Chelation Therapy for Non-Overload Conditions

Policy Number: 2019T0051S
Effective Date: March 1, 2019

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVERAGE RATIONALE</td>
<td>1</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>1</td>
</tr>
<tr>
<td>DESCRIPTION OF SERVICES</td>
<td>1</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>2</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>4</td>
</tr>
<tr>
<td>CENTERS FOR MEDICARE AND MEDICAID SERVICES</td>
<td>4</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>5</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>5</td>
</tr>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>5</td>
</tr>
</tbody>
</table>

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 "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 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.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>M0300</td>
<td>IV chelation therapy (chemical endarterectomy)</td>
</tr>
<tr>
<td>S9355</td>
<td>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</td>
</tr>
</tbody>
</table>

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 (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. 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 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 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 reported some improvement in cognitive function or slowing of the rate of decline in patients treated with clioquinol or deferoxamine (Crappner Mcachlan, 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 (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**

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. (Accessed December 1, 2018)

**Rheumatoid Arthritis**

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 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 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, desferroxamine, 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)

The FDA reaffirmed its position 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)

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 December 12, 2018)

REFERENCES


Chelation Therapy for Non-Overload Conditions
UnitedHealthcare Commercial Medical Policy
Proprietary Information of UnitedHealthcare. Copyright 2019 United HealthCare Services, Inc.

Effective 03/01/2019


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2019</td>
<td>- Updated and reformatted coverage rationale:</td>
</tr>
<tr>
<td></td>
<td>o Simplified content</td>
</tr>
<tr>
<td></td>
<td>o Modified list of unproven and not medically necessary indications; replaced “chronic, progressive diseases (not involving heavy metal toxicity or overload conditions) and other disorders” with “chronic, progressive diseases associated with non-overload conditions”</td>
</tr>
<tr>
<td></td>
<td>- Updated supporting information to reflect the most current clinical evidence and references</td>
</tr>
<tr>
<td></td>
<td>- Archived previous policy version 2018T0051R</td>
</tr>
</tbody>
</table>

**INSTRUCTIONS FOR USE**

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state
mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies 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.