PROLIA® (denosumab)

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human receptor activator of nuclear factor kappa-B ligand (RANKL). Prolia binds to RANKL and prevents it from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

In many individuals, Prolia may lower calcium levels and ongoing monitoring is recommended. Hypocalcemia is a contraindication to Prolia treatment. If an individual develops hypocalcemia while on Prolia and is unable to take supplemental calcium, taking Prolia may be contraindicated.
PROLIA (denosumab) (cont.)

Definitions:

T-Scores are reported as standard deviations (SD) World Health Organization (WHO) criteria:
Normal: T-score within 1 SD
Osteopenia: T-score of -1 to -2.5 SD
Osteoporosis: T-score of -2.5 or worse SD
Severe Osteoporosis: T-score of -2.5 or worse SD with fragility fractures

High risk for fracture is defined as ONE of the following:

▪ Osteoporotic fracture
▪ Multiple risk factors for fracture (significantly low bone mass, frequent falls, limited movement, medical conditions likely to cause bone loss, medicines that may cause bone loss, e.g., seizure medicines, blood thinners, corticosteroids, high doses of vitamins A or D)
▪ Failed response (as defined by prescribing provider) to previous osteoporosis therapy
▪ Intolerant to previous osteoporosis therapy

Fragility fracture:
▪ A fracture occurring spontaneously or after a minor trauma.

Fracture Risk Assessment Tool (FRAX tool):
The World Health Organization developed a risk assessment tool to assist providers in evaluating osteopenic individuals. The tool uses clinically proven risk factors to determine a 10 year probability of hip fracture and a 10 year probability for a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fractures). Treatment may be considered if the 10-year risk is 3% or more for hip fracture or if the risk for other bone fracture is 20% or more.

The tool can obtained at https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

Osteonecrosis of the jaw (ONJ): According to the American College of Rheumatology, ONJ can be diagnosed by the presence of exposed bone on oral examination, lasting more than eight weeks.

ONJ risk factors include: invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

Adult: Age 18 years and older
PROLIA (denosumab) (cont.)

Criteria:

Effective 03/01/18: For site of service requirements for Prolia, see BCBSAZ Medical Coverage Guideline #O1008, “Site of Service Requirements for Certain Medications”.

See Resources section for FDA-approved dosage and Glucocorticoid Equivalencies table.

- Initiation of Prolia for existing members or continued use of Prolia for members on Prolia therapy prior to their BCBSAZ original effective date (OED) of coverage is considered **medically necessary** with documentation of **ALL** of the following:

1. **ONE** of the following diagnosis:
   - Postmenopausal woman with osteoporosis at high risk for fracture
   - To increase bone mass in a woman at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
   - To increase bone mass in men with osteoporosis at high risk for fracture
   - To increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
   - Glucocorticoid-induced osteoporosis in men and woman at high risk for fracture associated with initiating or continuing systemic glucocorticoids in a daily dose equivalent to 7.5 mg or more of prednisone and expected to remain on glucocorticoids for a minimum of 6 months

2. **ONE** of the following:
   - A **female** with a T-score of -2.5 or worse (e.g., -3.0, -3.5, etc.), with or without osteoporotic fracture
   - A **male** with a T-score of -2.0 or worse at the lumbar spine or femoral neck, with or without osteoporotic fracture
   - T-score of -1.0 or worse at the lumbar spine or femoral neck with a history of prior fragility fracture
   - A low trauma fragility bone fracture
   - High risk for fracture as evidenced by multiple factors such as significantly low bone mass, frequent falls, limited movement, medical conditions likely to cause bone loss, medicines that may cause bone loss, (e.g., seizure medicines, blood thinners, corticosteroids, high doses of vitamins A or D)
   - A FRAX 10-year probability risk of 3% or more for a hip fracture **OR** 20% or more for other bone fracture, as assessed by the World Health Organization Fracture Risk Assessment Tool (FRAX tool) that can be obtained at: [https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9](https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9)
PROLIA (denosumab) (cont.)

Criteria: (cont.)

- Initiation of Prolia for existing members or continued use of Prolia for members on Prolia therapy prior to their BCBSAZ original effective date (OED) of coverage is considered **medically necessary** with documentation of **ALL** of the following: (cont.)

3. Individual has failed, or is intolerant to, or has a contraindication to at least TWO of the following agents:
   - Alendronate
   - Etidronate
   - Ibandronate
   - Risedronate
   - Zoledronic acid

4. Individual of child bearing potential is not pregnant prior to initiating Prolia
5. Individual of child bearing potential must use effective contraception during and after Prolia therapy
6. No evidence of hypocalcemia, has a serum calcium or corrected serum calcium within the normal range
7. Absence of hypersensitivity to the active substance or to any of the excipients
8. Individual is receiving supplemental calcium **and** vitamin D with doses adjusted per usual laboratory monitoring
9. Individual is not receiving another agent with the same active ingredient denosumab
10. A routine oral examination must be performed by a medical provider or dentist prior to treatment. Individuals with risk factors for ONJ (see Definition section) should receive appropriate preventive dentistry prior to initiation of Prolia.
PROLIA (denosumab) (cont.)

Criteria: (cont.)

- Continuation of coverage for members already approved by BCBSAZ is considered **medically necessary** with documentation of **ALL** of the following:

  1. Achieved and maintains **TWO** of the following:
     - Reduced incidence of new vertebral fractures in previously undeformed vertebrae
     - Reduced incidence of non-vertebral fractures (e.g., ankle/foot, hip, humerus, pelvis, wrists, or other sites)
     - Increased bone mineral density (e.g., lumbar spine, femoral neck, or total hip)

  2. Individual is receiving supplemental calcium and vitamin D with doses adjusted per usual laboratory monitoring

  3. Individual is not receiving another agent with the same active ingredient denosumab

  4. Individual has not developed any unacceptable drug toxicity, contraindications or other exclusions to its continued use

- Prolia for all other indications not previously listed or if above criteria not met is considered **experimental or investigational** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and

  2. Insufficient evidence to support improvement of the net health outcome.

These indications include, **but are not limited to:**

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
PROLIA (denosumab) (cont.)

Resources:

Literature reviewed 07/05/18. We do not include marketing materials, poster boards and non-published literature in our review.


Prolia™ (denosumab). Package Insert. 05/18/2018:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>•For the treatment of postmenopausal women with osteoporosis at high risk for fracture.</td>
<td>The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months.</td>
</tr>
<tr>
<td>•Treatment to increase bone mass in men with osteoporosis at high risk for fracture.</td>
<td></td>
</tr>
<tr>
<td>•Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>•Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.</td>
<td></td>
</tr>
<tr>
<td>•Treatment of glucocorticoid-induced osteoporosis in men and woman at high risk for fracture</td>
<td></td>
</tr>
<tr>
<td>Safety and effectiveness of PROLIA have not been established in pediatric patients.</td>
<td></td>
</tr>
</tbody>
</table>
PROLIA (denosumab) (cont.)

Resources: (cont.)

Initial Approval Duration:
3 months

Renewal Approval Duration:
12 months

Glucocorticoid Equivalencies:

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.75 mg</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25 mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5 mg</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4 mg</td>
</tr>
</tbody>
</table>
PROLIA (denosumab) (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah níllingíí Blue Cross Blue Shield of Arizona haada yít’éego bína’ídíldíkgo éi doodago Háída bíjá aniyeedígíí t’áadoof le’í yina’ídíldíkgo bee hazaad’ehí háká a’doowolggo bee haza’ doo báah ilílgíó. Atá’ halne’íígi kojí bích’í hodílínih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thợ dịch viên, xin gọi 877-475-4799.

Arabic:
إذا كنت او أدى شخص تسامحه أسئلة بخصوص الضرورية بلغتك من دون أي تكلفة ، للتحدث مع مترجم القبل. 877-475-4799.
PROLIA (denosumab) (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay maaaring katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuhang tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumanaw sa 877-475-4799.

Korean: 만약 궁할 또는 궁할이 들고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 가까이 절으면 궁할의 궁할을 궁할히 연락을 비용 부담없이 접할 수 있는 권리가 있습니다. 그렇게 하시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳をお尋ねされる場合、877-475-4799 までお電話ください。

Farsi: 

از کدام کاری که شما به آن یا کمک می‌کنید، سوالات مورد اطلاعات به زبان یا به طاهر وایگان در ورودی گفتنی 877-475-4799 و به همکاری نمایید.

Assyrian:

Blue Cross Blue Shield of Arizona

Serbo-Croatian: Ukoliko Vi ili neko kom Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobiête pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคุณและส่งถึงกันทราบถึง Blue Cross Blue Shield of Arizona คุณสามารถจะได้รับความช่วยเหลือและข้อมูลภาษา ของคุณโดยไม่ต้องจ่ายค่า ที่สาย 877-475-4799