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CHELATION THERAPY FOR NON-OVERLOAD CONDITIONS (FOR LOUISIANA ONLY)

Policy Number: CS016LA.1H

Effective Date: ~~TBD~~ March 1, 2019

[Instructions for Use](#) ⓘ

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COVERAGE RATIONALE

Chelation for heavy metal toxicity and overload conditions (e.g., iron, copper, lead, aluminum) is proven and medically necessary and not addressed in this policy.

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- **Chelation therapy for treating any chronic, progressive diseases associated with non-overload conditions**
- Chelation therapy for treating "mercury toxicity" from dental amalgam fillings
- ~~Chelation therapy for treating any chronic, progressive diseases associated with non-overload conditions~~

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J3490	Unclassified drugs
<u>J0470</u>	<u>Injection, dimercaprol, per 100 mg</u>
<u>J0600</u>	<u>Injection, edetate calcium disodium, up to 1000 mg</u>
<u>J0895</u>	<u>Injection, deferoxamine mesylate, 500 mg</u>
<u>J8499</u>	<u>Prescription drug, oral, nonchemotherapeutic, NOS</u>
M0300	IV chelation therapy (chemical endarterectomy)

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HCPCS Code	Description
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

DESCRIPTION OF SERVICES

Chelation therapy **is an established treatment for the removal of metal toxins from the body.** This involves the administration of naturally occurring or chemically designed molecules to bind and excrete a specific toxin in the body. The specific medication, route, method and site of administration of the chelating agent varies depending on the specific agent used, the level of toxicity, and other clinical indications. Heavy metal toxicity most often treated with chelation therapy includes that caused by iron, copper, lead, aluminum, and mercury.

Non-Overload Conditions

Chelation therapy has been proposed as a treatment for a variety of non-overload conditions, **where acute or chronic heavy metal toxicity has not been demonstrated, and** in which the removal of heavy metal ions is hypothesized to reduce oxidative damage caused by the production of hydroxyl radicals. However, the possible mechanism of chelators as therapeutic agents for non-overload conditions is not fully understood. Chelation has been investigated as a treatment of numerous non-overload conditions including, but not limited to, cardiovascular disease, rheumatoid arthritis (RA), cancer, and diabetes.

Mercury Poisoning

Chelation therapy has been proposed to treat metal toxicity from dental amalgam fillings, but it has not been shown that mercury amalgams cause harm to individuals with dental fillings, except in rare cases of allergy.

CLINICAL EVIDENCE

Non-Overload Conditions

Well-designed, published and peer-reviewed studies do not support chelation treatment for chronic, progressive diseases such as cardiovascular disease, atherosclerosis, diabetes, cancer, Alzheimer's disease, autism spectrum disorder, or RA. There are no studies available regarding chelation therapy for the treatment of apoplectic coma, chronic fatigue syndrome, chronic renal insufficiency, defective hearing, diabetic ulcer, cholelithiasis, gout, erectile dysfunction, multiple sclerosis, osteoarthritis, osteoporosis, Parkinson's disease, Raynaud's disease, renal calculus, schizophrenia, scleroderma, snake venom poisoning, varicose veins, or vision disorders. There is insufficient evidence that chelation therapy is safe and effective to remove other undesirable metabolites or toxins, or have a positive impact on clinical outcomes for other disease states.

Alzheimer's Disease (AD)

Increased levels of aluminum have been discovered in several brain regions of individuals with AD. Epidemiological studies have linked the concentration of aluminum in drinking water and the increased occurrence of the disease. **Some** scientists have postulated that chelation therapy might promote beneficial results in AD patients by inhibiting the deposition of aluminum in the brain or by preventing iron from catalyzing the formation of toxic hydroxyl radicals. Aluminum chelators may also reactivate aluminumized metalloenzyme complexes in AD patients and permit redistribution of aluminum in the brain.

A Cochrane systematic review was conducted by Sampson et al. to evaluate the efficacy of metal protein attenuating compounds (MPACs) for the treatment of cognitive impairment due to AD. The primary outcome measure was cognitive function (measured by psychometric tests). Two MPAC trials were identified. One trial compared clioquinol (PBT1) with placebo in 36 patients and 32 had sufficient data for per protocol analysis. There was no statistically significant difference in cognition (as measured on the AD Assessment Scale - Cognition (ADAS-Cog)) between the active treatment and placebo groups at 36 weeks, and there was no significant impact on non-cognitive symptoms or clinical global impression. In the second trial a successor compound, PBT2, was compared with placebo in 78 participants with mild AD. There was no significant difference in the Neuropsychological Test Battery (NTB) composite

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or memory between placebo and PBT2 at week 12. However, 2 executive function component tests of the NTB showed significant improvement over placebo in the PBT2 250 mg group from baseline to week 12. There was no significant effect on cognition on Mini-Mental State Examination (MMSE) or ADAS-Cog scales. PBT2 did have a favorable safety profile. The authors concluded that there is an absence of evidence as to whether clioquinol (PBT1) is safe or has any positive clinical benefit for patients with AD, and cited that further development of PBT1 has been abandoned. The second trial of PBT2 was more rigorously conducted and appeared to be safe and well tolerated in individuals with mild AD after 12 weeks. Larger trials are now required to demonstrate cognitive efficacy (2014).

Several studies have ~~suggested~~~~reported some~~ improvement in cognitive function or ~~biomarkers~~~~slowing of the rate of decline~~ in patients treated with clioquinol or deferoxamine (Crapper Mclachlan, 1991; Regland, 2001; Ritchie, 2003). However, these studies were small, only two were placebo-controlled, and none were double-blind, and therefore no conclusions regarding the clinical efficacy of chelation therapy for AD can be made on the basis of these studies.

Autism Spectrum Disorder (ASD)

A Cochrane systematic evidence review found no clinical trial evidence to suggest that pharmaceutical chelation is an effective intervention for ASD. One study was found, which was conducted in 2 phases. During phase 1, 77 children with ASD were randomly assigned to receive 7 days of glutathione lotion or placebo lotion, followed by 3 days of oral dimercaptosuccinic acid (DMSA). A total of 49 children who were found to be high excreters of heavy metals during phase 1 continued on to phase 2 and received 3 days of oral DMSA or placebo followed by 11 days off, with the cycle repeated up to 6 times. The second phase assessed the effectiveness of multiple doses of oral DMSA compared with placebo in children who were high excreters of heavy metals and who received a 3 day course of oral DMSA. Overall, no evidence suggests that multiple rounds of oral DMSA had an effect on ASD symptoms. The authors concluded that given prior reports of serious adverse events, such as hypocalcaemia, renal impairment and reported death, the risks of using chelation for ASD currently outweigh proven benefits. In their opinion, evidence that supports a causal link between heavy metals and autism must be identified and methods that ensure the safety of participants is imperative before further trials are conducted (James, et al. 2015).

~~A National Institute for Health and Care Excellence (NICE) guideline on autism does not recommend the use of chelation for the management of core symptoms of autism in adults. (2016)~~

Cardiovascular Disease (CVD)

~~Chelation therapy has been proposed as a treatment of coronary artery disease, based in part on the hypothesis that chelation could remove atherosclerotic calcium deposits or provide an antioxidant benefit.~~

In November 2012, the American Heart Association (AHA) announced preliminary results of the Trial to Assess Chelation Therapy (TACT). TACT was a multicenter, double-blind, randomized efficacy trial that took place from 2002 to 2011. Patients (n=1700) were randomized to receive 40 infusions of a 500-mL chelation solution or a placebo infusion, with a second randomization to an oral vitamin and mineral regimen or an oral placebo. Each patient received 40 infusions, each lasting at least 3 hours. Researchers found that patients receiving the chelation solution had fewer serious cardiovascular events than the control group: 26% versus 30%. Cardiovascular events were defined as death, heart attack, stroke, coronary revascularization, and hospitalization for angina. Because the level of statistical difference between the groups was small, it is not known whether the effect will be reproducible in a real-world scenario. Investigators cautioned that the results need to be reproduced and understood before consideration of clinical application.

Further analysis of the TACT data by Lamas et al. (2013) reported that in stable patients with a history of myocardial infarction (MI), the use of an intravenous chelation regimen with Edetate calcium disodium (EDTA) modestly reduced the risk of a variety of adverse cardiovascular outcomes compared to placebo. The findings of the primary outcome barely reached the pre-specified statistical significance level, and therefore the role of chance in these findings is unclear. None of the findings on the secondary outcomes were statistically significant. Therefore, independent replication of the findings would be necessary to consider this treatment as proven. The authors stated that while these results should guide further research, there still is not sufficient evidence to support routine use of chelation therapy in post-MI patients.

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Using the TACT data, an initial subgroup analysis showed a greater effect of EDTA treatment among participants with a self-reported history of diabetes. Further examination of the data in patients with diabetes demonstrated a 41% overall reduction in the risk of any cardiovascular event; a 40% reduction in risk of cardiovascular mortality, non-fatal stroke, or non-fatal MI; a 52% reduction in recurrent heart attacks; and a 43% reduction in death from any cause. In contrast, there was no significant benefit of EDTA treatment in the subgroup of 1,045 participants who did not have diabetes. The authors note that results of this analysis support the initiation of clinical trials in patients with diabetes and vascular disease to replicate these findings, and to define the mechanisms of benefit. However, it was also concluded that there is not enough evidence to support the routine use of chelation therapy for this population (Escobar et al. 2013).

~~Trial to Assess Chelation Therapy 2 (TACT2) is a randomized, double-blind controlled factorial clinical trial of edetate disodium-based chelation and high-dose oral vitamins and minerals to prevent recurrent cardiac events in diabetic patients with a prior MI. This study is currently recruiting participants. Additional information is available at www.clinicaltrials.gov. (Accessed December 1, 2018)~~

Rheumatoid Arthritis

No randomized controlled trials evaluating chelation therapy for rheumatoid arthritis were identified.

~~In a review of chelation for non-overload conditions, Voest et al. (1994) summarized the available literature regarding RA. In 6 small studies with patient populations ranging from 6 to 18 patients, deferoxamine improved the clinical symptoms and reduced anemia in the majority of patients. However, the authors concede that the preponderance of evidence regarding chelation for RA is derived from small numbers of patients treated for a short amount of time. The authors assert that larger studies are needed to determine the role of iron chelators in the treatment of RA.~~

~~In a second review, Ghio et al. (1997) hypothesized that iron chelation may play a vital role in reducing neutrophilic inflammation. Thus, these investigators also contend that additional trials of iron chelation for RA are warranted.~~

Professional Societies

American Academy of Family Physicians (AAFP)

In its clinical policy on chelation therapy, the AAFP states that chelation therapy is appropriate for cases of heavy metal intoxication, when diagnosed using validated testing in appropriate biological samples. The use of chelation therapy for other problems remains investigational and should not be recommended (2018).

American College of Cardiology (ACC)

The ACC concluded that although disodium EDTA is approved by the U.S. Food and Drug Administration for specific indications, such as iron overload and lead poisoning, it is not approved for use in preventing or treating cardiovascular disease. Accordingly, the group finds that the usefulness of chelation therapy in cardiac disease is highly questionable (Fihn et al. 2014).

American College of Physicians (ACP)

A clinical practice guideline published by the ACP recommended against the use of chelation therapy to prevent MI or to reduce symptomatic angina (Snow et al. 2004).

Mercury "Toxicity" from Dental Amalgam Fillings Poisoning

While no study were identified that addressed directly chelation therapy for mercury "toxicity" from amalgam fillings, indirect high-quality evidence support the lack of such toxicity. Randomized controlled trials have concluded that mercury amalgams used in dental restorations cause no harm to patients (Shenker et al., 2008; Bellinger et al., 2006; DeRouen et al., 2006).

~~Langworth et al (2002) conducted a study evaluating residents in the Stockholm County area with morbidities attributed to dental fillings ('amalgam disease'). Participants were referred to a special Amalgam Clinic and received examination by a dentist (n=428), a physician (n=379), and a psychologist (n=360). Gender ratio was 69% women and 31% men and the mean patient age was 46 years. No positive correlation was found between the amount of~~

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~~amalgam and somatic symptoms or psychological effect parameters. The authors concluded that the data gathered did not support the hypothesis that release of mercury from amalgam fillings is the cause of 'amalgam disease', but suggest that there may be various explanations for the patients' complaints.~~

Professional Societies

American Dental Association (ADA)

The ADA website contains statements from a number of organizations that there is no known association between dental amalgam and a specific disease. Examples of these organizations include but are not limited to:

- Alzheimer's Association
- Lupus Foundation of America
- Mayo Clinic
- National Multiple Sclerosis Society

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Edetate calcium disodium, also called EDTA is approved for the treatment of lead poisoning in adults and children.

Desferal which is the trade name for DFO (deferoxamine mesylate, deferoxamine B mesylate, deferoxamine, desferrioxamine, desferrioxamine) and Jadenu (deferasirox) are FDA-approved chelators for iron overload.

Dimercaprol (BAL oil) is also approved for the heavy metal chelation of iron. Deferiprone (Ferriprox) is FDA approved for the treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy.

Additional information is available at: <http://www.accessdata.fda.gov/scripts/Cder/ob/default.cfm>.

(Accessed ~~December 11, 2018~~ **March 26, 2020**)

The FDA reaffirmed its position **in January 2015** that amalgam is a safe and effective dental material after thoroughly reviewing the current science and updating its consumer advisory on dental amalgam fillings. Additional information is available at: <http://www.ada.org/en/press-room/news-releases/2015-archive/january/fda-updates-consumer-advisory>.

(Accessed ~~December 11, 2018~~ **March 26, 2020**)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover chelation therapy for non-overload conditions. Refer to the National Coverage Determinations (NCDs) for Chelation Therapy for Treatment of Atherosclerosis (20.21) and Ethylenediamine-Tetra-Acetic (EDTA) Chelation Therapy for Treatment of Atherosclerosis (20.22). Local Coverage Determinations (LCDs) do not exist at this time.

(Accessed April 3, 2020)

~~Medicare does not cover chelation therapy for non-overload conditions. Refer to the National Coverage Determinations (NCDs) for Chelation Therapy for Treatment of Atherosclerosis (20.21) and Ethylenediamine Tetra-Acetic (EDTA) Chelation Therapy for Treatment of Atherosclerosis (20.22). Local Coverage Determinations (LCDs) do not exist at this time.~~

(Accessed ~~December 12, 2018~~)

REFERENCES

American Academy of Family Physicians. Chelation therapy. Website. July 2018. ~~Accessed December 11, 2018.~~

American Dental Association. Dental Amalgam: What Others Say. Website. Updated April 2016. ~~Accessed December 11, 2018.~~

Bellinger DC, Trachtenberg F, Barregard L, et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1775-83.

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Crapper McLachlan DR, Dalton AJ, Kruck TP, et al. Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet*. 1991;337(8753):1304-1308.

DeRouen TA, Martin MD, Leroux BG, et al. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. *JAMA*. 2006 Apr 19;295(15):1784-92.

Doll J, Granger C. Updated Recommendations for the Management of Stable Ischemic Heart Disease. American Heart Association (AHA). July 28, 2014.

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*. 2014 Jan;7(1):15-24.

Fihn SD, Blankenship JC, Alexander KP, et al. 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* 2014;64:1929-49.

Ghio AJ, Piantadosi CA, Crumbliss AL. Hypothesis: iron chelation plays a vital role in neutrophilic inflammation. *Biometals*. 1997;10(2):135-142.

James S, Stevenson SW, Silove N, et al. Chelation for autism spectrum disorder (ASD). *Cochrane Database Systematic Review*. 2015 May 11.

Lamas GA, Goertz C, Boineau R, et al. Design of the Trial to Assess Chelation Therapy (TACT). *Am Heart J*. 2012 Jan;163(1):7-12.

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* 2013;309:1241-50.

Langworth S, Björkman L, Elinder CG, et al. Multidisciplinary examination of patients with illness attributed to dental fillings. *J Oral Rehabil*. 2002 Aug;29(8):705-13.

National Institute for Health and Care Excellence (NICE), Clinical guideline {CG142}:Autism spectrum disorder in adults: Diagnosis and management. Updated Aug 2016 .

Regland B, Lehmann W, Abedini I, et al. Treatment of Alzheimer's disease with clioquinol. *Dement Geriatr Cogn Disord*.2001;12(6):408-414.

Ritchie CW, Bush AI, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Ab amyloid deposition and toxicity in Alzheimer Disease. *Arch Neurol*. 2003;60(12):1685-1691.

Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev*. 2014 Feb 21;(2):CD005380.

Shenker BJ, Maserejian NN, Zhang A, et al. Immune function effects of dental amalgam in children: A randomized clinical trial. *J Am Dent Assoc*. 2008;139(11):1496-1505.

Snow V, Barry P, Fihn SD, et al. American College of Physicians; American College of Cardiology Chronic Stable Angina Panel. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2004 Oct 5;141(7):562-7. Erratum in: *Ann Intern Med*. 2005 Jan 4;142(1):79.

U.S. Food and Drug Administration Center for Devices and Radiological Health (CDRH). CDRH consumer information. Dental amalgams. Updated December 5, 2017. Rockville, MD: FDA.

Voest EE, Vreugdenhil G, Marx JJM. Iron-chelating agents in non-iron overload conditions. *Ann Intern Med*. 1994;120(6):490-499.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
<p><u>TBD</u></p>	<p><u>Applicable Codes</u></p> <ul style="list-style-type: none"> • <u>Addition of the following HCPCS codes J0470, J0600, J0895, J8499</u> <p><u>Supporting Information</u></p> <ul style="list-style-type: none"> • <u>Updated Description of Services, Clinical Evidence, FDA, CMS, and References sections to reflect the most current information; no change to Coverage Rationale or Applicable Codes</u> • <u>Archived previous policy version CS016.H</u>

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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