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Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

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

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

DESCRIPTION

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This protocol does not address indications for chelation therapy approved by the U.S. Food and Drug Administration. Instead, it addresses off-label indications, including Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

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 (e.g., 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.

POLICY

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

- Alzheimer disease
- atherosclerosis (e.g., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
- autism

- diabetes
- multiple sclerosis
- arthritis (includes rheumatoid arthritis).

POLICY GUIDELINES

A number of indications for which chelation therapy have received FDA approval, and for which chelation therapy is considered standard of care treatment, 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 two bullet points, 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.

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

Table 1. Toxic or Normal Concentrations of Heavy Metals⁴⁰

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24-h urine: $\geq 50 \mu\text{g/L}$ urine or $100 \mu\text{g/g}$ creatinine
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or $\geq 15 \mu\text{g/g}$ creatinine
Chromium	No clear reference standard
Cobalt	Normative excretion: $0.1\text{-}1.2 \mu\text{g/L}$ (serum), $0.1\text{-}2.2 \mu\text{g/L}$ (urine)
Copper	Normative excretion: $25 \mu\text{g}/24 \text{ h}$ (urine)
Iron	<ul style="list-style-type: none"> • Nontoxic: $< 300 \mu\text{g/dL}$ • Severe: $> 500 \mu\text{g/dL}$
Lead	<p>Pediatric</p> <ul style="list-style-type: none"> • Symptoms or blood lead level $\geq 45 \mu\text{g/dL}$ (blood) • CDC level of concern: $5 \mu\text{g/dL}$⁴⁰ <p>Adult</p> <ul style="list-style-type: none"> • Symptoms or blood lead level $\geq 70 \mu\text{g/dL}$ • CDC level of concern: $10 \mu\text{g/dL}$⁴¹
Manganese	No clear reference standard
Mercury	Background exposure normative limits: one to eight $8 \mu\text{g/L}$ (whole blood); four to five $\mu\text{g/L}$ (urine) ^{42, a}
Nickel	<ul style="list-style-type: none"> • Excessive exposure: $\geq \text{eight } \mu\text{g/L}$ (blood) • Severe poisoning: $\geq 500 \mu\text{g/L}$ (eight-h urine)
Selenium	<ul style="list-style-type: none"> • Mild toxicity: $> \text{one mg/L}$ (serum) • Serious toxicity: $> \text{two mg/L}$
Silver	Asymptomatic workers have mean levels of $11 \mu\text{g/L}$ (serum) and $2.6 \mu\text{g/L}$ (spot urine)

Metal	Toxic Levels (Normal Levels Where Indicated)
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

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 Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (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 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 β-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 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 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 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 patients ages two 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-transfu-

sion-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 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 the 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 the FDA-approved chelating agents would be available by prescription only.³ There are no FDA-approved over-the-counter chelation products.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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