Overview

Denosumab is a monoclonal antibody used for the treatment of osteoporosis in postmenopausal women with a high risk of bone fractures that were not successful with other osteoporosis therapies. Denosumab reduces the possibility of fractures of the hip and vertebral and non-vertebral fractures because it is a RANK Ligand inhibitor. It works by binding to the Rank Ligand inhibiting osteoclast formation, function, and survival, therefore preventing the osteoclasts from resorbing bone.

The FDA has approved the use of denosumab (Prolia). Medicare has determined under Section 1861(t) that this drug may be paid when it is administered incident to a physician’s service and is determined to be reasonable and necessary.

This policy guideline supplements but does not replace, modify or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for chemotherapeutic drug and biological services. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this policy. All providers who report services for UnitedHealthcare payment must fully understand and follow all existing laws, regulations and rules for Medicare payment for chemotherapeutic drug and biological services and must properly submit only valid claims for them. Please review and understand them and apply the medical necessity provisions in the policy within the context of the manual rules. Relevant CMS manual instructions and policies regarding chemotherapeutic drug and biological services are found in the following Internet-Only Manuals (IOMs) published on the CMS Web site:

- Medicare Benefit Policy Manual - Pub. 100-02, Chapter 15, Section 50
- National Coverage Determinations (NCD) Manual - Pub. 100-03
- Medicare Claims Processing Manual – Pub. 100-04, Chapter 17, Section 40
- Correct Coding Initiative - Medicare Contractor Beneficiary and Provider Communications Manual - Pub. 100-09, Chapter 5.

Social Security Act (Title XVIII) Standard References, Sections:
- 1862(a)(1)(A) Medically Reasonable & Necessary
- 1862(a)(1)(D) Investigational or Experimental
- 1833(e) Incomplete Claim

Generally, drugs and biologicals are covered only if all of the following requirements are met:

- They meet the definition of drugs or biologicals;
- They are of the type that are not usually self-administered by the patients who take them;
- They meet all the general requirements for coverage of items as incident to a physician’s services;
- They are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice;
- They are not excluded as immunizations; and
- They have not been determined by the FDA to be less than effective.
In reading this document, please note that there is a difference between the section of the statute which defines the overall Medicare benefit for coverage of drugs and biologicals, and the section of the statute which states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury. This policy gives information about the overall Medicare benefit for coverage of drugs and biologicals.

Guidelines

Note: This policy does not describe drug and biological coverage under the Medicare Part D benefit.

Indications

- For the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fractures.
- For the treatment of postmenopausal women with osteoporosis who have failed or are intolerant to other available osteoporosis therapy.
- For patients with significant renal failure where treatment with bisphosphonate is not indicated, CrCl less than 35 ml/min.
- Effective 11/18/2010, the FDA approved a second indication for denosumab (Xgeva). Xgeva is approved for the treatment of patients with bone metastases from solid tumors.
- Effective 09/16/2011, the FDA approved denosumab (Prolia) as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures.
- Prolia is also indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Effective 09/02/2012, the FDA approved denosumab (Prolia) as a treatment to increase bone mass in men with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Effective 06/12/2013, the FDA approved denosumab (XGEVA) for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Hypercalcemia of malignancy refractory to bisphosphonate therapy. (Effective December 5, 2014 based on (FDA) approval)
- Effective for dates of service on or after 01/04/2018, the FDA has approved denosumab (Xgeva®) for the treatment of skeletal-related events in patients with multiple myeloma.

Supplemental calcium and vitamin D are required. Hypocalcemia must be corrected prior to initiation of denosumab therapy.

Limitations

Prolia is contraindicated for the following condition:
- Hypocalcemia
- Patients receiving Xgeva

Xgeva is contraindicated for the following conditions:
- Hypocalcemia
- Hypersensitivity to Xgeva
- Patients receiving Prolia

It is not appropriate to bill UnitedHealthcare for services that are not covered (as described by this entire policy guideline) as if they are covered. When billing for non-covered services, use the appropriate modifier (see "Coding Guidelines" section in this policy). Unless certain specified conditions are met, UnitedHealthcare will not reimburse for unlabeled use of non-self-administered drugs, since unlabeled use of the drug is considered an investigational use. UnitedHealthcare is not allowed to pay for investigational treatments. However, FDA-approved drugs used for indications other than what is indicated on the official label may be covered by UnitedHealthcare when Medicare determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice. In the case of unlabeled use for anti-cancer drugs, the conditions for Medicare coverage and reimbursement have been especially well outlined.

Notice: This policy guideline imposes diagnosis limitations that support diagnosis to procedure code automated denials. However, services performed for any given diagnosis must meet all of the indications and limitations stated in this policy, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.
As published in [CMS IOM 100-08, Section 13.5.1](https://www.cms.gov/Regulatory-Information/Legislation/Regulations-and-Guidance/collections/IOM-100-08), in order to be covered under Medicare, a service shall be reasonable and necessary. UnitedHealthcare shall consider a service to be reasonable and necessary if we determine that the service is:

- Safe and effective.
- Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, that meet the requirements of the Clinical Trials NCD are considered reasonable and necessary).
- Appropriate, including the duration and frequency that is considered appropriate for the service, in terms of whether it is:
  - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member.
  - Furnished in a setting appropriate to the patient's medical needs and condition.
  - Ordered and furnished by qualified personnel.
  - One that meets, but does not exceed, the patient’s medical needs.
  - At least as beneficial as an existing and available medically appropriate alternative.

Drugs and biologicals must be determined to meet the statutory definition. Under the statute §1861(t)(1), payment may be made for a drug or biological only where it is included, or approved for inclusion, in the latest official edition of the United States Pharmacopeia National Formulary (USP-NF), the United States Pharmacopoeia-Drug Information (USD-DI), or the American Dental Association (ADA) Guide to Dental Therapeutics, except for those drugs and biologicals unfavorably evaluated in the ADA Guide to Dental Therapeutics. The inclusion of an item in the USP DI does not necessarily mean that the item is a drug or biological. The USP DI is a database of drug information developed by the U.S. Pharmacopoeia but maintained by Micromedex, which contains medically accepted uses for generic and brand name drug products. Inclusion in such reference (or approval by a hospital committee) is a necessary condition for a product to be considered a drug or biological under the Medicare program, however, it is not enough. Rather, the product must also meet all other program requirements to be determined to be a drug or biological. Combination drugs are also included in the definition of drugs if the combination itself or all of the therapeutic ingredients of the combination are included, or approved for inclusion, in any of the above drug compendia.

Drugs and biologicals are considered approved for inclusion in a compendium if approved under the established procedure by the professional organization responsible for revision of the compendium.

Drugs that are usually self-administered by the patient, such as those in pill form, or are used for self-injection, are generally not covered by Part B. However, there are a limited number of self-administered drugs that are covered because the Medicare statute explicitly provides coverage. Examples of drugs that are usually self-administered by the patient and are covered include: blood thinning factors, drugs used in immunosuppressive therapy, erythropoietin for dialysis patients, and osteoporosis drugs for certain homebound patients. [See the Medicare Advantage Policy Guideline titled](#) Self-Administered Drug(s) (SAD) Generally when a physician gives a patient pills or other oral medication, these drugs are excluded from coverage since the form of the drug is self-administered. Similarly, if a physician gives a patient an injection that is usually self-injected this drug is excluded from coverage, unless administered to the patient in an emergency situation.

In order to meet all the general requirements for coverage under the incident-to provision, an FDA approved drug or biological must be of a form that cannot be self-administered and must be administered by a physician or by auxiliary personnel employed by him/her under his/her personal supervision. To be covered, drugs and biologicals must be an expense to the physician billing for the service. For example, if a patient purchases a drug and the physician administers it, the drug is not covered. However, the administration of the drug, regardless of the source, is a service that represents an expense to the physician. Therefore, administration of the drug is payable if the drug would have been covered if the physician purchased it.

Use of the drug or biological must be safe and effective and otherwise reasonable and necessary. Drugs or biologicals and cancer chemotherapeutic agents approved for marketing by the Food and Drug Administration (FDA) are considered safe and effective for purposes of this requirement when used for indications specified on the label.

Therefore, payment may be made for an FDA-approved chemotherapeutic drug or biological, if:

- It was injected on or after the date of the FDA’s approval;
- It is reasonable and necessary for the individual patient; and
- All other applicable coverage requirements are met.

An unlabeled use of a drug is a use that is not included as an indication on the drug’s label as approved by the FDA. FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the contractor determines the use to be medically accepted, taking into consideration the major drug

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compendia, authoritative medical literature and/or accepted standards of medical practice. The following guidelines identify three categories in which medications would not be reasonable and necessary according to accepted standards of medical practice.

- **Not for Particular Illness** - Medications given for a purpose other than the treatment of a particular condition, illness, or injury are not covered (except for certain immunizations).

- **Injection Method Not Indicated** - Medication given by injection (parenterally) is not covered if standard medical practice indicates that the administration of the medication by mouth (orally) is effective and is an accepted or preferred method of administration.

- **Excessive Medications** - Medications administered for treatment of a disease which exceed the frequency or duration of injections indicated by accepted standards of medical practice are not covered.

If a medication is determined not to be reasonable and necessary for diagnosis or treatment of an illness or injury according to these guidelines, the entire charge will be excluded (i.e., for both the drug and its administration). Also excluded from payment is any charge for other services (such as office visits) which are primarily for the purpose of administering a non-covered injection (i.e., an injection that is not reasonable and necessary for the diagnosis or treatment of an illness or injury).

- A drug that is less than effective is not eligible for reimbursement, i.e., one that the Food and Drug Administration has determined to lack substantial evidence of effectiveness for all labeled indications. Any other drug product that is identical, similar, or related, will also be ineligible.

- If a use is identified as not indicated by CMS or the FDA or if a use is specifically identified as not indicated (in one or more of the three compendia mentioned) or if it is determined (based on peer reviewed medical literature) that a particular use of a drug is not safe and effective, the off-label usage is not supported and, therefore, the drug is not covered. In this instance, the administration is also not covered.

**Medicare Benefit Policy Manual - Pub. 100-02, Chapter 15, Section 50**, describes national policy regarding Medicare guidelines for coverage of drugs and biologicals.

Coverage for medication is based on the patient's condition, the appropriateness of the dose and route of administration, based on the clinical condition and the standard of medical practice regarding the effectiveness of the drug for the diagnosis and condition. The drug must be used according to the indication and protocol listed in the accepted compendia ratings listed below.

- National Comprehensive Cancer Network (NCCN) Drugs and Biologies Compendium
- Thomson Micromedex DrugDex
- American Hospital Formulary Service-Drug Information (AHFS-DI)
- Clinical Pharmacology

The compendia employ various rating and recommendation systems that may not be readily cross-walked from compendium to compendium. In general, a use is identified by a compendium as medically accepted if the:

- Indication is a Category 1 or 2A in NCCN
- Class I, Class IIa, or Class IIb in DrugDex; or,
- Narrative text in AHFS or Clinical Pharmacology is supportive.

Self-administered drugs are not covered and should not be submitted to UnitedHealthcare unless requested to do so by the beneficiary. [See the Medicare Advantage Policy Guideline titled Self-Administered Drug(s) (SAD).]

**Documentation Requirements**

The patient's medical record should contain documentation that fully supports the medical necessity for the administration of the denosumab (Prolia). For postmenopausal osteoporosis at high risk for fracture such documentation should include 1 through 5 and for men the documentation should include 2 through 5, but is not limited to:

- Patient's age, sex and menopausal status.
- Documentation supporting the diagnosis of osteoporosis.
- Previous treatment of osteoporosis, agents used, outcomes and adverse reactions if any.
- History of previous fractures, including type of fracture, cause and time since occurrence.
- Risk factors for future fracture including preventive measures.

The patient's medical record should contain documentation that fully supports the medical necessity for the administration of the denosumab (Xgeva). Such documentation should include, but is not limited to documentation of bone metastasis from a solid tumor and adequate calcium levels as well as the use of Vitamin D if indicated.
APPLICABLE CODES

The following list(s) of codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

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<th>HCPCS Code</th>
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<td>J0897</td>
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<td>EJ</td>
<td>Subsequent claims for a defined course of therapy, e.g., EPO, sodium hyaluronate, infliximab</td>
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ICD-10 Diagnosis Codes

Xgeva®, Prolia® (Denosumab): ICD-10 Diagnosis Code List

DEFINITIONS

Off-Label Drug Use: An off-label/unlabeled use of a drug is defined as a use for a non-FDA approved indication, that is, one that is not listed on the drug's official label/prescribing information. An indication is defined as a diagnosis, illness, injury, syndrome, condition, or other clinical parameter for which a drug may be given. Off-label use is further defined as giving the drug in a way that deviates significantly from the labeled prescribing information for a particular indication. This includes but is not necessarily limited to, dosage, route of administration, duration and frequency of administration, and population to whom the drug would be administered. Drugs used for indications other than those in the approved labeling may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literatures and/or accepted standards of medical practice. Determinations as to whether medication is reasonable and necessary for an individual patient are made on appeal on the same basis as all other such determinations (i.e., with support from the peer-reviewed literature, with the advice of medical consultants, with reference to accepted standards of medical practice, and in consideration of the medical circumstance of the individual case).

PURPOSE

The Medicare Advantage Policy Guideline documents are generally used to support UnitedHealthcare Medicare Advantage claims processing activities and facilitate providers' submission of accurate claims for the specified services. The document can be used as a guide to help determine applicable:
- Medicare coding or billing requirements, and/or
- Medical necessity coverage guidelines; including documentation requirements.

UnitedHealthcare follows Medicare guidelines such as LCDs, NCDs, and other Medicare manuals for the purposes of determining coverage. It is expected providers retain or have access to appropriate documentation when requested to support coverage. Please utilize the links in the References section below to view the Medicare source materials used to develop this resource document. This document is not a replacement for the Medicare source materials that outline Medicare coverage requirements. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

REFERENCES

CMS Local Coverage Determinations (LCDs)

<table>
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<th>LCD</th>
<th>Medicare Part A</th>
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<td>L33270 (Bisphosphonates (Intravenous [IV]) and Monoclonal Antibodies in the Treatment of Osteoporosis and Their Other Indications) First Coast</td>
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### LCD

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<td>L33394 (Drugs and Biologicals, Coverage of, for Label and Off-Label Uses) NGS</td>
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### CMS Articles

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<td>A52399 (Denosumab (Prolia™, Xgeva™) - Related to LCD L33394) NGS</td>
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<td>A52424 (Denosumab (Prolia™, Xgeva™)) CGS</td>
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<td>A52855 (Drugs and Biologicals, Coding Article) NGS</td>
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### CMS Benefit Policy Manual

**Chapter 15: § 50 Drugs and Biologicals**

### CMS Claims Processing Manual

**Chapter 17: § 40 Discarded Drugs and Biologicals**

**Chapter 32 Billing Requirements for Special Services**

### CMS Transmittals

**Transmittal 2378, Change Request 7682, Dated 12/29/2011 (January 2012 Update of the Ambulatory Surgery Center Payment System (ASC))**

### MLN Matters

**Article MM7672, January 2012 Update of the Hospital Outpatient Prospective Payment System (OPPS)**

### Others

**Chemo and Biological Drug Chart**

**CGS Coding, Drugs and Biological Drug Chart, CMS Website**

**Medicare Program Integrity Manual, Chapter 13 Local Coverage Determinations; § 13.5.1 Reasonable and Necessary Provisions in LCDs**

**NCCN Drugs & Biologics Compendium, National Comprehensive Cancer Network Website**

Social Security Act (Title XVIII) Standard References, Sections:

- 1862(a)(1)(A) Medically Reasonable & Necessary
- 1862(a)(1)(D) Investigational or Experimental
- 1833(e) Incomplete Claim
- 1861(t) (1) Drugs and Biologicals

### GUIDELINE HISTORY/REVISION INFORMATION

Revisions to this summary document do not in any way modify the requirement that services be provided and documented in accordance with the Medicare guidelines in effect on the date of service in question.

<table>
<thead>
<tr>
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| 05/01/2019 | • Reorganized policy template; relocated Terms and Conditions and Purpose section  
|           | • Reformatted list of applicable ICD-10 diagnosis codes |
| 12/12/2018 | • ICD updates from sourcing                             |

### TERMS AND CONDITIONS

The Medicare Advantage Policy Guidelines are applicable to UnitedHealthcare Medicare Advantage Plans offered by UnitedHealthcare and its affiliates.

These Policy Guidelines are provided for informational purposes, and do not constitute medical advice. Treating physicians and healthcare providers are solely responsible for determining what care to provide to their patients. Members should always consult their physician before making any decisions about medical care.

Benefit coverage for health services is determined by the member specific benefit plan document* and applicable laws that may require coverage for a specific service. The member specific benefit plan document identifies which services...
are covered, which are excluded, and which are subject to limitations. In the event of a conflict, the member specific benefit plan document supersedes the Medicare Advantage Policy Guidelines.

Medicare Advantage Policy Guidelines are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support UnitedHealthcare coverage decision making. UnitedHealthcare may modify these Policy Guidelines at any time by publishing a new version of the policy on this website. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the Medicare Advantage Policy Guidelines is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

You are responsible for submission of accurate claims. Medicare Advantage Policy Guidelines are intended to ensure that coverage decisions are made accurately based on the code or codes that correctly describe the health care services provided. UnitedHealthcare Medicare Advantage Policy Guidelines use Current Procedural Terminology (CPT®), Centers for Medicare and Medicaid Services (CMS), or other coding guidelines. References to CPT® or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee claims payment.

Medicare Advantage Policy Guidelines are the property of UnitedHealthcare. Unauthorized copying, use and distribution of this information are strictly prohibited.

*For more information on a specific member's benefit coverage, please call the customer service number on the back of the member ID card or refer to the Administrative Guide.