XGEVA™ (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.

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.
XGEVA (denosumab) (cont.)

**Description:**

XGEVA™ (denosumab) is a human monoclonal antibody and a RANK Ligand (RANKL) inhibitor indicated for the prevention of skeletal-related events (SKEs) (e.g., pathologic fractures and spinal cord compression) in individuals with multiple myeloma and individuals with bone metastases from solid tumors. When tumor cells invade bone, bone cells increase production of RANKL which drives formation and survival of osteoclasts, leading to bone resorption and destruction. XGEVA binds RANKL, preventing maturation of osteoclasts and decreasing bone resorption and destruction.

**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
XGEVA (denosumab) (cont.)

Criteria:

See Resources section for FDA-approved dosage.

- XGEVA is considered *medically necessary* with documentation of **ALL** of the following:

  1. **ONE** of the following:
     - Prevention of skeletal-related events in individuals 18 years of age or older with multiple myeloma
     - Prevention of skeletal-related events in individuals 18 years of age or older with bone metastases from solid tumors
     - Treatment of giant cell tumor of the bone in individuals 13 years of age or older who are skeletally mature (radiographic evidence of epiphyseal closure) **AND** giant cell tumor of bone is unresectable **OR** surgical resection is likely to result in severe morbidity
     - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy in individuals 18 years of age or older

  2. Not concurrently treated with another agent with the same active ingredient denosumab
  3. Absence of hypersensitivity to the active substance or to any of the excipients
  4. 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 XGEVA.
  5. No evidence of hypocalcemia, with calcium or corrected calcium within the normal range
  6. Individual is receiving supplemental calcium and vitamin D when used in **EITHER** bone metastasis from solid tumor **OR** giant cell tumor of bone
  7. Individual of child bearing potential is not pregnant prior to initiation of therapy and is on effective contraception thereafter

- **XGEVA** 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
**XGEVA (denosumab) (cont.)**

**Resources:**

Literature reviewed 03/07/18. We do not include marketing materials, poster boards and non-published literature in our review.

Xgeva Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the prevention of skeletal-related events in patients with multiple</td>
<td>The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. Correct</td>
</tr>
<tr>
<td>myeloma and bone metastases from solid tumors.</td>
<td>hypocalcemia prior to initiating Xgeva. Monitor calcium levels and administer calcium, magnesium and vitamin D as necessary to treat or prevent</td>
</tr>
<tr>
<td></td>
<td>hypocalcemia.</td>
</tr>
<tr>
<td></td>
<td>Monitor for symptoms of osteonecrosis of the jaw. Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and</td>
</tr>
<tr>
<td></td>
<td>periodically during Xgeva therapy.</td>
</tr>
<tr>
<td></td>
<td>Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of</td>
</tr>
<tr>
<td></td>
<td>Xgeva.</td>
</tr>
<tr>
<td></td>
<td>Pediatric patients: Safety and efficacy has not been established.</td>
</tr>
<tr>
<td>Treatment of adults and skeletally mature adolescents with giant cell</td>
<td>The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first</td>
</tr>
<tr>
<td>tumor of bone that is unresectable or where surgical resection is likely</td>
<td>month of therapy in the upper arm, upper thigh, or abdomen. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and administer</td>
</tr>
<tr>
<td>to result in severe morbidity.</td>
<td>calcium, magnesium and vitamin D as necessary to treat or prevent hypocalcemia. Monitor for symptoms of osteonecrosis of the jaw. Perform an oral</td>
</tr>
<tr>
<td></td>
<td>examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise females of</td>
</tr>
<tr>
<td></td>
<td>reproductive potential of potential risk to the fetus and to use highly effective contraception and for at least 5 months after the last dose of Xgeva.</td>
</tr>
<tr>
<td></td>
<td>Pediatric patients: The safety and efficacy of Xgeva have not been established in pediatric patients except in skeletally mature adolescents with giant cell tumors in the bone.</td>
</tr>
</tbody>
</table>
XGEVA (denosumab) (cont.)

Resources: (cont.)

Xgeva Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy | The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy in the upper arm, upper thigh, or abdomen. 
Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and administer calcium, magnesium and vitamin D as necessary to treat or prevent hypocalcemia. 
Monitor for symptoms of osteonecrosis of the jaw. Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. 
Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. 
Pediatric patients: Safety and efficacy has not been established. |
XGEVA (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 intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah nilínií Blue Cross Blue Shield of Arizona haadá yít’éego bína’idílikidgo éi doodago Háida bíjá anilyeeedíí t’áado le’í yína’idílikidgo beehaz’áaníi hólo díí t’áá hazaadk’éhíí háká a’dooallowgo bee haz’a doo báah ilínígóó. Ata’ halne’ígií koij’ bich’í’ hodilínih 877-475-4799.

Chinese: 如果您，或是您正在协助的对象，有关于插入项目的名称 Blue Cross Blue Shield of Arizona 方面的问题，您有权免费以您的母语得到帮助和讯息。洽询一位翻译员。请拨电话 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: لذا، يمكن للدكتور الحق في الحصول على المساعدة والمعلومات عن Blue Cross Blue Shield of Arizona من دون أي تكلفة، للتحدث مع مترجم اتصل ب 877-475-4799.
XGEVA (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, maaaring karatang na makakuhang ilong at impormasyon sa iyong wika ng walang gastos. Upunang makeasap ang isang tagsalas, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 하시려면 여기서는 877-475-4799 로 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 sans 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。通訳をお提供する場合、877-475-4799 までお電話ください。

Farsi: اگر شما یا کسی که شما با او کمک می‌کنید، سوالی در مورد اطلاعاتی باید بپردازد یا بتوانید به طور رایگان دریافت نمایید 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona, دەکەیە بە زبانەکەی کە لەوەکەیە لەوەکەیە لە دەکەیە بە زبانەکەی کە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە لەوەکەیە. 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 dobijate pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ขอความช่วยเหลือและข้อมูลในภาษาของคุณได้โดยไม่เสียเงิน ติดต่อเราที่ 877-475-4799.