Effective Date **9/1/2023**
Next Review Date **9/1/2024**
Coverage Policy Number **2028**

Drug and Biologic Medical Necessity (Non-Injectables) - medical benefits

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, 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 customer'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 customer's benefit plan document always supersedes 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 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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses coverage of Non-injectable Drugs and Biologics, not otherwise specified, allowed under plan medical benefits.

Non-Injectable agents include, but not limited to:
- Oral agents
- Inhaled agents
- Intranasal agents
- Intrauterine agents
- Topical agents
- Transdermal agents

Cigna maintains individual and/or group topic Coverage Policies describing medical necessity criteria for certain drug and biologic products requiring precertification. Use the Pharmacy (Drugs & Biologics) A-Z Index search box with a specific product name to locate additional coverage policies.

Oncology medications are addressed in a separate coverage policy. Please refer to the related coverage policy link above.

Coverage Policy

Absent specific coverage policies, Non-Injectable Drugs or Biologics are considered medically necessary, in accordance with benefit plan specifications, when EITHER of the following criteria is met:

- Use is approved and listed in the FDA product information (Label)
- Use is supported by standard medical reference compendia [for example, American Hospital Formulary Service-Drug Information (AHFS-DI)], and not contraindicated or otherwise not recommended in the FDA product information (Label)

When coverage is available and medical necessary, the dosage, frequency, duration of therapy, and site of administration should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Any other use is considered experimental, investigational or unproven.

Dose, duration, frequency, or quantity exceeding generally accepted medical practice standards is considered not medically necessary.

Documentation: When documentation is required, the prescriber must provide written documentation supporting the trials of these other agents. Documentation may include, but is not limited to, chart notes, prescription claims records, and/or prescription receipts.

Products Subject to Medically Necessity Review

The following list of drugs may be subject to medical necessity review if dose, duration, frequency, or quantity exceed generally accepted medical practice standards supported by the FDA product information (Label), standard medical reference compendia, and/or evidence-based literature: (this list may not be all-inclusive and is subject to change)

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
C9046	Cocaine hydrochloride nasal solution for topical administration, 1 mg (C-topical)	Topical medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult Topical anesthesia (and vasoconstriction) for mucous membranes of the oral, laryngeal, or nasal cavities	Adult Max dose: no well-established maximum dose for the approved indication according to the prescribing information Usual dose: the lowest dose necessary to produce adequate anesthesia should be used; concentrations of 1% to 10% may be used, with 4% being the most frequently used concentration (maximum total dose: 3 mg/kg or 200 mg). Pediatric Safety and effectiveness have not been established.
J0604	Cinacalcet, oral, 1 mg, (for ESRD on dialysis) (Sensipar)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit	Adult Max dose: no well-established maximum doses for the approved

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
		policy as applicable to verify coverage of this drug under medical benefit. <u>Adult</u> • Treatment of hypercalcemia in adults with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy. • Treatment of secondary hyperparathyroidism in adults with chronic kidney disease on dialysis. • Treatment of hypercalcemia in adults with parathyroid carcinoma	indications according to the prescribing information. Usual dose: • Initial 30 mg twice daily • Increase dose incrementally every 2 to 4 weeks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 or 4 times/day) as necessary to normalize serum calcium levels <u>Pediatric</u> Safety and efficacy have not been established.
J1097	phenylephrine 10.16 mg/ml and ketorolac 2.88 mg/ml ophthalmic irrigation solution, 1 ml (Omidria)	Ophthalmic medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult / Pediatric</u> • Ophthalmic surgical irrigation used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain	<u>Adult / Pediatric</u> Max dose: no well-established maximum dose according to the prescribing information. Usual dose: • 4 mL of Omidria is diluted in 500 mL of ocular irrigating solution • Irrigation solution is to be used as needed for the surgical procedure for a single patient
J2545	Pentamidine isethionate, inhalation solution, FDA-approved final product, non-compounded (Nebupent)	Inhaled medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult / Pediatric (5 years and older)</u> • Prevention of Pneumocystis jirovecii pneumonia (PCP) in high-risk, patients with HIV defined by 1 or both of the following criteria: o A history of 1 or more episodes of PCP. o A peripheral CD4+ (T4 helper/inducer) lymphocyte count less than or equal to 200/mm3.	<u>Adult</u> Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: • 300 mg once every 4 weeks <u>Pediatric (5 years and older)</u> Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: • 300 mg every month
J7502	Cyclosporine, oral (Gengraf, Neoral, Sandimmune)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit.	<u>Adult</u> Max does: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose:

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
		Adult / Pediatric • Transplant rejection prophylaxis Adult • Psoriasis (Neoral and Gengraf only) o Treatment of severe, recalcitrant plaque psoriasis in nonimmunocompromised adults unresponsive to or unable to tolerate other systemic therapy	• Transplant rejection prophylaxis: o Cyclosporine (Sandimmune) ▪ Initial dosage: a single dose of 15 mg/kg given 4 to 12 hours prior to transplantation. ▪ Maintenance dosage: the initial single daily dose is continued postoperatively for 1 to 2 weeks and then tapered by 5% per week to a maintenance dosage of 5 to 10 mg/kg/day. o Cyclosporine modified (Gengraf or Neoral) ▪ Initial dosage: in newly transplanted patients, the initial oral dose of Neoral and Gengraf are the same as the initial dose of Sandimmune. Pediatric Max dose: Transplant rejection prophylaxis: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: • Transplant rejection prophylaxis: the same dose and dosing regimen may be used as in adults. Adult • Psoriasis (Neoral and Gengraf only) o 4 mg/kg/day according to the prescribing information
J7503	Tacrolimus, extended release, oral, 0.25 mg (Envarsus XR)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult / Pediatric • Organ rejection prophylaxis	Adult Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: 0.14 mg/kg/day Pediatric Safety and efficacy have not been established for ER formulations.
J7507	Tacrolimus, oral (Prograf)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan	Adult Max dose: no well-established maximum dose for the approved

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
		Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult / Pediatric</u> • Organ rejection prophylaxis • Prophylaxis of Organ Rejection in Kidney, Liver, Heart, and Lung Transplant	indication according to the prescribing information. Usual dose: • Organ rejection prophylaxis: o Initial dosage: ▪ Heart transplant: 0.075 mg/kg/day ▪ Kidney transplant: 0.2 mg/kg/day in combination with azathioprine or 0.1 mg/kg/day in combination with mycophenolate mofetil. ▪ Liver transplant: 0.1 to 0.15 mg/kg/day ▪ Lung transplant: 0.075 mg/kg/day, in combination with azathioprine or MMF <u>Pediatric</u> Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: • Organ rejection prophylaxis: o Liver transplant: 0.15 to 0.2 mg/kg/day (capsules) or 0.2 mg/kg/day (granules for oral suspension) in 2 divided doses every 12 hours initially o Heart transplant: 0.3 mg/kg/day (capsules or granules for oral suspension) in 2 divided doses every 12 hours; initiate with 0.1 mg/kg/day if cell depleting induction treatment is administered o Kidney transplant: 0.3 mg/kg/day (capsules or granules for oral suspension) in 2 divided doses every 12 hours
J7508	Tacrolimus, extended release, oral, 0.1 mg (Astagraf XL)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult / Pediatric</u>	<u>Adult</u> Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose:

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
		• Organ rejection prophylaxis (kidney transplant)	• Organ rejection prophylaxis (kidney transplant): o With basiliximab induction: 0.15 to 0.2 mg/kg/day. o Without basiliximab induction: 0.1 mg/kg/day (preoperative); 0.2 mg/kg/day (postoperative) Pediatric Safety and efficacy have not been established for ER formulations.
J7518	Mycophenolic acid, oral (Myfortic)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult • Prophylaxis of organ rejection in patients receiving renal, cardiac, or hepatic transplants • Rejection in liver transplant patients unable to tolerate tacrolimus or cyclosporine due to toxicity Pediatric • Prophylaxis of organ rejection in patients receiving renal transplants	Adult Max dose: no well-established maximum dose for the approved indication according to the prescribing information. Usual dose: • Cardiac/Hepatic transplantation (mycophenolate mofetil) o 1,500 mg twice daily. • Renal transplantation: o Mycophenolate mofetil: 1,000 mg twice daily. Doses > 2,000 mg daily are not recommended. o Mycophenolate sodium: 720 mg twice daily. Pediatric Max dose: • Mycophenolate mofetil o 3 months and older: 1,000 mg twice daily for the oral suspension according to the prescribing information o There is no well-established maximum dose for the other dose forms according to the prescribing information • Mycophenolate sodium o 5 years and older: 720 mg twice daily according to the prescribing information Usual dose: • Kidney transplant: o Mycophenolate mofetil (3 months and older): 1,000 mg twice daily for the oral suspension according to the prescribing information. No well-established maximum dose for the other dose forms according

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
			to the prescribing information ○ Mycophenolate sodium (5 years and older): 720 mg twice daily according to the prescribing information.
J7520	Sirolimus, oral (Rapamune)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult</u> • Prophylaxis of organ rejection in patient receiving renal transplants <u>Pediatric</u> • Prophylaxis of organ rejection in patient receiving renal transplants	<u>Adult</u> • Lymphangioleiomyomatosis ○ Initial dosage: 2 mg once daily. ○ Maintenance dosage: adjust dose to maintain a target concentration of 5 to 15 ng/mL. • Renal transplantation ○ High immunologic risk: Maximum dosage 40 mg/day. ○ Low to moderate immunologic risk: Maximum dosage 40 mg/day <u>Pediatric</u> • Renal transplantation ○ High immunologic risk: safety and efficacy not established. ○ Low to moderate immunologic risk (13 years and older): Maximum dosage 40 mg/day.
J7527	Everolimus 0.25 mg, oral (Zortress)	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. <u>Adult</u> • Prophylaxis of allograft rejection in liver transplantation • Prophylaxis of organ rejection in renal transplant patients at low to moderate immunologic risk • Heart transplantation • Lung transplantation	<u>Adult</u> • Liver transplantation ○ Initial dosage 1 mg orally twice daily in combination with reduced dose tacrolimus and a corticosteroid • Renal transplantation ○ Initial dosage 0.75 mg twice daily in combination with basiliximab induction, a corticosteroid, and a reduced dose of cyclosporine • Heart transplantation (≥3 months post-transplantation): 0.75 mg twice daily initially (in combination with reduced dose cyclosporine and a corticosteroid) • Lung transplantation (>1 month post-transplantation): 0.75 to 1.5 mg twice daily initially

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
			Pediatric The safety and efficacy of Zortress has not been established in pediatric patients (less than 18 years).
J7605	Arformoterol, inhalation solution, FDA-approved final product, non-compounded (Brovana)	Inhaled medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult • Chronic obstructive pulmonary disease	Adult • 30 mcg/day according to the prescribing information Pediatric Safety and efficacy have not been established.
J7606	Formoterol fumarate, inhalation solution, FDA approved final product, non-compounded (Perforomist)	Inhaled medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult • Chronic obstructive pulmonary disease	Adult • Chronic obstructive pulmonary disease o Dry powder inhaler ▪ Usual dosage: 12 mcg every 12 hours ▪ Maximum dosage: 24 mcg/day o Nebulization solution ▪ Usual dosage: 20 mcg twice daily. ▪ Maximum dosage: 40 mcg/day. Pediatric Safety and efficacy have not been established.
J7620	Albuterol, up to 2.5 mg and ipratropium bromide, up to 0.5 mg, FDA-approved final product, non-compounded, (DuoNeb)	Inhaled medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult / Pediatric • Acute asthma (exacerbations) Adult • Chronic obstructive pulmonary disease	Adult • COPD; nebulized solution: o Usual dosage: 1 vial (3 mL) via nebulization every 6 hours o Maximum dosage: 6 vials (18 mL)/day according to the prescribing information • Acute asthma (exacerbations); nebulization solution: 1 vial (3 mL) inhaled every 20 minutes for 3 doses, then as needed Pediatric Asthma, acute exacerbation; nebulization solution (ipratropium bromide 0.5 mg/albuterol 2.5 mg) • Adolescents: 3 mL every 20 minutes for 3 doses, then as needed for up to 3 hours • Infants and children: 1.5 to 3 mL every 20 minutes for 3 doses, then as needed for up to 3 hours.

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
J7674	Methacholine chloride administered as inhalation solution through a nebulizer (Provocholine)	Inhaled medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Adult / Pediatric • Diagnosis of bronchial airway hyperreactivity in adults and pediatric patients ≥ 5 years of age who do not have clinically apparent asthma	Adult / Pediatrics (≥ 5 years of age) • 1 to 3 mcg inhalation initial dose via nebulizer followed by a stepwise doubling or quadrupling of dose based on nebulizer device output per minute, particle size distribution (to assess lower airway delivery), time of tidal breathing, and ratio of inspiratory time to total breathing time. Note: the above dosages are according to the American Thoracic Society (ATS) guidelines and European Respiratory Society (ERS).
J8540	Dexamethasone, oral	Oral medications are typically covered under a Prescription Drug benefit plan. Please refer to Standard Plan Document and coordination of benefit policy as applicable to verify coverage of this drug under medical benefit. Refer to Policy 1403, Oncology Medications for all oncology uses. For Non-oncology uses: Adult / Pediatric • Anti-inflammatory or immunosuppressant agent • Acute mountain sickness/high-altitude cerebral edema • Asthma, acute exacerbation Adult • Coronavirus disease 2019 (COVID-19), treatment (severe or critical)	Adult Max dose: no well-established doses for the approved indications according to the prescribing information. Usual dose: • 4 to 20 mg/day given in a single daily dose or in 2 to 4 divided doses. • High dose: 0.4 to 0.8 mg/kg/day (usually not to exceed 40 mg/day). • Acute mountain sickness/High-altitude cerebral edema: 2 mg every 6 hours or 4 mg every 12 hours; may be discontinued after staying at the same elevation for 2 to 4 days or if descent is initiated. Due to adverse effects, limit duration to ≤10 days • Asthma, acute exacerbation: 16 mg daily for 2 days only • COVID-19: 6 mg once daily for up to 10 days Pediatric Max dose: no well-established doses for the approved indications according to the prescribing information. However, max dosing guidance has been established by Other Supported evidence. Usual dose: • 0.02 to 0.3 mg/kg/day or 0.6 to 9 mg/m^2/day in divided doses every 6 to 12 hours initially;

CPT / HCPC Code	Drug (Brand Name)	Covered Indications / Other Supported Uses	Recommended Dosing (where available)
			dose depends upon condition being treated and response of patient; dosage for infants and children should be based on disease severity and patient response • Acute mountain sickness/high-altitude cerebral edema: 0.15 mg/kg/dose every 6 hours; maximum dose: 4 mg/dose • Asthma, acute exacerbation: 0.6 mg/kg once daily as a single dose or once daily for 2 days; maximum dose: 16 mg/dose

General Background

Drugs intended for human use are evaluated by FDA's Center for Drug Evaluation and Research (CDER) to ensure that drugs marketed in the United States are safe and effective. Biological products are evaluated by FDA's Center for Biologics Evaluation and Research (CBER). Federal law generally requires that prescription drugs in the U.S. be shown to be both safe and effective prior to marketing for all indications or uses. FDA's review of the applicant's labeling insures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use. (U.S. FDA, 2020a, 2020b)

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence. This use is called "off-label" and the FDA generally allows an FDA-approved, marketed product used in this manner when the intent is the "practice of medicine". (U.S. FDA, 2020c)

Employers and health care organizations have an interest in promoting positive patient outcomes. One resource employed to achieve this goal is the medication precertification ,process. This process takes into consideration evidence of a particular medication's efficacy and safety to promote appropriate utilization and thereby minimize waste and error.

Where medical precertification is a part of a benefit plan, specific criteria must be met to promote appropriate use:

- Benefit plan coverage parameters
- Medical necessity, including appropriate clinical use

Standard Medical Reference Compendia
Standard medical reference compendia utilized to establish medical necessity include, but not limited to: American Hospital Formulary Service-Drug Information (AHFS), Elsevier/Gold Standard Clinical Pharmacology, Truven Health Analytics Micromedex DrugDEX® (DrugDEX), and Facts & Comparisons®.

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