

## Corporate Medical Policy

### Chelation Therapy

<b>File Name:</b>	chelation_therapy
<b>Origination:</b>	12/1995
<b>Last CAP Review:</b>	2/2019
<b>Next CAP Review:</b>	2/2020
<b>Last Review:</b>	2/2019

#### Description of Procedure or Service

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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 consists of intravenous or oral administration of chelating agents that remove metal ions such as lead, aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body..

Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not Food and Drug Administration [FDA] approved) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (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'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 A $\beta$ -amyloid protein 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's disease. However, no MPACs have received FDA approval for the treatment of Alzheimer's disease.

Chelation therapy has also been investigated 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

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

Several iron chelating agents are FDA approved:

- Deferoxamine (Desferal®; Novartis) for subcutaneous, intramuscular, or intravenous injections for treating acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved.
- Deferasirox (Exjade®; Novartis), 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, the FDA expanded the indications for deferasirox in 2013 to include the treatment of patients age 10 and older with chronic iron overload due to nontransfusion-dependent thalassemia syndromes and specific liver iron

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concentration and serum ferritin levels.. 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.

- Deferiprone (Ferriprox®) for the treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox® carries a black box warning because it can cause agranulocytosis that 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 are available by prescription only. There are no FDA-approved over-the-counter chelation products.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**BCBSNC will provide coverage for Chelation Therapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Chelation Therapy is covered

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Parenteral chelation therapy may be considered medically necessary for the treatment of documented systemic iron overload (hemochromatosis), lead poisoning, or other heavy metal toxicity as defined below:

- Hemochromatosis: Clinical symptoms of chronic iron toxicity should correlate with an elevated serum ferritin. Parenteral chelation therapy is not medically necessary in genetic or hereditary hemochromatosis. Subcutaneous infusion of desferoxamine via a portable pump may be considered medically necessary for acquired hemochromatosis complicating a chronic hemolytic anemia such as thalassemia or sideroblastic anemia or when hypoproteinemia precludes phlebotomy as treatment.
- Acute iron poisoning: Parenteral desferoxamine is medically necessary in patients with serum iron level greater than 50umol/L (300ug/dL) or in whom a desferoxamine challenge test is positive.
- Lead: parenteral chelation therapy may meet medical necessity requirements in adults with blood lead levels greater than 1.7umol/L (35ug/dL) or in children with levels greater than 25 ug/dL. Parenteral EDTA and/or dimercaprol may be allowed until blood lead levels decrease (usually one to two 5-day courses of therapy).
- Other heavy metals: arsenic, cadmium, gold, mercury, and thallium poisoning are generally suspected based upon a positive urine screen for heavy metals in a symptomatic individual. Toxic levels should be confirmed with blood levels where appropriate.

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- Parenteral chelation agents are not always appropriate and should be reviewed for approved indications against the specific heavy metal identified.
- Parenteral chelation therapy may also be medically necessary for the following indications:
  - Control of ventricular arrhythmias or heart block associated with digitalis toxicity
  - Emergency treatment of hypercalcemia
  - Extreme conditions of metal toxicity
  - Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NTDT)
  - Wilson’s Disease (Hepatolenticular degeneration)
  - Lead poisoning

**Note:** for control of ventricular arrhythmias or heart block associated with digitalis toxicity most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. The FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

## When Chelation Therapy is not covered

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Chelation therapy is considered investigational, including, but not limited to, the following conditions:

- Heavy metal toxicity or iron or lead poisoning where toxic levels are not documented by standard testing methods
- Atherosclerosis (e.g., coronary artery disease, peripheral vascular disease, secondary prevention in patients with myocardial infarction)
- Multiple sclerosis
- Arthritis (includes rheumatoid arthritis)
- Diabetes
- Autism
- Alzheimer’s disease
- Other indications not listed under “when chelation therapy is covered”

## Policy Guidelines

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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.

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.

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.

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

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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.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: J0470, J0600, J0895, J3520, S9355, M0300*

***Documentation Requirements:***

*Laboratory results must be provided by a certified (CLIA) lab.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual - 12/95

Circulation, 1997;96(5):1031-3

Harrison's Principles of Internal Medicine, Isselbacher, et.al., McGraw Hill, 13th ed. 1145-2496

Nelson's Textbook of Pediatrics, Behrman, et. al., Saunders, 15th ed.

DeSwarte-Wallace J, Groncy PK, Finkelstein JZ, Iron Chelation with deferoxamine: comparing the results of a critical pathway to a national survey. J Pediatr Hematol Oncol 1999 Mar-Apr;21(2):136-41

Medical Policy Advisory Group - 10/99

Medical Policy Advisory Group - 3/1/2001

Specialty Matched Consultant Advisory Panel - 9/2002

BCBSA Medical Policy Reference Manual, 8.01.02, 7/12/02

Specialty Matched Consultant Advisory Panel - 4/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 10/9/03.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 4/12/12.

Specialty Matched Consultant Advisory Panel- 2/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 6/13/13.

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Specialty Matched Consultant Advisory Panel- 2/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 6/22/14.

Specialty Matched Consultant Advisory Panel- 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 6/11/15

Specialty Matched Consultant Advisory Panel 2/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 2/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 2/2017

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for CHELATION THERAPY for Treatment of Atherosclerosis (20.21). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=86&ncdver=1&CoverageSelection=National&Keyword=Chelation+Therapy&KeywordLookUp=Title&KeywordSearchType=And&bc=gAAAACAAAAAAAA%3d%3d&>.

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for CHELATION THERAPY for Treatment of Atherosclerosis (20.21). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=86&ncdver=1&CoverageSelection=National&Keyword=Chelation+Therapy&KeywordLookUp=Title&KeywordSearchType=And&bc=gAAAACAAAAAAAA%3d%3d&>.

National Institute for Health and Care Excellence. Autism spectrum disorder in adults: diagnosis and management [CG142]. 2016; <https://www.nice.org.uk/guidance/CG142>.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.02, 2/2018

## Policy Implementation/Update Information

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| 12/97 | Revised: Previous policy archived. See M0300.ARC. Additional information added to Policy for understanding of therapy.   |
| 8/99  | Reformatted, Medical Term Definitions added.   |
| 10/99 | Medical Policy Advisory Group - Added that statement that laboratory results must be provided by a certified lab   |
| 10/00 | System coding changes.   |
| 3/01  | Medical Policy Advisory Group review. Corrected typos. Medical Term Definitions clarified. Approve. J codes added to coding section. System changes.   |
| 4/02  | Revised the description section and added, "Chelating agents may be given by mouth or by parenteral infusion". Revised bullet number 2 under when it is not covered to include, "by standard testing methods". |
| 10/02 | Specialty Matched Consultant Advisory Panel review. No change in policy.   |
| 5/03  | Specialty Matched Consultant Advisory Panel review. No change in policy. Reaffirm.   |

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- 4/7/05 Specialty Matched Consultant Advisory Panel [MPAG] review on 3/10/2005. No changes made in policy criteria. Reference added. Policy status changed to: "Active policy, no longer scheduled for routine literature review."
- 6/22/10 Policy Number(s) removed (amw)
- 11/27/12 Revised description section. Changed status of policy to active from active archive. Added autism, alzheimer's disease and rheumatoid arthritis as investigational indications under "When Not Covered" section. Reference added. Notification given 11/27/12 for effective date 2/26/13. Medical director review 11/2012. (lpr)
- 3/12/13 Specialty Matched Consultant Advisory panel review meeting 2/20/13. No change to policy statement. (lpr)
- 7/16/13 Under "When Covered" section: added extreme conditions of metal toxicity; treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NDDT); lead poisoning. Under "When Not Covered" section: added: "secondary prevention in patients with myocardial infarction" as investigational indication to 2<sup>nd</sup> bullet Atherosclerosis. Updated Regulatory status. Reference updated. Notification date 7/16/13 for effective date 10/1/13. (lpr)
- 3/11/14 Specialty Matched Consultant Advisory Panel review meeting 2/25/2014. No change to policy statement. (lpr)
- 8/12/14 Updated description section, Regulatory status, and policy guidelines. Reference added.(lpr)
- 3/10/15 Minor updates to Description section. Specialty matched consultant advisory panel review meeting 2/25/2015. No change to policy statement. (lpr)
- 7/28/15 Under "When Not Covered" section, deleted "hypoglycemia" as this indication is not reviewed in this policy. Reference added. (lpr)
- 4/1/16 Added J0895 to Billing/Coding section. Specialty Matched Consultant Advisory Panel review 2/24/2016. (adn)
- 3/31/17 Updated Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 2/22/2017. No change to policy statement. (an)
- 3/29/18 Updated Description section. Specialty Matched Consultant Advisory Panel review 2/28/2018. Reference added. No change to policy statement. (an)
- 3/12/19 Minor updates to Description section. Policy Guidelines section updated. References added. Specialty Matched Consultant Advisory Panel review 2/20/2019. (an)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.