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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.
PROLIA (denosumab) (cont.)

Description:

Prolia 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.

Definitions:

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:

See Resources section for FDA-approved dosage.

- 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 **ONE** of the following:

  1. Female with **ALL** of the following:

     - **ONE** of the following:
       - T-score of -2.5 or worse (e.g., -3.0, -3.5), 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
       - 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)
       - Receiving adjuvant aromatase inhibitor therapy for breast cancer and individual is intolerant to a bisphosphonate or has contraindication to a bisphosphonate
       - Failed response (as defined by prescribing provider) to previous osteoporosis therapy
       - Intolerant to previous osteoporosis therapy

     - No evidence of hypocalcemia, with calcium or corrected calcium within the normal range
     - Individual is receiving supplemental calcium and vitamin D
     - Individual is not receiving another agent with the same active ingredient denosumab
     - Absence of hypersensitivity to the active substance or to any of the excipients
     - Dental examination with appropriate preventive dentistry, prior to treatment with Prolia in individuals with risk factors for ONJ
     - Individual of child bearing potential is on effective contraception prior to initiation of therapy until postmenopausal status is fully established
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 ONE of the following: (cont.)

2. Male at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer and ALL of the following:
   - ONE of the following:
     - T-score at the lumbar spine, total hip or femoral neck of -1.0 or worse
     - History of an osteoporotic fracture or fragility fracture
   - No evidence of hypocalcemia, with calcium or corrected calcium within the normal range
   - Individual is receiving supplemental calcium and vitamin D
   - Individual is not receiving another agent with the same active ingredient denosumab
   - Absence of hypersensitivity to the active substance or to any of the excipients
   - Dental examination with appropriate preventive dentistry, prior to treatment with Prolia in individuals with risk factors for ONJ

3. Male with ALL of the following:
   - ONE of the following:
     - 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
     - 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)
     - Failed response (as defined by prescribing provider) to previous osteoporosis therapy
     - Intolerant to previous osteoporosis therapy
   - No evidence of hypocalcemia, with calcium or corrected calcium within the normal range
   - Individual is receiving supplemental calcium and vitamin D
   - Individual is not receiving another agent with the same active ingredient denosumab
   - Absence of hypersensitivity to the active substance or to any of the excipients
   - Dental examination with appropriate preventive dentistry, prior to treatment with Prolia in individuals with risk factors for ONJ
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. The individual has benefited from therapy but remains at high risk for development of osteoporotic fractures
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any 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

Resources:

*Literature reviewed 06/20/17. We do not include marketing materials, poster boards and non-published literature in our review.*


**PROLIA (denosumab) (cont.)**

**Resources:** (cont.)

Prolia™ (denosumab). Package Insert. 05/26/2017:

- 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></td>
<td>Safety and effectiveness of PROLIA have not been established in pediatric patients.</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/file/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 interprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah niiłiNiíí Blue Cross Blue Shield of Arizona haada yi’teego bìna’i’dilkidgo éí doodago Háìda bìjá aniyeédígíí t’áado le’é yìna’i’dilkidgo bee хаахаááanií hólo díí t’aá hazaad’ek’ehí háká a’dooowolgo bee хаa’ doo báąh ilínígóló. Ata’ halne’ígíí koj’ bìch’í’ hodiilínih 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 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 thống dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعد أسلطة بخصوص Blue Cross Blue Shield of Arizona الضرورة بلغت من دون أي تكلفة .للتواصل مع مرتب تسجيل +1 877-475-4799.
PROLIA (denosumab) (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutuuan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makeasap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 돕역사와 얘기하기 위해서는 877-475-4799로 전화하십시오.

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。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi: 

آگر شما یا کسی که شما به او کمک می‌کنید، سوالی در مورد اطلاعاتی به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian: 

Blue Cross Blue Shield of Arizona ئایندا، ئینی نین نیشکری مۆر نین، نین بگوو، نین مۆسه، وەکەکە ئایندا، ئایندا نین نین بگوو، نین مۆرهە، ئایندا 877-475-4799.

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

Thai: หากคุณ หรือคนที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่เสียค่าใช้จ่าย โปรดโทรตาม โทร 877-475-4799.