



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date.....11/15/2010
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Subject Chelation Therapy

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Hyperlink to Related Coverage Policies

Autism Spectrum Disorders/Pervasive
 Developmental Disorders: Assessment
 and Treatment
 Chemical Hair Analysis
 Complementary and Alternative Medicine
 Genetic Testing for Hemoglobinopathies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

Services for or in connection with an injury or illness arising out of, or in the course of, any employment for wage or profit are explicitly excluded under most CIGNA benefit plans. Therefore, treatment of metal toxicity that occurs as a result of occupational exposure is generally not covered.

CIGNA covers each respective Chelation Therapy agent as medically necessary for the usage/FDA approved indication(s) and associated condition(s) listed below:

Drug Name	Condition	Usage / FDA Approved Indication
Deferasirox (Exjade [®])	iron overload due to transfusion-dependent anemias (e.g., thalassemias, sickle cell anemia, Cooley's anemia) or secondary hemochromatosis	Chronic iron overload due to blood transfusions in patients two years old or older
Deferoxamine mesylate (Desferal [®])		Desferal is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias
Deferoxamine mesylate (Desferal [®])	aluminum overload due to hemodialysis	Accepted Off Label Use: Aluminum toxicity in patients with chronic renal failure undergoing hemodialysis
Dexrazoxane (Zinecard [®])	prophylaxis against doxorubicin-induced cardiomyopathy	Zinecard is indicated for reducing the incidence and severity of cardiomyopathy associated with

		doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m ² and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy
Dimercaprol (BAL in Oil™)	heavy metal overload or toxicity confirmed by appropriate laboratory results (e.g., blood, plasma, and/or urine) or clinical findings consistent with metal toxicity	BAL in Oil (Dimercaprol Injection USP) is indicated in the treatment of arsenic, gold and mercury poisoning. It is indicated in acute lead poisoning when used concomitantly with Edetate Calcium Disodium Injection USP. Dimercaprol Injection USP is effective for use in acute poisoning by mercury salts if therapy is begun within one or two hours following ingestion. It is not very effective for chronic mercury poisoning. Dimercaprol Injection USP is of questionable value in poisoning caused by other heavy metals such as antimony and bismuth. It should not be used in iron, cadmium, or selenium poisoning because the resulting dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.
Edetate Calcium Disodium (Calcium EDTA) (Calcium Disodium Versenate®)		Edetate calcium disodium is indicated for the reduction of blood levels and depot stores of lead in lead poisoning (acute and chronic) and lead encephalopathy, in both pediatric populations and adults. Chelation therapy should not replace effective measures to eliminate or reduce further exposure to lead.
Succimer (DMSA) (Chemet®)		Lead poisoning in pediatric patients with blood lead levels above 45 mcg/dL
Edetate Disodium (EDTA) (Endrate®)	<ul style="list-style-type: none"> • emergency treatment of hypercalcemia • control of ventricular arrhythmias associated with cardiac glycoside (e.g., digitalis) toxicity 	Endrate (Edetate Disodium Injection, USP) is indicated in selected patients for the emergency treatment of hypercalcemia and for the control of ventricular arrhythmias associated with digitalis toxicity
Penicillamine (Cuprimine®, Depen®)	copper overload/toxicity secondary to Wilson's disease	Cuprimine is indicated in the treatment of Wilson's disease
Trientine Hydrochloride (Syprine®)		Syprine is indicated in the treatment of patients with Wilson's disease who are intolerant of penicillamine
Pentetate Calcium Trisodium (Ca-DTPA)	internal plutonium, americium, or curium contamination	Internal plutonium, americium, or curium contamination to increase the rates of elimination
Pentetate Zinc Trisodium (Zn-DTPA)		Internal plutonium, americium, or curium contamination to increase the rates of elimination
Penicillamine (Cuprimine®, Depen®)	cystinuria	Cuprimine is indicated in the treatment of cystinuria
Penicillamine (Cuprimine®, Depen®)	rheumatoid arthritis	Cuprimine is indicated in the treatment of patients with severe, active rheumatoid arthritis

		who have failed to respond to an adequate trial of conventional therapy
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NOTE: Due to pharmacological property differences and mechanisms of action, each chelation agent should only be used as indicated by the FDA or for the recognized off label usage noted.

CIGNA does not cover Chelation Therapy for any of the following indications because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- atherosclerotic vascular diseases
- coronary artery disease
- reperfusion injury during coronary angioplasty or cardiopulmonary bypass surgery
- progressive renal insufficiency in Type II diabetic nephropathy
- Alzheimer's disease
- Parkinson's disease
- primary biliary cirrhosis
- ankylosing spondylitis
- autism
- glioblastoma
- scleroderma
- porphyria
- hypercholesterolemia

FDA Approved Indications

Please refer to above table for approved indications for each chelation agent.

FDA Recommended Dosing

The following table outlines the FDA recommended dosing by drug name:

Generic Drug Name	Brand Name	Recommended Dosing
Deferasirox	Exjade	20 mg/kg body weight
Deferoxamine mesylate	Desferal	<ul style="list-style-type: none"> • 1000 mg administered initially • May be followed by 500 mg every 4 hours for two doses • Depending upon the clinical response, subsequent doses of 500 mg may be administered every 4-12 hours • Total amount should not exceed 6000 mg in 24 hours
Dexrazoxane	Zinecard	<ul style="list-style-type: none"> • The recommended dosage ratio of Zinecard doxorubicin is 10:1 (eg - 500 mg/m² Zinecard: 50 mg/m² doxorubicin) • In patients with moderate to severe renal dysfunction (creatinine clearance values < 40 mL/min), the recommended dosage ratio of Zinecard:doxorubicin is 5:1 (eg. 250 mg/m² Zinecard: 50 mg/m² doxorubicin)
Dimercapro	BAL in Oil	<ul style="list-style-type: none"> • Mild arsenic or gold poisoning - 2.5 mg/kg of body weight four times daily for two days, two times on the third day, and once daily thereafter for ten days • Severe arsenic or gold poisoning - 3 mg/kg every four hours for two-days, four

		<p>times on the third day, then twice daily thereafter for ten days</p> <ul style="list-style-type: none"> • Mercury poisoning - 5 mg/kg initially, followed by 2.5 mg/kg one or two times daily for ten days • Acute lead encephalopathy - 4 mg/kg body weight is given alone in the first dose and thereafter at four-hour intervals in combination with Edetate Calcium Disodium administered at a separate site • Less severe poisoning - dose can be reduced to 3 mg/kg after the first dose then treatment is maintained for two to seven days depending on clinical response
Edetate Calcium Disodium (Calcium EDTA)	Calcium Disodium Versenate	<ul style="list-style-type: none"> • Asymptomatic adults and pediatric patients whose blood lead level is <70 mcg/dl but >20 mcg/dl (World Health Organization recommended upper allowable level) is 1000 mg/m²/day given IV or IM • Adults with lead nephropathy - 500 mg/m² every 24 hours for 5 days for patients with serum creatinine levels of 2-3 mg/dl, every 48 hours for 3 doses for patients with creatinine levels of 3-4 mg/dl, and once weekly for patients with creatinine levels above 4 mg/dl. These regimens may be repeated at one month intervals
Succimer (DMSA)	Chemet	<ul style="list-style-type: none"> • Start dosage at 10 mg/kg or 350 mg/m² every eight hours for five days • Reduce frequency of administration to 10 mg/kg or 350 mg/m² every 12 hours for an additional two weeks of therapy • A course of treatment lasts 19 days. Repeated courses may be necessary if indicated by weekly monitoring of blood lead concentration • A minimum of two weeks between courses is recommended unless blood lead levels indicate the need for more prompt treatment
Edetate Disodium (EDTA)	Endrate	<ul style="list-style-type: none"> • Adults: IV 50 mg/kg/day (max 3g/day) administered in 5 consecutive daily doses followed by 2 days without medication with repeated courses as needed for a total of 15 doses • Children: IV 40mg/kg/day (max 70/mg/kg/day) or 15-50 mg/kg/day (max 3g/day) with 5 days between courses
Penicillamine	Cuprimine	<ul style="list-style-type: none"> • Wilson's Disease: Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. In the absence of any drug reaction, a dose between

		<p>0.75 and 1.5 g should be continued for about three months. It is seldom necessary to exceed a dosage of 2 g/day. In patients who cannot tolerate as much as 1 g/day initially, initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug.</p> <ul style="list-style-type: none"> • Cystinuria: The usual dosage is 2 g/day for adults, with a range of 1 to 4 g/day. For pediatric patients, dosage can be based on 30 mg/kg/day. The total daily amount should be divided into four doses. If four equal doses are not feasible, give the larger portion at bedtime. If adverse reactions necessitate a reduction in dosage, it is important to retain the bedtime dose. • Rheumatoid Arthritis: The recommended dosage regimen begins with a single daily dose of 125 mg or 250 mg, which is thereafter increased at one to three month intervals, by 125 mg or 250 mg/day, as patient response and tolerance indicate
Penicillamine	Depen	<ul style="list-style-type: none"> • Wilson's Disease: Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. In the absence of any drug reaction, a dose between 0.75 and 1.5 g should be continued for about three months. It is seldom necessary to exceed a dosage of 2 g/day. In patients who cannot tolerate as much as 1 g/day initially, initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug. • Cystinuria: The usual dosage is 2 g/day for adults, with a range of 1 to 4 g/day. For pediatric patients, dosage can be based on 30 mg/kg/day. The total daily amount should be divided into four doses. If four equal doses are not feasible, give the larger portion at bedtime. If adverse reactions necessitate a reduction in dosage, it is important to retain the bedtime dose. • Rheumatoid Arthritis: The recommended dosage regimen begins with a single daily dose of 125 mg or 250 mg, which is thereafter increased at one to three month intervals, by 125 mg or 250 mg/day, as patient response and tolerance indicate
Trientine Hydrochloride	Syprine	The recommended initial dose of Syprine is 500-750 mg/day for pediatric patients and

		750-1250 mg/day for adults given in divided doses two, three or four times daily. This may be increased to a maximum of 2000 mg/day for adults or 1500 mg/day for pediatric patients age 12 or under
Pentetate Calcium Trisodium	Ca-DTPA	<ul style="list-style-type: none"> Adults and Adolescents: A single 1.0 gram initial dose of Ca-DTPA administered intravenously Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously not exceed 1.0 gram
Pentetate Zinc Trisodium	Zn-DTPA	<p>IT IS PREFERABLE TO ADMINISTER CA-DTPA, IF AVAILABLE, AS THE INITIAL DOSE DURING THE FIRST 24 HOURS AFTER INTERNAL CONTAMINATION BECAUSE CA-DTPA IS MORE EFFECTIVE THAN ZN-DTPA DURING THIS TIME PERIOD. AFTER 24 HOURS, ZN-DTPA AND CADTPA ARE EQUALLY EFFECTIVE.</p> <ul style="list-style-type: none"> Adults and Adolescents: A single 1.0 gram initial dose of Zn-DTPA administered intravenously Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously not to exceed 1.0 gram

Drug Availability

The following table outlines the drug availability per FDA labeling:

Generic Drug Name	Brand Name	Drug Availability
Deferasirox	Exjade	<ul style="list-style-type: none"> 125 mg tablets - Off-white, round, flat tablet with beveled edge and imprinted with "J" and "125" on one side and "NVR" on the other 250 mg tablets - Off-white, round, flat tablet with beveled edge and imprinted with "J" and "250" on one side and "NVR" on the other 500 mg tablets - Off-white, round, flat tablet with beveled edge and imprinted with "J" and "500" on one side and "NVR" on the other
Deferoxamine mesylate	Desferal	<ul style="list-style-type: none"> Vials containing 500 mg of sterile, lyophilized deferoxamine mesylate Vials containing 2 g of sterile, lyophilized deferoxamine mesylate
Dexrazoxane	Zinecard	<ul style="list-style-type: none"> Zinecard is available in a 250 mg single dose vial with a red flip-top seal, packaged in single vial packs Zinecard is available in a 500 mg single dose vial with a blue flip-top seal, packaged in single vial packs

Dimercapro	BAL in Oil	3 mL (100 mg/mL) ampules in a box of 10
Edetate Calcium Disodium (Calcium EDTA)	Calcium Disodium Versenate	2.5 ml ampul containing 200 mg of edetate calcium disodium per ml (500 mg per ampul), in boxes containing 10 ampuls
Succimer (DMSA)	Chemet	100 mg capsules in a bottle of 100
Edetate Disodium (EDTA)	Endrate	Supplied in 20 mL (3 g) ampuls
Penicillamine	Cuprimine	250 mg ivory-colored capsules containing a white or nearly white powder, and coded CUPRIMINE and MSD 602. Supplied in bottles of 100
Penicillamine	Depen	250mg white oval cored tablets
Trientine Hydrochloride	Syprine	Syprine 250 mg capsules are light brown opaque capsules coded Syprine on one side and MSD 661 on the other. They are supplied in bottles of 100
Pentetate Calcium Trisodium	Ca-DTPA	Supplied as a sterile solution in 5 mL single-use clear glass ampules at a concentration of 200 mg/mL for IV use. Each ampoule contains the equivalent of 1000 mg of pentetate calcium trisodium in a package of 10.
Pentetate Zinc Trisodium	Zn-DTPA	Supplied as a sterile solution in 5 mL single-use clear glass ampoules at a concentration of 200 mg/mL for IV use. Each ampule contains the equivalent of 1000 mg of pentetate zinc trisodium in a package of 10.

General Background

Pharmacology

Chelation therapy reduces the accumulation of essential heavy metals (e.g., iron and copper) or non-essential metals (e.g., lead and aluminum) in the body. Chelating agents bind with heavy metal ions and enhance the urinary and fecal excretion of these toxic metals. Chelation therapy is performed in cases of iron, lead, copper and aluminum overload and in some heavy metal toxicities.

Guidelines

All of the following documentation from the following society's recommendations are current and were checked for this current revision year.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of chronic ischemic heart disease indicate that chelation therapy is categorized as a Class III recommendation, defined as "Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful" (Lee, 2001).

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."

The AHA states, "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, 2005).

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).

Ongoing Studies

Chelation therapy has been proposed for other non-overload conditions such as: atherosclerotic vascular diseases; coronary artery disease; reperfusion injury during coronary angioplasty or cardiopulmonary bypass surgery; progressive renal insufficiency in Type II diabetic nephropathy; Alzheimer's disease; glioblastoma; primary biliary cirrhosis; Parkinson's disease; ankylosing spondylitis; autism; scleroderma; porphyria; and hypercholesterolemia. However, there remains a lack of evidence to support these indications. Additional research is needed to determine the safety and efficacy of chelation therapy for these conditions.

Atherosclerotic Vascular Disease

Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been proposed as a noninvasive treatment alternative to established techniques of angioplasty and bypass surgery for atherosclerotic vascular disease. It is theorized that by removing iron and copper from the body, the generation of free radicals and propagation of lipid peroxidation are impaired and that low-density lipoproteins are lowered (Miller, et al., 2004; Villarruz, et al., 2004).

The National Center for Complimentary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) has launched the Trial to Assess Chelation Therapy (TACT). This phase III, large-scale, multi-center study to assess the safety and efficacy of chelation therapy in patients with coronary artery disease is still ongoing and expected to reach completion in 2012. This randomized, placebo-controlled, double-blind study currently enrolls 1700 participants age 50 years and older with a history of myocardial infarction at least 6 weeks prior to start of study. It is still recruiting new participants while the study is underway. (Clinical Trials, 2009).

Seely et al. (2005) in a systematic review of seven articles from 1963 to 2005 assessed the potential use of EDTA chelation therapy for the treatment of cardiovascular disease. It is proposed that repeated administration of EDTA in combination with vitamins and minerals is a safe alternative treatment for atherosclerosis. The proposed action of EDTA is to reverse atherosclerosis and includes: calcium chelation to dissolve plaques, free radical scavenging action, reduction of iron stores, cell membrane stabilization, arterial dilation, improved arterial wall elasticity and increased production of nitric oxide. Their conclusion was that using EDTA as a treatment for cardiovascular disease is not supported by the literature. Most of the literature relied on uncontrolled evidence, thus indicating the need for a controlled trial such as the Trial to Assess Chelation Therapy discussed below that is currently being conducted.

Villarruz et al. (2004) conducted a systematic review of the literature (last reviewed July 2002) of all randomized controlled trials of chelation therapy for atherosclerotic cardiovascular disease. The authors reported on seven trials which compared EDTA to placebo, which was either an isotonic solution or distilled water. The authors concluded that the studies failed to demonstrate benefit with the use of EDTA chelation therapy in patients with peripheral vascular disease. They stated, “There was insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improveing clinical outcomes among patients with atherosclerotic cardiovascular disease.”

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.

Dessai and Grossberg (2005) in their updated review of diagnosis and treatment of Alzheimer's disease state there is no cure for Alzheimer's disease. Current treatment focuses on early diagnosis and institution of cholinesterase inhibitors and/or N-methyl-D-aspartate (NMDA) receptor-targeted therapy. New treatment options are urgently needed. It is proposed that chelation therapy will decrease the effects of metals in the brain. The use of chelation therapy in Alzheimer's disease is still investigational.

Parkinson's Disease

Researchers have implied that iron and iron chelators play a crucial role in the process of dopaminergic neurodegeneration and neuroprotection. No human studies have been published which evaluate the efficacy of iron chelation in the treatment of Parkinson's disease.

Summary Statement

There is good evidence that chelation therapy is effective for the reduction of the accumulation of certain heavy metals (e.g., iron and copper) or non-essential metals (e.g., lead and aluminum) in the body. Chelation therapy is performed in cases of iron, lead, copper and aluminum overload and in some heavy metal toxicities.

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. Specifically, chelation therapy remains experimental, investigational, or unproven for the treatment of chronic ischemic heart disease, Alzheimer's disease, and Parkinson's disease.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPSC Codes	Description
J0470	Injection, dimercaprol, per 100 mg
J0600	Injection, edentate calcium disodium, [calcium disodium versenate], up to 1,000 mg
J0895	Injection, deferoxamine mesylate, [Desferal] 500 mg
J1190	Injection, dexrazoxane hydrochloride, per 250 mg
J3520	Edetate disodium , per 150 mg

ICD-9-CM Diagnosis Codes	Description
270.0	Disorders of amino acid transport; cystinuria
275.0	Disorders of iron metabolism
275.1	Disorders of copper metabolism
425.9	Secondary cardiomyopathy, unspecified
714.0	Rheumatoid arthritis
964.0	Poisoning by agents primarily affecting blood constituents; iron and its compounds
972.1	Poisoning by agents primarily affecting the cardiovascular system; cardiotonic glycosides and drugs of similar action
984.0	Toxic effect of lead and its compounds (including fumes); inorganic lead compounds
984.1	Toxic effect of lead and its compounds (including fumes);organic lead compounds
984.8	Toxic effect of lead and its compounds (including fumes);other lead compounds
984.9	Toxic effect of lead and its compounds (including fumes);unspecified lead compound
985.0	Toxic effect of other metals; Mercury and its compounds
985.1	Toxic effect of other metals; Arsenic and its compounds

985.8	Toxic effect of other metals; Other specified metals
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Experimental/Investigational/Unproven/Not Covered:

HCCPS Codes	Description
M0300	IV chelation therapy (chemical endarterectomy)

ICD-9-CM Diagnosis Codes	Description
191.9	Malignant neoplasm of brain, unspecified
277.1	Disorders of porphyrin metabolism
299.00-299.91	Pervasive developmental disorders
331.0	Alzheimer's Disease
332.0	Parkinson's Disease; Paralysis agitans
414.00-414.05	Coronary atherosclerosis
440.0-440.9	Atherosclerosis
571.6	Biliary cirrhosis
710.1	Systemic sclerosis
720.0	Ankylosing spondylitis
	Multiple/varied

***Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.**

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