BlueCross BlueShield of Louisiana

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Chelation Therapy

Policy # 00014
Original Effective Date: 06/24/2002
Current Effective Date: 10/16/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider chelation therapy for heavy metal toxicity to be **eligible for coverage.**

Patient Selection Criteria
The use of chelation therapy for heavy metal toxicity, including thalassemia with hemosiderosis, may be considered for coverage eligibility only when the following treatment parameters have been satisfied:

- Treatment complies with standard medical reference based on the blood level of the specific heavy metal identified; AND.
- The route of delivery of the chelation agent follows appropriate standard medical reference based on the specific heavy metal identified.
  For example:
  - Mercury toxicity can be treated with oral agents
  - Parenteral edentate calcium disodium (EDTA) would be appropriate to treat lead toxicity in patients with blood lead levels of > 45µg/dL.

Based on review of available data, the Company may consider chelation therapy to be **eligible for coverage** for ANY of the following conditions:

- Control of ventricular arrhythmias or heart block associated with digitalis toxicity; OR
- Emergency treatment of hypercalcemia; OR
- Wilson's disease (hepatolenticular degeneration); or
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion dependent thalassemia (NDTD).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of chelation therapy when patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of chelation therapy for non-FDA approved indications to be **investigational.***

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Based on review of available data, the Company considers all other applications of chelation therapy, including but not limited to the following, to be **investigational*:**

- Atherosclerosis (i.e., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease);
- Multiple sclerosis;
- Arthritis (includes rheumatoid arthritis);
- Hypoglycemia;
- Autism;
- Alzheimer's disease;
- Diabetes;
- Heavy metal toxicity, or iron or lead poisoning when toxic levels are not documented by blood levels.

Background/Overview

Chelation therapy, an established treatment for treating heavy metal toxicities, has been investigated for a variety of other applications including treatment of atherosclerosis, Alzheimer's disease, and autism.

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 consists of the 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, desferroxamine is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (-EDTA) is used for patients with lead poisoning. Note that 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's 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's disease, they promote the solubilization and clearance of Aβ-amyloid protein by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt two putative pathogenic processes of Alzheimer's disease. However, no MPACs have received U.S. Food and Drug Administration (FDA) approval for the treatment of Alzheimer's disease. Chelation therapy has also been discussed as a treatment for other indications including atherosclerosis and autism. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Calcium-EDTA was approved by the FDA for lowering blood lead levels among patients with lead poisoning. Disodium-EDTA was approved by the FDA for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with the drug, digitalis. In 2008, the FDA

withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.

Several iron chelating agents have received FDA approval. Deferoxamine for subcutaneous, intramuscular, or intravenous injections was approved for treating acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Deferasirox, approved in 2005, is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients age 2 years and older. Under the accelerated approval program, the FDA expanded approval of deferasirox in 2013 to include the treatment of patients age 10 and older with chronic iron overload due to nontransfusion-dependent thalassemia (NTDT). In 2011, the FDA approved the iron chelator deferiprone for the treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form for oral use.

Rationale/Source

The policy was updated regularly with literature searches using MEDLINE, most recently the literature was searched from the period February 2012 through April 24, 2013.

Chelation therapy is an established treatment for the indications listed in the medically necessary policy statement, particularly for the treatment of metal toxicity and transfusional hemosiderosis. Thus, literature searches have focused on the use of chelation therapy for other conditions including, but not limited to, atherosclerosis, autism, Alzheimer's disease, multiple sclerosis, and diabetes.

Atherosclerosis

In 2002, a Cochrane review was published evaluating studies on EDTA chelation therapy for treating patients with atherosclerotic cardiovascular disease. Five placebo-controlled randomized-controlled trials (RCTs) were identified, none of which reported mortality, non-fatal events, and cerebrovascular vascular events. Four of the 5 studies (total n=250) found no significant benefits of EDTA chelation therapy on outcomes reported including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study, which included only 10 patients, was apparently stopped early due to benefit, but relevant outcome data were not available. The Cochrane reviewers concluded that there was insufficient evidence to draw conclusions of the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were needed.

Among the published RCTs, Knudtson and colleagues randomized 84 patients with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo, 3 hours per treatment twice weekly for 15 weeks, and once per month for an additional 3 months. The main outcome measures included change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the two groups. Another double-blind, randomized controlled study of EDTA chelation or placebo showed no change in short- or long-term improvement in vasomotor response to EDTA when compared to placebo. Two small randomized trials have also reported no benefit of chelation therapy as a treatment of peripheral arterial disease.

Section summary: Several RCTs have been published on chelation therapy for treating atherosclerosis; these have generally reported intermediate outcomes and have not found EDTA chelation therapy to be

more effective than placebo. Additional RCTs that report health outcomes are needed to establish the efficacy of this treatment.

Autism
Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard and colleagues hypothesized a link between environmental mercury and autism. This theory was rejected by Nelson and Bauman, who found that many of the characteristics of mercury poisoning such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children. In 2007, a systematic review by Ng and colleagues concluded that there was no association between mercury poisoning and autism.

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and did not identify any studies that included a control group. The author stated the case series suggest that chelation might be a viable form of treatment in some autistic individuals with known elevated heavy metal levels and that this possibility needs to be further investigated in controlled studies.

Section summary: There is a lack of controlled studies on the effect of chelation therapy on health outcomes in patients with autism.

Alzheimer's Disease
A 2008 Cochrane Review evaluated MPAC for treating Alzheimer's disease The review identified one placebo-controlled RCT. This study, by Richie and colleagues, was published in 2003. Patients were treated with PBT1, an MPAC also known as clioquinol, an anti-fungal medication that crosses the blood-brain barrier. Clioquinol was withdrawn for oral use in 1970 because of its association with subacute myelo-optic neuropathy. In the study, oral clioquinol was administered in doses increasing to 375 mg twice daily to 16 Alzheimer's disease patients, and the effects were compared to 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog scale). One patient in the treatment group developed impaired visual acuity and color vision during weeks 31 to 36 while she was receiving clioquinol, 375 mg twice daily. Her symptoms resolved on treatment cessation.

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt and colleagues completed a double-blind, placebo-controlled RCT in which 78 Alzheimer's disease patients were treated for 12 weeks with 50 mg PBT2 (n=20), 250 mg PBT2 (n=29), or placebo (n=29). There was no statistically significant difference in ADAS-Cog scale or Mini-Mental Status Exam scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis and transient ischemic event) were reported, both by patients receiving placebo.

Ongoing investigations in chelation therapy for the treatment of Alzheimer's disease and other neurodegenerative diseases include linking a carbohydrate moiety to drug molecules to enhance drug delivery across the blood-brain barrier; this strategy may solve the potential problem of premature and indiscriminate metal binding. In addition, multi-function drugs that not only bind metal but also have significant antioxidant capacity are in development.

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Section summary: There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer's disease. The few published RCTs did not find that the treatment was superior to placebo for improving health outcomes.

Diabetes

Cardiovascular disease in patients with diabetes

A 2009 trial by Cooper and colleagues in New Zealand evaluated the effect of copper chelation using oral trientine on left-ventricular hypertrophy in 30 patients with type 2 diabetes. A total of 21/30 (70%) of the participants completed the 12-month follow-up. At 12 months, there was a significantly greater change in left ventricular mass indexed to body surface area (LVM) in the group receiving active treatment compared to placebo (-10.6 g/m2 vs. -0.1 g/m2, p=0.01). The study was limited by the small sample size and high drop-out rate.

Diabetic nephropathy

Chen and colleagues in China investigated the effect of chelation therapy on the progression of diabetic nephropathy in patients with high-normal lead levels. Their 2012 single-blind study included 50 patients with diabetes, high-normal body lead burden (80-6,000 *u*g) and serum creatinine 3.8 mg/dL or lower. At baseline, the mean blood lead level was 6.3 *u*g/dL in the treatment group and 7.1 *u*g/dL in the control group and the mean body lead burden was 151 *u*g for patients in the treatment group and 142 *u*g for patients in the control group. According to the U.S. Occupational and Health Safety Administration (OSHA), the maximum acceptable blood lead level in adults is 40 *u*g/dL. Patients were randomized to 3 months of calcium disodium EDTA or placebo. During the following 24 months, patients in the chelation group received additional chelation treatments as needed (i.e., if serum creatinine level exceeded pre-treatment levels or body lead burden was >60 *u*g) and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month study. The primary outcome was change in estimated glomerular filtration rate (eGFR). The yearly rate of decrease in eGFR was 5.6 mL/min/173 m^2 (standard deviation [SD]: 5.0) in the chelation group and 9.2 mL/min/173 m^2 (SD: 3.6) in the control group. The difference between groups was statistically significant, p=0.04. The secondary endpoint was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. A total of 9 patients (36%) in the treatment group and 17 (68%) in the control group attainted the secondary endpoint; the difference between groups was statistically significant (p=0.02). There were no reported side effects of chelation therapy during the 27-month study period.

Section summary: Two small RCTs with limitations represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients and that report health outcomes such as cardiovascular events, end-stage renal disease and mortality are needed.

Myocardial infarction (MI)

In 2013, findings of the randomized double-blind multicenter Trial to Assess Chelation Therapy (TACT) study were published. The study included 1,708 individuals, age 50 or older, who had a history of a myocardial infarction at least 6 weeks previous and a serum creatinine level of 2.0 mg/dL or less. Patients

were randomized to receive 40 infusions of disodium EDTA (n=839) or placebo (n=869). The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. The primary endpoint was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization or hospitalization for angina at 5 years. A total of 361 patients in the chelation group (43%) and 464 patients in the placebo group (57%) discontinued treatment after starting it, withdrew consent during follow-up or were lost to follow-up. The Kaplan-Meier 5-year estimates for the primary endpoint were 32.8% (95% confidence interval [CI]: 29.1% to 36.5%) in the chelation group and 38.5% (95% CI: 34.6% to 42.3%) in the control group. The difference between groups was statistically significant; the p value was 0.035, which was below the significance threshold required due to multiple interim analyses, 0.036. The most common individual clinical endpoint was coronary revascularization, which occurred in 130 of 839 patients (15%) in the chelation group and 157 of 869 patients (18%) in the control group, *p* value=0.08. The next most frequent endpoint was death. This occurred in 87 of 839 (10%) of patients in the chelation group and 93 of 869 (11%) of patients in the placebo group, *p* value=0.64. None of the individual components of the primary outcome differed significantly between groups; however, the study was not powered to detect difference in individual components. Four severe adverse events occurred that were definitely or possibly related to study therapy. There were 2 events each in the treatment and control group, including 1 death in each group.

The study is limited by the low follow-up rate, including a greater number of patients who withdrew consent in the placebo group compared to the treatment group. The primary endpoint included components of varying clinical significance, with most of the difference between groups occurring for revascularization events. The primary endpoint barely met the significance threshold and if more patients had been retained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the publication, 60% of patients were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in a population that is not generalizable to that seen in clinical care.

Section summary: One RCT with limitations, including high dropout with differential drop-out between groups, reported that cardiovascular events are reduced in patients treated with chelation therapy. However, this was not a high-quality trial and therefore the results could have arisen from bias. Further trials that are of high quality are needed to corroborate whether chelation therapy improves outcomes in patients with prior MI.

Other potential indications
No RCTs or other controlled studies were identified that evaluated the safety and efficacy of chelation therapy for other conditions such as multiple sclerosis or arthritis.

Summary
Chelation therapy is an established treatment for the medically necessary indications listed in the policy statement, such as treatment of metal toxicity and transfusional hemosiderosis. There is insufficient evidence that chelation therapy improves health outcomes for patients with other conditions including, but not limited to, atherosclerosis, autism, Alzheimer's disease, diabetes and arthritis. Thus, chelation therapy for these other applications is considered investigational.

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No code
HCPCS	J0470, J0600, J0895, J3520, M0300, S9355
ICD-9 Diagnosis	250.00 thru 250.93, 251.0, 251.1, 275.01 thru 275.09, 275.1, 275.2, 275.40, 275.42, 275.49, 282.40 thru 282.49, 282.5, 299.00, 299.01, 331.0, 340, 414.00 thru 414.9, 440.0 thru 440.9, 711.00 thru 711.99, 714.0 thru 714.9, 715.00 thru 715.98, 716.00 thru 716.99, 984.0 thru 984.9, 985.0 thru 985.9
ICD-9 Procedure	99.16

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06/20/2002	Medical Policy Committee review. Format revision. No substance change to policy.
06/24/2002	Managed Care Advisory Council approval
07/14/2005	Medical Director review
07/19/2005	Medical Policy Committee review. Format revision. Rationale/Source added. Patient selection criteria defined and: "Heavy metal toxicity, or iron or lead poisoning when toxic levels are not documented by blood levels" added to investigational statement.
08/24/2005	Managed Care Advisory Council approval
07/07/2006	Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval. No changes to policy guidelines.
10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008	Medical Director review

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10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee approval
10/14/2009	Medical Policy Implementation Committee approval. Added that when patient selection criteria are not met, or if chelation therapy is used for non-FDA approved indications, to deny investigational.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Autism and Alzheimer's disease added to investigational indications.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
2/4/2013	Coding revised
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. "Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion dependent thalassemia (NDTD)" was added as eligible for coverage. Investigational statements clarified.

Next Scheduled Review Date: 10/2014

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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