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MEDICAL POLICY – 8.01.535

Chelation Therapy

BCBSA Ref. Policy:	8.01.02	
Effective Date:	May 1, 2023	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 10, 2023	None
Replaces:	8.01.02	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Chelation is a process to remove certain heavy metals from the blood. In this treatment, a chemical solution is injected into the bloodstream or taken by mouth. Molecules then bind to heavy metals and/or minerals. The heavy metals are then cleared out of the body through urination. Chelation therapy has been studied and approved by the Food and Drug administration to treat certain conditions. This includes removing dangerously high levels of iron, as well as lead or mercury. Thinking that the process of chelation could also remove the buildup of some other substances in the body, some doctors have tried to use it to try to treat other conditions. Examples of these other conditions include Alzheimer disease, autism, diabetes, and plaque inside of arteries (atherosclerosis). Scientific research has not proven that using chelation therapy treatment for these or other conditions is effective. For this reason, chelation therapy for many conditions is considered investigational (unproven).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Medical Necessity
Chelation therapy	**Chelation therapy may be considered medically necessary, when toxic levels are documented by standard testing methods, as a treatment for the following conditions:** • Chronic iron overload due to blood transfusions (transfusional hemosiderosis) • Chronic iron overload due to non-transfusion-dependent thalassemia (NTDT) • Digitalis toxicity with ventricular arrhythmias or heart block • Extreme conditions of metal toxicity (see **Table 1** for select heavy metals) • Hypercalcemia emergency treatment • Lead poisoning • Wilson disease (hepatolenticular degeneration [copper build up]) **Notes:** For the two conditions listed below, generally other treatments are used in place of chelation therapy o Control of ventricular arrhythmias or heart block associated with digitalis toxicity (e.g., currently treated, in most individuals, with digoxin immune fragment antigen-binding [Fab] monoclonal antibodies). o Emergency treatment of hypercalcemia using IV hydration and other pharmacologic agents is individualized based on the root cause[38]

Service	Investigational
Chelation therapy	**Off-label applications of chelation therapy are considered investigational, including, but not limited to:** • Alzheimer disease • Arthritis (includes rheumatoid arthritis) • Atherosclerosis (e.g., coronary artery disease, secondary prevention in individuals with myocardial infarction, or peripheral vascular disease)

Service	Investigational
	• Autism • Diabetes • Multiple sclerosis • Other indications not listed as medically necessary above

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Standard testing result showing toxic levels for the following conditions:
  - Chronic iron overload due to blood transfusions (transfusional hemosiderosis)
  - Chronic iron overload due to non-transfusion-dependent thalassemia (NTDT)
  - Digitalis toxicity with ventricular arrhythmias or heart block
  - Heavy metal poisoning (e.g., arsenic, cadmium, cobalt, copper, gold, iron, lead, mercury)
  - Hypercalcemia (high levels of calcium in the blood) emergency treatment
  - Lead poisoning
  - Wilson disease (hepatolenticular degeneration [copper build up])

Coding

Code	Description
HCPCS	
J0470	Injection, dimercaprol injection, per 100 mg
J0600	Injection, edetate calcium disodium, up to 1,000 mg
J0895	Injection, deferoxamine mesylate, 500 mg
J3520	Edetate disodium, per 150 mg
M0300	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

Related Information

Table 1. Toxic or Normal Concentrations of Heavy Metals[1-3,5]

Metal	Toxic Levels (Normal levels where indicated)
Arsenic	24-h urine: ≥50 µg/L urine or 100 µg/g creatinine
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or ≥15 µg/g creatinine
Chromium	No clear reference standard
Cobalt	Normal excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)
Copper	Normal excretion: 25 µg/24 h (urine)
Iron	Nontoxic: <300 µg/dL Severe: >500 µg/dL
Lead	Pediatric: Symptoms or blood lead level ≥45 µg/dL, (blood) CDC level of concern: 3.5 µg/dL[37]
	Adult: Symptoms or blood lead level ≥70 µg/dL CDC level of concern: 10 µg/dL[38]
Manganese	No clear reference standard
Mercury	Background exposure normal limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[39 a]
Nickel	Excessive exposure: ≥8 µg/L (blood), Severe poisoning: ≥500 µg/L (8-h urine)
Selenium	Mild toxicity: >1 mg/L (serum), Serious toxicity: >2 mg/L
Silver	Asymptomatic workers have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)
Thallium	24-hour urine thallium >5 µg/[L40]
Zinc	Normal range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

Adapted from Adal (2018).[41]

CDC: Centers for Disease Control and Prevention.

[a] Hair analysis is useful to assess mercury exposure in epidemiologic studies. However, hair analysis in individual patients must be interpreted with consideration of the patient's history, signs, and symptoms, and possible alternative explanations.

Measurement of blood and urine mercury levels can exclude exogenous contamination; therefore, blood or urine mercury levels may be more robust measures of exposure in individual patients.[42]

Evidence Review

Description

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This policy addresses indications for chelation therapy approved by the U.S. Food and Drug Administration (FDA) as well as off-label indications, including Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

Background

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 comprises 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 (see **Table 1**). Specific chelating agents are used for particular heavy metal toxicities. For example, deferoxamine is used for individuals with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for individuals with lead poisoning. Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.[1]

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer 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 disease, MPACs promote the solubilization and clearance of β-amyloid by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. Therefore, MPACs, interrupt two putative pathogenic processes of Alzheimer disease. However, no MPACs have received FDA approval for treating Alzheimer disease.

Chelation therapy has also been considered as a treatment for other indications, including atherosclerosis and autism spectrum disorder. For example, EDTA chelation therapy has been proposed in individuals with atherosclerosis as a method of decreasing obstruction in the arteries.

Summary of Evidence

For individuals who have Alzheimer disease, or cardiovascular disease, or autism spectrum disorder, or diabetes, or multiple sclerosis or arthritis who receive chelation therapy, the evidence includes a small number of randomized controlled trials (RCTs) and case series. Relevant outcomes include symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One RCT (the Trial to Assess Chelation Therapy) reported that chelation therapy reduced cardiovascular events in individuals with previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations (e.g., high dropout rates) and, therefore, conclusions are not definitive. For other conditions, the available RCTs did not report improvements in health outcomes with chelation therapy and, as evidence, the case series are inadequate to determine efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05111821	Long-term Iron Chelation in the Prevention of Secondary Remote Degeneration After Stroke	100	Jun 2024
NCT02733185	Trial to Assess Chelation Therapy 2	1000	Jun 2023
Unpublished			
NCT02728843[a]	A Dose-Ranging Study of the Efficacy, Safety, and Pharmacokinetics of Deferiprone Delayed-Release Tablets in Patients With Parkinson's Disease	140	Sep 2019 (completed)

NCT: national clinical trial

[a] Denotes industry-sponsored or cosponsored trial

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association and American College of Cardiology

In 2016, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a joint guideline on the management of individuals with lower extremity peripheral artery disease, which recommended that chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for the treatment of claudication.[31]

In 2014, the ACC and AHA published a focused update of the guideline for the management of stable ischemic heart disease, in conjunction with the American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. This update included a revised recommendation on chelation therapy stating that the "usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable ischemic heart disease (IHD)."[32] Compared to the original publication of this guideline in 2012, the recommendation was upgraded from a class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies).[33]

American Academy of Pediatrics

In 2019, the American Academy of Pediatrics published guidance for the management of children with autism spectrum disorder. The guidance cautioned against the use of chelation therapy due to safety concerns and lack of supporting efficacy data.[34]

Medicare National Coverage

The Centers for Medicare & Medicaid have issued two national coverage determinations on chelation therapy relevant to this policy. Section 20.21 states[35]:

> 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.

Section 20.22 states[36]:

> The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA [U.S. Food and Drug Administration] as an approved use is not covered. Any such use of EDTA is considered experimental.

These national coverage decisions are long-standing; effective dates of these versions have not been posted.

Regulatory Status

In 1953, EDTA (Versenate) was approved by the FDA for lowering blood lead levels among both pediatric and adult patients with lead poisoning. In 1991, succimer (Chemet) was approved by the FDA for the treatment of lead poisoning in pediatric patients only. The FDA approved disodium-EDTA for use in select patients with hypercalcemia and use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, the FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.[2]

Several iron chelating agents are FDA-approved:

- In 1968, deferoxamine (Desferal®, Novartis) was approved by the FDA for subcutaneous, intramuscular, or intravenous injections to treat acute iron intoxication and chronic iron

overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved by the FDA.

- In 2005, deferasirox (Exjade®, Novartis) was approved by the FDA: it is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients aged 2 years and older. Under the accelerated approval program, the FDA expanded the indications for deferasirox in 2013 to include treatment of patients aged 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia syndromes and specific liver iron concentration and serum ferritin levels. A generic version of deferasirox tablet for oral suspension has also been approved by the FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu®) was approved by the FDA. All formulations of deferasirox carry a black box warning because it may cause serious and fatal renal toxicity and failure, hepatic toxicity and failure, and gastrointestinal hemorrhage. As a result, treatment with deferasirox requires close patient monitoring, including laboratory tests of renal and hepatic function.
- In 2011, the iron chelator deferiprone (Ferriprox®), was approved by the FDA for treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form and oral solution. Ferriprox® carries a black box warning because it can cause agranulocytosis, which can lead to serious infections and death. As a result, absolute neutrophil count should be monitored before and during treatment.

In a June 2014 warning to consumers, the FDA advised that FDA-approved chelating agents would be available by prescription only. There are no FDA-approved over-the-counter chelation products.

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History

Date	Comments
04/01/16	New policy, replaces deleted policy 8.01.02. Approved March 8, 2016. Chelation therapy for FDA approved indications may be considered medically necessary when criteria are met. All other indications are considered investigational.
05/01/17	Annual Review, approved April 11, 2017. No change to policy statements. No references added.
11/10/17	Policy moved into new format; no change to policy statements.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; no references added. Policy statement unchanged. Removed HCPCS codes J3490 and J3520.
01/01/19	Coding update, added new HCPCS code G0068 (new code effective 1/1/19)
02/02/19	Minor update, added Documentation Requirements section.
05/01/19	Annual Review, approved April 18, 2019. Policy updated with literature review through January 2019; no references added. Clinical trials table updated with revised completion dates. Policy statement unchanged.
05/01/20	Annual Review, approved April 7, 2020. Policy updated with literature review through December 2019; no references added. Policy statement unchanged.
05/01/21	Annual Review, approved April 1, 2021. Policy updated with literature review through December 8, 2020; references added. Policy statement unchanged.
05/01/22	Annual Review, approved April 11, 2022. Policy updated with literature review through November 15, 2021; no references added. Policy statements unchanged. Added HCPCS code J3520.
07/01/22	Coding update. Removed HCPCS code G0068.
05/01/23	Annual Review, approved April 10, 2023. Policy updated with literature review through December 28, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Discrimination is Against the Law

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY：711）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auaunaga fesoasoan, e fai fua e leai se totogi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 800-722-1471 (TTY: 711).

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 （TTY:711）まで、お電話にてご連絡ください。

PAKDAAR: Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតឈ្នួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

ማስታወሻ: የሚናገሩት ቋንቋ ኣማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው፡ 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-722-1471 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS : 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

توجه: اگر به زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.