Denosumab - Oncology Medical Drug Criteria with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
3/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Xgeva® (denosumab) Subcutaneous use	• Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumors • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or resection likely to result in severe morbidity • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Giant cell tumor of bone(2)	Giant cell tumor of bone (GCTB) is a rare benign primary tumor of the bone predominant in young adults. In the United States, GCTB accounts for approximately 3 to 5 percent of all primary bone tumors and 15 to 20 percent of all benign bone tumors. GCTB usually occurs after skeletal maturity, with a peak incidence in patients between 20 and 39 years old. Intralesional excision with or without an effective adjuvant is an adequate primary treatment for resectable tumors. Serial embolizations and/or denosumab are preferred options for lesions that are resectable with unacceptable morbidity or unresectable axial lesions as primary treatment in the National Comprehensive Cancer Network (NCCN) guidelines. Interferon-alfa-2b is also another primary treatment option.(2)
Multiple myeloma(3)	The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for Multiple Myeloma recommend bisphosphonates or denosumab as preventative options for skeletal-related events for all patients receiving primary treatment. The preferred bisphosphonate in NCCN guidelines is zoledronic acid for these events. If the patient has renal insufficiency NCCN prefers denosumab over bisphosphonates.
Prostate cancer(4)	The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for (prostate cancer) prefer denosumab (category 1, preferred) to zoledronic acid to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.
Solid tumor(5-8)	The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for several solid tumor types (i.e., thyroid, non-small cell lung cancer, kidney cancer, breast cancer, prostate cancer) recommend IV bisphosphonates or sub-cutaneous

	denosumab as therapeutics options to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.
Hypercalcemia of malignancy	Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases. There are three major mechanisms by which hypercalcemia of malignancy can occur: tumor secretion of parathyroid hormone-related protein, osteolytic metastases with local release of cytokines, and tumor production of 1,25-dihydroxyvitamin D (calcitriol).(9) Mild hypercalcemia is defined as calcium between 10.5 and 11.9 mg/dL. Moderate hypercalcemia is defined as calcium between 12 and 13.9 mg/dL. Severe hypercalcemia is defined as calcium greater than or equal to 14 mg/dL. Calcium in serum is bound to proteins, principally albumin. As a result, total serum calcium concentrations in patients with low or high serum albumin levels may not accurately reflect the physiologically important ionized (or free) calcium concentration. In patients with hypoalbuminemia or hyperalbuminemia, the measured serum calcium concentration should be corrected for the abnormality in albumin or for standard units.(10,11) While evidence-based guidelines are lacking, in individuals with only mildly symptomatic disease immediate treatment can be deferred and the calcium may self correct. In patients with moderate hypercalcemia therapy should be based on symptoms and the clinician. Given the efficacy, tolerability, and cost effectiveness of the treatments involved, it may be reasonable to treat such individuals similar to those with more severe degrees of hypercalcemia. Patients with severe hypercalcemia should be promptly treated with current available regimens.(12) Treatment of the underlying malignancy is always the primary goal of therapy. However, additional therapies, especially for moderate to severe hypercalcemia are essential when simultaneously treating the underlying malignancy. Bisphosphonates are first-line therapy and the mainstay for long-term therapy. Through direct mechanisms they induce osteoclast apoptosis, and indirectly by acting on the osteoblasts they can reduce osteoclastic bone resorption. Bisphosphonates affect proliferation and differentiation of osteoblasts and prevent their apoptosis, and they can also neutralize the RANKL-mediated stimulation of osteoclasts. After receiving the first dose of pamidronate or zoledronic acid patients can be retreated if serum calcium does not return to normal or remain normal. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.(10,11)
Efficacy(1)	Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.
Efficacy - Bone metastases from solid tumors(1)	The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized, double-blind, active-controlled, non-inferiority trials (Study 20050136, Study 20050244, and Study 20050103) comparing Xgeva with zoledronic acid. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE. An SRE was defined as any of the following: pathologic fracture,

radiation therapy to bone, surgery to bone, or spinal cord compression. The results of these studies are summarized in the table below.

	Study 20050136 Metastatic Breast Cancer		**Study 20050244 Metastatic Solid Tumors or Multiple Myeloma**		**Study 20050103 Metastatic CRPC***	
	Xgeva N=1026	**Zoledronic Acid N=1020**	**Xgeva N=866**	**Zoledronic Acid N=890**	**Xgeva N=950**	**Zoledronic Acid N=951**
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21(2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR**	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71 ,0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	less than 0.001		less than 0.001		less than 0.001	
Superiority p-value***	0.010		0.060		0.008	
First and Subsequent SRE**						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value***	0.001		0.145		0.009	

*CRPC = castrate-resistant prostate cancer

**NR = not reached

***Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid with trial

****All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event

Adjusted p-values are presented

<table>
<tr>
<td>Efficacy - Multiple myeloma(1)</td>
<td>The efficacy of Xgeva for the prevention of skeletal-related events (SRE) in newly diagnosed multiple myeloma patients was evaluated in an international, randomized, double-blind, active-controlled, non-inferiority trial (Study 20090482) comparing Xgeva with zoledronic acid. The main efficacy outcome measure was non-inferiority of time to first SRE. Additional efficacy outcome measures were superiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results of this study are summarized in the table below.

<table>
<tr><th></th><th colspan="2">Study 20090482

Multiple Myeloma</th></tr>
<tr><th></th><th>Xgeva

N = 859</th><th>Zoledronic Acid

N = 859</th></tr>
<tr><td>First On-study SRE</td><td colspan="2"></td></tr>
<tr><td>Number of Patients who had SREs (%)</td><td>376 (43.8)</td><td>383 (44.6)</td></tr>
<tr><td>Components of First SRE</td><td colspan="2"></td></tr>
<tr><td>Radiation to Bone</td><td>47 (5.5)</td><td>62 (7.2)</td></tr>
<tr><td>Pathological Fracture</td><td>342 (39.8)</td><td>338 (39.3)</td></tr>
<tr><td>Surgery to Bone</td><td>37 (4.3)</td><td>48 (5.6)</td></tr>
<tr><td>Spinal Cord Compression</td><td>6 (0.7)</td><td>4 (0.5)</td></tr>
<tr><td>Median time to SRE (months)

(95% CI)</td><td>22.8

(14.7, NE*)</td><td>24

(16.6, 33.3)</td></tr>
<tr><td>Hazard Ratio (95% CI)</td><td colspan="2">0.98 (0.85, 1.14)</td></tr>
</table>
*NE = not estimable</td>
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<td>Efficacy - Giant cell tumor of bone(1)</td>
<td>The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Study 20062004 and Study 20040215) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity.

Study 20062004 was a single arm, pharmacodynamic, and proof concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic imaging (MRI) obtained within 28 prior to study enrollment.

Study 20040215 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease; Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity; Cohort 3 enrolled 11 patients who previously participated in Study 20062004.</td>
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	The primary endpoint in both Study 20062004 and Study 20040215 was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The RECIST 1.1 overall in both studies was 25% (95% CI; 19,32). All responses were partial responses.
Efficacy - Hypercalcemia of malignancy(1)	The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Study 20070315) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy. In this trial. refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of greater than 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of Xgeva therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium less than or equal to 11.5 mg/dL. A complete response was defined as corrected serum calcium less than or equal to 10.8 mg/dL. By day ten 63.6% had a response (95% CI). The median time to response was 9 days (95% CI), and the median duration of response was 104 days (95% CI). By day ten 36.4% of patients had a complete response (95% CI). The median time to complete response was 23 days (95% CI) and the median duration of complete response was 34 days (95% CI).
Safety(1)	Hypocalcemia is contraindicated when using denosumab. The patient's calcium level should be corrected prior to use. This agent should not be used in pregnancy as it may cause fetal harm. Osteonecrosis of the jaw (ONJ) has been reported with the use of denosumab. A routine oral exam should be performed by the prescriber prior to therapy initiation and appropriate preventive dentistry should be considered prior to therapy in patients with risk factors for ONJ. Good oral hygiene should be maintained during therapy with denosumab. Denosumab carries the following contraindications: • Hypocalcemia • Known hypersensitivity to denosumab For additional clinical information see the Prime Therapeutics Formulary Chapter 4.9A Calcium Regulators/ Osteoporosis Agents.

REFERENCES

Number	Reference
1	Xgeva prescribing information. Amgen pharmaceuticals. June 2020.
2	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Bone Cancer. Version 2.2022.
3	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Multiple Myeloma. Version 5.2022.
4	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Prostate Cancer. Version 4.2022.
5	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology – Thyroid Cancer. Version 2.2022.

Number	Reference
6	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology – Non-Small Cell Lung Cancer. Version 3.2022.
7	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology – Kidney Cancer. Version 4.2022.
8	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Breast Cancer. Version 3.2022.
9	Goldner W. Cancer-Related Hypercalcemia. DOI 10.1200/JOP.2016.011155 Journal of Oncology Practice 12, no. 5 (May 1 2016) 426-432.
10	Aredia Prescribing Information. Novartis Pharmaceutical Corporation. May 1998.
11	Zometa Prescribing Information. Novartis Pharmaceutical Corporation. December 2018.
12	Sternlicht H, Glezeman IG. Hypercalcemia of malignancy and new treatment options. Ther Clin Manag. 2015; 11: 1779-1788.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
J0897	Xgeva	Denosumab Inj 120 MG/1.7ML	120 MG/1.7ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Xgeva	Denosumab Inj 120 MG/1.7ML	120 MG/1.7 ML	1.0	SYRNG	28	Days				

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Xgeva	Denosumab Inj 120 MG/1.7ML	120 MG/1.7ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Xgeva	Denosumab Inj 120 MG/1.7ML	120 MG/1.7ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL the following are met: 1. ONE of the following: A. If the requested agent is eligible for continuation of therapy, BOTH of the following: **Agents Eligible for Continuation of Therapy** Xgeva (denosumab) 1. ONE of the following: A. Information has been provided that indicates the patient has been treated with the requested agent within the past 180 days **OR** B. The prescriber states the patient has been treated with the requested agent within the past 180 days AND is at risk if therapy is changed **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to zoledronic acid or pamidronate (medical records required) **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to zoledronic acid or pamidronate (medical records required) **OR** C. The patient has an FDA labeled contraindication to zoledronic acid or pamidronate (medical records required) **OR** D. The requested agent is a NCCN category 1 preferred agent for the requested indication **OR** B. The patient has a diagnosis of multiple myeloma and BOTH of the following: 1. The request agent will be used for the prevention of skeletal-related events **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to pamidronate OR zoledronic acid (medical records required) **OR** B. The patient has an intolerance or hypersensitivity to pamidronate OR zoledronic acid (medical records required) **OR** C. The patient has an FDA labeled contraindication to BOTH pamidronate and zoledronic acid (medical records required) **OR** D. The patient has renal insufficiency **OR** E. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** C. The patient has a diagnosis of prostate cancer AND has documented bone metastases **OR** D. The patient has a diagnosis of breast cancer with documented bone metastases and ONE of the following: 1. The patient has tried and had an inadequate response to pamidronate OR zoledronic acid (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to pamidronate OR zoledronic acid (medical records required) **OR** 3. The patient has an FDA labeled contraindication to BOTH pamidronate and zoledronic acid (medical records required) **OR** 4. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** E. The patient has another solid tumor cancer diagnosis (e.g., thyroid, non-small cell lung, kidney cancer) with documented bone metastases and ONE of the following: 1. The patient has tried and had an inadequate response to zoledronic acid (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to zoledronic acid (medical records required) **OR** 3. The patient has an FDA labeled contraindication to zoledronic acid (medical records required) **OR** 4. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** F. The patient has a diagnosis of systemic mastocytosis and ONE of the following: 1. BOTH of the following: A. The patient has tried zoledronic acid (medical records required) **AND** B. The patient has persistent bone pain **OR** 2. The patient has an intolerance or hypersensitivity to zoledronic acid (medical records required) **OR** 3. The patient has an FDA labeled contraindication to zoledronic acid (medical records required) **OR** 4. The patient has renal insufficiency **OR** 5. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** G. The patient has a diagnosis of giant cell tumor of bone and BOTH of the following: 1. The patient is an adult or skeletally mature adolescent (must be greater than or equal to 12 years of age) **AND** 2. ONE of the following: A. The tumor is recurrent **OR** B. The tumor is unresectable **OR** C. Resection is likely to result in severe morbidity **OR** H. The patient has a diagnosis of hypercalcemia of malignancy and ONE of the following:

Module	Clinical Criteria for Approval
	1. BOTH of the following: (medical records required) A. The patient has had at least 2 doses of intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid) **AND** B. The patient has failed or is refractory to intravenous bisphosphonate therapy (i.e., albumin-corrected calcium of greater than or equal to 12.0 mg/dL [3.0 mmol/L]) **OR** 2. The patient has an intolerance or hypersensitivity to intravenous bisphosphonate therapy (medical records required) **OR** 3. The patient has an FDA labeled contraindication to intravenous bisphosphonate therapy (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with Prolia **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. ONE of the following: A. The requested quantity (dose) does NOT exceed the program quantity limit **OR** B. ALL of the following: 1. The requested quantity (dose) is greater than the program quantity limit **AND** 2. The requested quantity (dose) does not exceed the FDA labeled dose for the requested indication **AND** 3. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit **OR** C. ALL of the following: 1. The requested quantity (dose) is greater than the program quantity limit **AND** 2. The requested quantity (dose) is greater than the FDA labeled dose for the requested indication **AND** 3. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of approval:** 12 months