano (Ilocano):

Daytoy a Pakadaa ket nagloan iti Napateg nga Impormasion. Daytoy a pakadaa mabalin nga adda ket nagloan iti napateg nga imporsmasion maipanggep iti aplikasyono nenow coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang saksay dagiti partikular a naaltinga nga adda aldaw tapo mapagtailanido ay coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong ti bukodyo a pagasang nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Premera Blue Cross. In order to preserve the integrity of your health and life insurance policies, you must take action by a specific date to keep your coverage. This notification may contain important dates you need to note to ensure you are covered when you need health or life insurance. This notification also contains important information about your enrollment in Premera Blue Cross. This document is designed to provide you with the necessary information to make informed decisions about your health and life insurance coverage. If you have any questions regarding this notification, please call 800-722-1471 (TTY: 800-842-5357) at Premera Blue Cross. Please review this notification to ensure you understand all the important dates and information provided. If you have any questions, please contact Premera Blue Cross at 800-722-1471 (TTY: 800-842-5357).