CHELATION THERAPY FOR NON-OVERLOAD CONDITIONS

Protocol: OTH036
Effective Date: June 1, 2017

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INSTRUCTIONS FOR USE

This protocol 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 Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

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.

COMMERCIAL & MEDICAID COVERAGE RATIONALE

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

Chelation therapy is **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 **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 calculus
• 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.

MEDICARE COVERAGE RATIONALE

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) for Nevada do not exist at this time. (Accessed April 2017).

Chelation Therapy for Treatment of Atherosclerosis (20.21)
Indications and Limitations of Coverage
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.

**Ethylenediamine-Tetra-Acetic (EDTA) Chelation Therapy for Treatment of Atherosclerosis**

**(20.22)**

**Indications and Limitations of Coverage**

The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA as an approved use is **not covered**. Any such use of EDTA is considered experimental.

**For Medicare and Medicaid Determinations Related to States Outside of Nevada:**


**Important Note:** Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare & Medicaid Services’ Web site.

**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 vary 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, schizophrinia, 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**

Increased levels of aluminum have been discovered in several brain regions of patients with Alzheimer’s disease (AD). Epidemiological studies have linked the concentration of aluminum in drinking water and the increased occurrence of the disease. 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 aluminized metalloenzyme complexes in AD patients and permit redistribution of aluminum in the brain.

A Cochrane systematic evidence review found insufficient evidence for the use of chelation (metal protein attenuating compounds) in AD (Sampson, et al., American 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 AD. Chelation of these metal ions promotes dissolution of beta amyloid, thus presenting a potential therapeutic target for AD. The Cochrane systematic evidence review found one randomized controlled trial (n=36) of metal protein attenuating compounds in AD 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 AD.

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 AD can be made on the basis of these studies.

**Autism Spectrum Disorder**

A Cochrane systematic evidence review found no clinical trial evidence to suggest that pharmaceutical chelation is an effective intervention for autism spectrum disorder (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 three 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**

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 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.

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 (Escolar 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.
Professional Societies

American Academy of Family Physicians (AAFP)
The 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” (2013).

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 myocardial infarction or to reduce symptomatic angina (Snow et al. 2004).

Rheumatoid Arthritis
In a review of chelation for non-overload conditions, Voest et al. (1994) summarized the available literature regarding rheumatoid arthritis (RA). In 6 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 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.

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).

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 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 Cancer Society (ACS)
The ACS 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 (2014).

**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, desferoxamine, 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.


**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 the member specific benefit plan 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 claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
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<tr>
<td>M0300</td>
<td>IV chelation therapy (chemical endarterectomy)</td>
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<tr>
<td>S9355</td>
<td>Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies</td>
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and equipment (drugs and nursing visits coded separately), per diem

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REFERENCES


The foregoing Health Plan of Nevada/Sierra Health & Life Healthcare Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.