

FEP 8.01.02 Chelation Therapy for Off-Label Uses

Effective Date: July 15, 2018

Related Policies: None

Chelation Therapy for Off-Label Uses

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 evidence review 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.

FDA 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.

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- 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 STATEMENT

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

- Alzheimer disease
- atherosclerosis (eg, 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 chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care. They include:

- extreme conditions of metal toxicity
- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and 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 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 Appendix Table 1.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

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

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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.

SUPPLEMENTAL INFORMATION

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 2005³² and 2011³³ 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.

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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 states³⁸:

“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 states³⁹:

“The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA [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.

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- the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. Mar 21 2006;113(11):e463-654. PMID 16549646
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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
September 2013	Update Policy	Policy updated with literature review. References 16-21 added, others removed or renumbered. Chronic iron overload due to nontransfusion-dependent thalassemia (NDTD) added to medically necessary statement based on new FDA approval. Secondary prevention in patients with myocardial infarction added to bullet point in investigational statement on atherosclerosis; in that bullet point, "i.e." changed to "e.g."
September 2014	Update Policy	Policy updated with literature review through May 21, 2014; references 14, 22-24, and 28-29 added; references 2, 19, and 25 updated. Title changed to "Chelation Therapy for Off-Label Uses." Medically necessary

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September 2015	Update Policy	policy statement for on-label uses deleted from policy statement and moved to policy guidelines. Investigational policy statement unchanged. Policy updated with literature review through May 21, 2015; references 3, 4, 23-25, 27, 33, 35, 36, 38 and 41 added. Hypoglycemia deleted from policy statement; this indication is not reviewed in the policy. Policy statements otherwise unchanged.
June 2018	Update Policy	Policy updated with literature review through December 11, 2017; reference 8 removed; reference 38 and 44 updated; reference 39 added. Policy statement unchanged.

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 $\mu\text{g/L}$ urine or 100 $\mu\text{g/g}$ creatinine
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or ≥ 15 $\mu\text{g/g}$ creatinine
Chromium	No clear reference standard
Cobalt	Normative excretion: 0.1-1.2 $\mu\text{g/L}$ (serum), 0.1-2.2 $\mu\text{g/L}$ (urine)
Copper	Normative excretion: 25 $\mu\text{g}/24$ h (urine)
Iron	<ul style="list-style-type: none"> • Nontoxic: < 300 $\mu\text{g/dL}$ • Severe: > 500 $\mu\text{g/dL}$
Lead	Pediatric <ul style="list-style-type: none"> • Symptoms or blood lead level ≥ 45 $\mu\text{g/dL}$ (blood) • CDC level of concern: 5 $\mu\text{g/dL}$⁴⁰ Adult <ul style="list-style-type: none"> • Symptoms or blood lead level ≥ 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: 1-8 $\mu\text{g/L}$ (whole blood); 4-5 $\mu\text{g/L}$ (urine) ^{42,a}
Nickel	<ul style="list-style-type: none"> • Excessive exposure: ≥ 8 $\mu\text{g/L}$ (blood) • Severe poisoning: ≥ 500 $\mu\text{g/L}$ (8-h urine)
Selenium	<ul style="list-style-type: none"> • Mild toxicity: > 1 mg/L (serum) • Serious toxicity: > 2 mg/L
Silver	Asymptomatic workers have mean levels of 11 $\mu\text{g/L}$ (serum) and 2.6 $\mu\text{g/L}$ (spot urine)
Thallium	24-hour urine thallium > 5 $\mu\text{g/L}$ 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