Medical Coverage Policy | Chelation Therapy for Off-Label Uses

EFFECTIVE DATE: 01|01|2017
POLICY LAST REVIEWED: 03|20|2024

OVERVIEW

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 policy addresses the following off-label uses of chelation therapy:

- Alzheimer disease
- Arthritis (includes rheumatoid arthritis)
- Atherosclerosis (eg, coronary artery disease, secondary prevention in individuals with myocardial infarction, or peripheral vascular disease)
- Autism Spectrum Disorder
- Diabetes
- Multiple Sclerosis

This policy does not address the following U.S Food and Drug Administration (FDA)-approved indications for which chelation therapy is considered standard of care treatment:

- Control of ventricular arrhythmias or heart block associated with digitalis toxicity
- Emergency treatment of hypercalcemia
- Extreme conditions of metal toxicity
- Lead Poisoning
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia (NTDT)
- Wilson Disease (hepatolenticular degeneration)

This policy is applicable to Commercial Products only. For Medicare Advantage Plans, see related policy section.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Commercial Products

Off-label applications of chelation therapy (non-FDA-approved uses) are considered not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome for indications including but not limited to:

- Alzheimer disease
- Arthritis (includes rheumatoid arthritis)
- Atherosclerosis (eg, coronary artery disease, secondary prevention in individuals with myocardial infarction, or peripheral vascular disease)
- Autism Spectrum Disorder
- Diabetes

- Multiple Sclerosis

For Medicare Advantage Plans, see related policy section for the Medicare Advantage Plans National and Local Coverage Determinations policy.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable not medically necessary benefits/coverage.

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. Specific chelating agents are used for particular heavy metal toxicities. For example, deferoxamine 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.)

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 2 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 spectrum disorder. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

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.

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 boxed 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 boxed 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. There are no FDA-approved over-the-counter chelation products.

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 randomized controlled trials (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 that the technology results in an improvement in the net health outcome.

CODING

Commercial Products

The following HCPCS code(s) represents the infusion service only and is not separately reimbursed:

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.

Chemical Endarterectomy

The following HCPCS code(s) and any of the medications utilized as part of the service are not medically necessary when filed with the ICD-10 diagnosis codes below:

M0300 IV chelation therapy (chemical endarterectomy)

ICD-10 Diagnosis Codes:

E08.00-E13.9
F84.0-F84.9
G30.0-G30.9
G35
I25.10-I25.9
M05.00-M06.09
M15.0-M19.93

Failure of participating providers to report Chemical Endarterectomy using M0300 will be considered improper coding by Blue Cross & Blue Shield of Rhode Island.

RELATED POLICIES

Medicare Advantage Plans National and Local Coverage Determinations
Non-Reimbursable Health Service Codes

PUBLISHED

Provider Update, May 2024
Provider Update, May 2023
Provider Update, June 2022
Provider Update, June 2021

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Deaths associated with hypocalcemia from chelation therapy--Texas, Pennsylvania, and Oregon, 2003-2005. MMWR Morb Mortal Wkly Rep. Mar 03 2006; 55(8): 204-7. PMID 16511441
2. Food and Drug Administration. Hospira, Inc., et al.; Withdrawal of Approval of One New Drug Application and Two Abbreviated New Drug Application. Federal Register. 2008;73(113):33440-33441.
3. Sampson E, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's disease. Cochrane Database Syst Rev. Jan 23 2008; (1): CD005380. PMID 18254079
4. Ritchie CW, Bush AI, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch Neurol. Dec 2003; 60(12): 1685-91. PMID 14676042
5. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's dementia. Cochrane Database Syst Rev. Feb 21 2014; (2): CD005380. PMID 24563468
6. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's dementia. Cochrane Database Syst Rev. May 16 2012; 5(5): CD005380. PMID 22592705
7. Lannfelt L, Blennow K, Zetterberg H, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol. Sep 2008; 7(9): 779-86. PMID 18672400
8. Ravalli F, Vela Parada X, Ujueta F, et al. Chelation Therapy in Patients With Cardiovascular Disease: A Systematic Review. J Am Heart Assoc. Mar 15 2022; 11(6): e024648. PMID 35229619
9. Villarruz-Sulit MV, Forster R, Dans AL, et al. Chelation therapy for atherosclerotic cardiovascular disease. Cochrane Database Syst Rev. May 05 2020; 5(5): CD002785. PMID 32367513
10. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. JAMA. Mar 27 2013; 309(12): 1241-50. PMID 23532240
11. Mark DB, Anstrom KJ, Clapp-Channing NE, et al. Quality-of-life outcomes with a disodium EDTA chelation regimen for coronary disease: results from the trial to assess chelation therapy randomized trial. Circ Cardiovasc Qual Outcomes. Jul 2014; 7(4): 508-16. PMID 24987051
12. Lamas GA, Boineau R, Goertz C, et al. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: The factorial group results of the Trial to Assess Chelation Therapy. Am Heart J. Jul 2014; 168(1): 37-44.e5. PMID 24952858
13. Lewis EF, Ujueta F, Lamas GA, et al. Differential Outcomes With Edetate Disodium-Based Treatment Among Stable Post Anterior vs. Non-Anterior Myocardial Infarction Patients. Cardiovasc Revasc Med. Nov 2020; 21(11): 1389-1395. PMID 32303436
14. Nissen SE. Concerns about reliability in the Trial to Assess Chelation Therapy (TACT). JAMA. Mar 27 2013; 309(12): 1293-4. PMID 23532246
15. 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
16. Lamas GA, Anstrom KJ, Navas-Acien A, et al. The trial to assess chelation therapy 2 (TACT2): Rationale and design. Am Heart J. Oct 2022; 252: 1-11. PMID 35598636
17. Bernard S, Enayati A, Redwood L, et al. Autism: a novel form of mercury poisoning. Med Hypotheses. Apr 2001; 56(4): 462-71. PMID 11339848
18. Nelson KB, Bauman ML. Thimerosal and autism?. Pediatrics. Mar 2003; 111(3): 674-9. PMID 12612255
19. Ng DK, Chan CH, Soo MT, et al. Low-level chronic mercury exposure in children and adolescents: meta-analysis. Pediatr Int. Feb 2007; 49(1): 80-7. PMID 17250511
20. Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. Ann Clin Psychiatry. 2009; 21(4): 213-36. PMID 19917212

21. Cooper GJ, Young AA, Gamble GD, et al. A copper(II)-selective chelator ameliorates left-ventricular hypertrophy in type 2 diabetic patients: a randomised placebo-controlled study. Diabetologia. Apr 2009; 52(4): 715-22. PMID 19172243
22. Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). Circ Cardiovasc Qual Outcomes. Jan 2014; 7(1): 15-24. PMID 24254885
23. Ujueta F, Arenas IA, Escolar E, et al. The effect of EDTA-based chelation on patients with diabetes and peripheral artery disease in the Trial to Assess Chelation Therapy (TACT). J Diabetes Complications. Jul 2019; 33(7): 490-494. PMID 31101487
24. Escolar E, Ujueta F, Kim H, et al. Possible differential benefits of edetate disodium in post-myocardial infarction patients with diabetes treated with different hypoglycemic strategies in the Trial to Assess Chelation Therapy (TACT). J Diabetes Complications. Aug 2020; 34(8): 107616. PMID 32446881
25. Chen KH, Lin JL, Lin-Tan DT, et al. Effect of chelation therapy on progressive diabetic nephropathy in patients with type 2 diabetes and high-normal body lead burdens. Am J Kidney Dis. Oct 2012; 60(4): 530-8. PMID 22721929
26. U.S Food and Drug Administration. FDA warns consumers about potential health risks from using Thorne Research's Captomer products. 2014 June 12; https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-about-potential-health-risks-using-thorne-researchs-captomer-products. Accessed December 22, 2023.
27. Weinreb O, Mandel S, Youdim MBH, et al. Targeting dysregulation of brain iron homeostasis in Parkinson's disease by iron chelators. Free Radic Biol Med. Sep 2013; 62: 52-64. PMID 23376471
28. Grolez G, Moreau C, Sablonnière B, et al. Ceruloplasmin activity and iron chelation treatment of patients with Parkinson's disease. BMC Neurol. May 06 2015; 15: 74. PMID 25943368
29. van Eijk LT, Heemskerk S, van der Pluijm RW, et al. The effect of iron loading and iron chelation on the innate immune response and subclinical organ injury during human endotoxemia: a randomized trial. Haematologica. Mar 2014; 99(3): 579-87. PMID 24241495
30. Devos D, Labreuche J, Rascol O, et al. Trial of Deferiprone in Parkinson's Disease. N Engl J Med. Dec 01 2022; 387(22): 2045-2055. PMID 36449420
31. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. Mar 21 2017; 135(12): e726-e779. PMID 27840333
32. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. Nov 04 2014; 64(18): 1929-49. PMID 25077860
33. Qaseem A, Fihn SD, Dallas P, et al. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. Ann Intern Med. Nov 20 2012; 157(10): 735-43. PMID 23165665
34. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. Aug 29 2023; 148(9): e9-e119. PMID 37471501
35. Lamas GA, Bhatnagar A, Jones MR, et al. Contaminant Metals as Cardiovascular Risk Factors: A Scientific Statement From the American Heart Association. J Am Heart Assoc. Jul 04 2023; 12(13): e029852. PMID 37306302
36. Hyman SL, Levy SE, Myers SM, et al. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. Jan 2020; 145(1). PMID 31843864
37. 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. Accessed December 22, 2023.
38. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Ethylenediamine- Tetra-Acetic (EDTA) CHELATION THERAPY for Treatment of Atherosclerosis (20.22). n.d.; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=146&ncdver=1&bc=AAAAQAAAAAAA&. Accessed December 21, 2023.
39. Centers for Disease Control and Prevention (CDC). Childhood Lead Poisoning Prevention. December 2, 2022; http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm. Accessed December 22, 2023.
40. Centers for Disease Control and Prevention (CDC). Very high blood lead levels among adults - United States, 2002-2011. MMWR Morb Mortal Wkly Rep. Nov 29 2013; 62(47): 967-71. PMID 24280917
41. Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury. 2022; https://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf. Accessed December 22, 2023.
42. Centers for Disease Control and Prevention (CDC). Emergency preparedness and response. Case definition: thallium. April 4, 2018; https://emergency.cdc.gov/agent/thallium/casedef.asp. Accessed December 22, 2023.
43. Adal A. Medscape. Heavy metal toxicity. 2023; http://emedicine.medscape.com/article/814960-overview. Accessed December 22, 2023.
44. Kempson IM, Lombi E. Hair analysis as a biomonitor for toxicology, disease and health status. Chem Soc Rev. Jul 2011; 40(7): 3915-40. PMID 21468435

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS