CHELATION THERAPY FOR NON-OVERLOAD CONDITIONS

Policy Number: 2014T0051M
Effective Date: May 1, 2014

INSTRUCTIONS FOR USE
This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee’s specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group:
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage.
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.

Chelation therapy is unproven and not medically necessary for the treatment of "mercury toxicity" from dental amalgam fillings. Randomized controlled trials do not identify a causal association between amalgam fillings and various systemic symptoms and disorders attributed to mercury.

Chelation therapy is unproven and not medically necessary for the treatment of chronic, progressive diseases (not involving heavy metal toxicity or overload conditions) and other disorders including but not limited to:

- Alzheimer's disease
- apoplectic coma
- autism spectrum disorder
- cancer
- cardiovascular disease
- chronic fatigue syndrome
- chronic renal insufficiency
- defective hearing
- diabetes
- diabetic ulcer
- cholelithiasis
- gout
- erectile dysfunction
- multiple sclerosis
- osteoarthritis
- osteoporosis
- Parkinson's disease
- Raynaud's disease
- renal calculi
- rheumatoid arthritis
- schizophrenia
- scleroderma
- snake venom poisoning
- varicose veins
- vision disorders (glaucoma, cataracts, etc.)

Much of the evidence supporting chelation treatment for other chronic progressive disease is based on testimonials and single-case studies. Thus, there still is no scientific evidence that demonstrates any benefit from this form of therapy.

APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document 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 claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.
**HCPCS Code (Unproven)** | **Description**  
--- | ---  
J3490 | Unclassified drugs  
M0300 | IV chelation therapy (chemical endarterectomy)  
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 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 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, 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 patients 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 rheumatoid arthritis. 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:** A Cochrane systematic evidence review found insufficient evidence for the use of chelation (metal protein attenuating compounds) in Alzheimer's disease (Sampson, et al., 2008). Metal protein attenuating compounds have great affinity for copper and zinc ions, preventing them from binding to beta amyloid, a protein strongly implicated in the development of Alzheimer's disease. Chelation of these metal ions promotes dissolution of beta amyloid, thus presenting a potential therapeutic target for Alzheimer's disease. The Cochrane systematic evidence review found one randomized controlled trial (n = 36) of metal protein attenuating compounds in Alzheimer disease. That trial, of clioquinol (also known as PBT1) showed no statistically significant difference in cognition between active treatment and placebo groups at 36 weeks. The authors concluded that there is no current evidence that treatment with clioquinol (PBT1) has any significant effect on cognition (as measured by the ADAS-Cog scale) in patients with Alzheimer's disease.
Several studies have reported some improvement in cognitive function or 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 efficacy of chelation therapy for Alzheimer’s disease can be made on the basis of these studies.

Hayes conducted a review of literature from 1995-2005. Hayes concluded that there was no clinical evidence found regarding the efficacy of chelation therapy as an adjunctive treatment for Alzheimer's disease.

**Autism Spectrum Disorder:** Chelation therapy has been proposed to treat patients with autism based on the theory that the chelating agent will remove mercury from children with autism.

Some studies have evaluated the use of chelation for treating autism (Patel, 2007); however, no studies have proven the effectiveness of chelation for this indication. In 2008, the National Institute of Mental Health called off a study on chelation to treat autism in children. The study was halted due to safety concerns after another study linked a drug used in the treatment to brain problems in rats. Scientists had planned to test a chelation drug on autistic children to investigate whether mercury in childhood vaccines causes the disorder. (Smart Brief, 2008)

A retrospective review by Nataf et al. (2006) evaluated the impact of heavy metal exposure on porphyrinuria in 106 patients with autism. Eleven subjects were treated with dimercaptosuccinic acid. The control group consisted of 12 subjects with the same diagnosis who did not receive chelation therapy. Urinary uroporphyrin (URO) and coproporphyrin (COPRO) levels were compared before and after treatment. The chelation group had a decrease in prophyrin levels while the control group had essentially no change in levels. The authors note that despite the decrease in prophyrin levels in children receiving chelation therapy for heavy metal toxicity, they could not conclude that heavy metals are causally responsible for autism. In addition, children exposed to heavy metals are likely to be co-exposed to other environmental toxins that can also raise porphyrin levels.

A National Institute for Health and Clinical Excellence (NICE) clinical guideline on autism does not recommend the use of chelation for the management of core symptoms of autism in adults. (NICE 2012)

**Cardiovascular Disease:** 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.

Villarruz et al. (2002) conducted a systematic review of 5 randomized controlled trials on chelation therapy for atherosclerotic cardiovascular disease. The authors concluded that there is insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improving clinical outcomes of people with atherosclerotic cardiovascular disease.

Knudtson et al. (2002) conducted a double-blind, randomized controlled study of EDTA for the treatment of ischemic heart disease. A total of 84 patients were randomized to receive 33 infusions of EDTA (n=41) or placebo (n=43) solution. At 27 weeks, both groups significantly increased the exercise time to ischemia. There were no differences between the groups for any outcome measures or in the number of clinical ischemic events. These results indicate that EDTA treatment had no beneficial effect on ischemic heart disease. However, the study patients had mild disease, the results may not be representative of patients with more severe disease, and an effect of the vitamins and minerals in the infusion solution cannot be ruled out.

In a sub-study of the Knudtson et al. study, Anderson et al. (2003) conducted a double-blind, randomized controlled study to ascertain the effects of EDTA on endothelial function in patients with ischemic heart disease. A total of 47 patients were randomized to receive 33 infusions of EDTA (n=24) or placebo (n=23) solution. At 6 months post-treatment, the infusions had no
significant effect on brachial artery diameter, flow-mediated vasodilation, or nitroglycerin-mediated vasodilation for either group. The results suggest that EDTA therapy had no effect on brachial artery diameter in patients with CAD. This study is flawed by a small sample size.

In a systematic review of 7 articles assessing EDTA chelation therapy for cardiovascular disease, Seely et al. concluded that the best available evidence does not support the use of EDTA chelation for cardiovascular disease. (Seely, 2005)

In November 2012, the American Heart Association announced preliminary results of the Trial to Assess Chelation Therapy (TACT) trial. TACT was a multicenter, double-blind, efficacy trial that took place from 2002 to 2011. More than 1700 patients 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 (American Heart Association, 2012).

**Anthraclycline-Associated Cardiac Toxicity in Breast Cancer Patients:** Two studies, one a randomized controlled trial (Speyer, 1988) and the other a multicenter uncontrolled study (Kolaric, 1995), assessed chelation therapy for anthracycline-associated cardiac toxicity. Both studies reported a significant cardioprotective effect of dexrazoxane on anthracycline-induced toxicity. However, definitive conclusions regarding the benefits of dexrazoxane cannot be made since there was no long-term follow-up in either study and therefore, it is unknown whether chelation therapy had a positive impact on survival.

**Rheumatoid Arthritis:** In a review of chelation for non-overload conditions, Voest et al. (1994) summarized the available literature regarding rheumatoid arthritis. In six small studies with patient populations ranging from 6 to 18 patients, deferoxamine improved the clinical symptoms of arthritis and reduced anemia in the majority of patients. However, the authors concede that the preponderance of evidence regarding chelation for rheumatoid arthritis 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 rheumatoid arthritis. 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 rheumatoid arthritis are warranted.

Hayes conducted a review of literature from 1995-2005. Hayes concluded that there was no clinical evidence to support the use of chelating agents in the treatment of rheumatoid arthritis due to reduced production of hemoglobin.

**Mercury Poisoning:** 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)

The Journal of the American Dental Association (ADA) reported that researchers found "no significant association of Alzheimer's Disease with the number, surface area or history of having dental amalgam restorations" and "no statistically significant differences in brain mercury levels between subjects with Alzheimer's disease and control subjects." The ADA's position has been reaffirmed by the U.S. FDA Center for Devices and Radiological Health in 2002, 2006 and 2009. The ADA's 2010 amalgam safety update cites that "studies continue to support the position that dental amalgam is a safe restorative option for both children and adults."
Professional Societies
The American Academy of Family Physicians (AAFP) endorses the 1983 American Medical Association (AMA) Diagnostic and Therapeutic Assessment of Chelation Therapy which states, “Chelation therapy with ethylene diamine tetraacetic acid or its sodium salt is not an established treatment for atherosclerotic vascular disease” (AAFP, 2005).

American Cancer Society (ACS): In 2008, the ACC stated that chelation therapy is a proven treatment for lead poisoning and poisoning from other heavy metals. However, available scientific evidence does not support claims that the treatment benefits patients with cancer, heart disease, or any medical problems other than heavy-metal poisoning. (ACS, 2008)

In the American College of Cardiology Foundation (ACCF) complementary medicine expert consensus document (2005), the use of EDTA is proposed to remove calcium ions, thus possibly leading to the reduction of atherosclerotic plaques. The means by which this occurs is still unknown. The FDA has not approved the use of chelation therapy to treat coronary artery disease (CAD). At this time, the ACCF agrees with the American College of Cardiology (ACC) position statement, “there is insufficient scientific evidence to justify the application of chelation therapy for atherosclerosis on a clinical basis.”

American College of Cardiology (ACC): The ACC concluded in 2005 that there is insufficient scientific evidence to justify the application of chelation therapy for atherosclerosis on a clinical basis. At the present time, therefore, chelation therapy should be applied only under an investigational protocol. (Vogel, 2005)

American Heart Association (AHA): The AHA’s Clinical Science Committee has reviewed the available literature on the use of chelation (EDTA) in the treatment of arteriosclerotic heart or blood vessel disease and finds no scientific evidence to demonstrate any benefit of this form of therapy. Furthermore, employment of this form of unproven treatment may deprive patients of the well-established benefits attendant to the many other valuable methods of treating these diseases. (AHA, 2010)

American College of Physicians (ACP): A clinical practice guideline published in 2004 by the ACP recommended against the use of chelation therapy to prevent myocardial infarction or to reduce symptomatic angina. (Snow, 2004)

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, desferoxamine, desferrioxamine) and Exjade (deferasirox) are FDA-approved chelators for iron overload. Dimercaprol (BAL oil) is also approved for the heavy metal chelation of iron. Deferiprone (Ferrirprox) has received orphan drug status by the FDA, but is not yet approved for marketing. This drug is designated an orphan drug for the treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy.

The FDA approved dexrazoxane (Zinecard®) for marketing in parenteral form to reduce the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received an accumulative doxorubicin dose of 300 mg/kg and who, in their physician’s opinion, would benefit from continuing therapy with doxorubicin.

Additional information is available at: http://www.accessdata.fda.gov/scripts/Cder/ob/default.cfm
Accessed January 23, 2014
Medicare does not have a National Coverage Determination (NCD) for Chelation Therapy for the treatment of heavy metal poisoning. There is a NCD’s for Chelation Therapy for the non-coverage of EDTA chelation therapy for the treatment of atherosclerosis. Refer to the NCDs for Chelation Therapy for Treatment of Atherosclerosis (20.21) and Ethylenediamine Tetra Acetic (EDTA) Therapy for Treatment of Atherosclerosis (20.22). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Chelation Therapy.

(Accessed January 28, 2014)

REFERENCES


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POLICY HISTORY/REVISION INFORMATION

<table>
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<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>05/01/2014</td>
<td>• Reorganized policy content</td>
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<td>• Updated coverage rationale; added language to indicate if service is “medically necessary” or “not medically necessary” to applicable proven/unproven statement</td>
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<td>• Updated supporting information to reflect the most current description of services, clinical evidence, FDA and CMS information, and references</td>
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