Denosumab - Oncology Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
06-30-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Osenvelt® (denosumab-bmwo) Subcutaneous injection	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 where surgical resection is likely to result in severe morbidity Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy		15
Wyost® (denosumab-bbdz) Subcutaneous injection	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 where surgical resection is likely to result in severe morbidity Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy		14
Xgeva® (denosumab) Subcutaneous injection	• 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 where surgical resection is 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	Giant cell tumor of bone (GCTB) is a rare benign primary tumor of the bone accounting for about 3% to 5% of all primary bone tumors that usually occurs after skeletal maturity between 20 and 40 years of age. Although typically benign, GCTB can be malignant and locally aggressive leading to significant bone destruction.(2) National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for Bone Cancer recommend the following for denosumab treatment based on localized disease or metastatic disease at presentation:(2)

	Therapy as a single agent (preferred) or combined with serial embolization (preferred), and/or radiation therapy for resectable disease with unacceptable morbidity and/or unresectable axial lesions for patients with • localized disease • metastases at presentation • disease recurrence Preferred therapy as a single agent for • unresectable metastatic disease at presentation • unresectable metastatic recurrence • considered prior to surgery for resectable local recurrence *Efficacy* The safety and efficacy of denosumab 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.(1,14,15) Study 20040215 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.(1,14,15) Study 20062004 was a parallel-cohort, proof of concept, and safety trial conducted in 535 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 268 patients with surgically unsalvageable disease; Cohort 2 enrolled 252 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity; Cohort 3 enrolled 15 patients who previously participated in Study 20040215.(1,14,15) 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.(1,14,15)
Hypercalcemia of malignancy	Hypercalcemia is relatively common in patients with cancer, occurring in approximately 30 percent of cases. There are three major mechanisms by which hypercalcemia of malignancy can occur: tumor secretion of parathyroid hormone-related protein, osteolytic cytokine production, and excess 1,25-dihydroxyvitamin D (calcitriol) production.(9,12) 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. Total serum calcium measures both bound and unbound calcium and is the first step in the workup for suspected hypercalcemia. Calcium homeostasis is greatly affected by albumin concentrations as forty percent of calcium is bound to albumin. If the serum calcium is believed to be inaccurate, then ionized calcium can be used, but this is often not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation.(9-11)

	While evidence-based guidelines are lacking, in individuals with asymptomatic or mildly symptomatic hypercalcemia, immediate treatment can be deferred and they should be managed supportively until a definitive diagnosis has been established. In patients with moderate hypercalcemia therapy should be based on symptoms and the clinical judgment of the physician. Patients with severe hypercalcemia, especially when associated with severe renal or neurologic symptoms, requires prompt, often inpatient management to lower serum calcium levels.(9,12) 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.(9-11) *Efficacy* The safety and efficacy of denosumab 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.(1,14,15) 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 denosumab 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).(1,14,15)
Multiple myeloma	The NCCN Guidelines in Oncology for Multiple Myeloma recommend bisphosphonates or denosumab for all patients receiving therapy for symptomatic multiple myeloma regardless of documented bone disease. Denosumab is preferred over bisphosphonates by the NCCN Panel in patients with renal disease.(3) *Efficacy* The efficacy of denosumab 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 denosumab 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.(1,14,15)

	Study 20090482 **Multiple Myeloma**	
	Denosumab	**Zoledronic Acid**

		N = 859	**N = 859**
	First On-study SRE		
	Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
	Components of First SRE		
	Radiation to Bone	47 (5.5)	62 (7.2)
	Pathological Fracture	342 (39.8)	338 (39.3)
	Surgery to Bone	37 (4.3)	48 (5.6)
	Spinal Cord Compression	6 (0.7)	4 (0.5)
	Median time to SRE (months) (95% CI)	22.8 (14.7, NE*)	24 (16.6, 33.3)
	Hazard Ratio (95% CI)	0.98 (0.85, 1.14)	

*NE = not estimable

Prostate cancer

The NCCN Guidelines in Oncology for Prostate Cancer prefer denosumab (category 1, preferred) to zoledronic acid in patients with castration-resistant prostate cancer who have bone metastases to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or radiation therapy to bone. When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal-related events.(4)

Solid tumor

The 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 subcutaneous denosumab as therapeutics options to treat bone metastases related skeletal events, maintain or improve bone mineral density, and reduce risk of fractures.(5-8)

Efficacy

The safety and efficacy of denosumab 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 denosumab 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.(1,14,15)

	Study 20050136 **Metastatic Breast Cancer**		**Study 20050244** **Metastatic Solid Tumors or Multiple Myeloma**		**Study 20050103** **Metastatic CRPC***	
	Denosumab **N=1026**	**Zoledronic Acid** **N=1020**	**Denosumab** **N=866**	**Zoledronic Acid** **N=890**	**Denosumab** **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 post randomization; new events defined by occurrence greater than or equal to 21 days after preceding event
Adjusted p-values are presented

Systemic Mastocytosis	Mastocytosis is a group of heterogeneous disorders resulting from the clonal proliferation of abnormal mast cells and their accumulation in the skin and/or in various extracutaneous organs. Systemic mastocytosis is the most common form of mastocytosis diagnosed in adults, characterized by mast cell infiltration of one or more extracutaneous organs (with or without skin involvement). The NCCN Guidelines in Oncology for Systemic Mastocytosis recommend denosumab an alternative treatment option for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.(13)
Safety	Denosumab, denosumab-bbdz, and denosumab-bmwo have the following contraindications:(1,14,15) • Pre-existing hypocalcemia must be corrected prior to initiating therapy with denosumab • Patients with known clinically significant hypersensitivity to denosumab

REFERENCES

Number	Reference
1	Xgeva prescribing information. Amgen Inc. June 2020.

Number	Reference
2	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Bone Cancer. Version 2.2024.
3	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Multiple Myeloma. Version 3.2024.
4	National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology Prostate Cancer. Version 4.2024.
5	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Thyroid Cancer. Version 3.2024.
6	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer. Version 7.2024.
7	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Kidney Cancer. Version 1.2025.
8	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Breast Cancer. Version 4.2024.
9	Goldner W. Cancer-Related hypercalcemia. *Journal of Oncology Practice*. 2016;12(5):426-432. doi:10.1200/jop.2016.011155
10	Pamidronate disodium prescribing information. Bedford Laboratories. December 2014.
11	Zometa prescribing information. Novartis Pharmaceutical Corporation. December 2018.
12	Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. *Therapeutics and Clinical Risk Management*. Published online December 1, 2015:1779. doi:10.2147/tcrm.s83681
13	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Systemic Mastocytosis. Version 3.2024.
14	Wyost prescribing information. Sandoz Inc. March 2024.
15	Osenvelt prescribing information. Celltrion, Inc. February 2025.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
	Osenvelt	denosumab-bmwo inj	120 MG/1.7ML	M ; N ; O ; Y	N		
	Wyost	denosumab-bbdz inj	120 MG/1.7ML	M ; N ; O ; Y	N		
J0897	Xgeva	denosumab inj	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	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Osenvelt	denosumab-bmwo inj	120 MG/1.7 ML	1	Vial	28	DAYS			
Wyost	denosumab-bbdz inj	120 MG/1.7 ML	1	Vial	28	DAYS			
Xgeva	denosumab inj	120 MG/1.7 ML	1	Vial	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Osenvelt	denosumab-bmwo inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx
Wyost	denosumab-bbdz inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx
Xgeva	denosumab inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Osenvelt	denosumab-bmwo inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx
Wyost	denosumab-bbdz inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx
Xgeva	denosumab inj	120 MG/1.7ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
MDC	**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** All target agents are eligible for continuation of therapy 1. ONE of the following: A. 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** 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 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** C. The patient has a diagnosis of castration-resistant prostate cancer AND has documented bone metastases **OR**

Module	Clinical Criteria for Approval
	D. 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** E. The patient has a diagnosis of hypercalcemia of malignancy and ONE of the following: 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) **OR** F. The patient has a diagnosis of multiple myeloma and ONE of the following: 1. The patient has renal insufficiency **OR** 2. The patient has tried and had an inadequate response to pamidronate OR zoledronic acid (medical records required) **OR** 3. The patient has an intolerance or hypersensitivity to pamidronate OR zoledronic acid (medical records required) **OR** 4. The patient has an FDA labeled contraindication to BOTH pamidronate and zoledronic acid (medical records required) **OR** 5. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** G. 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 or pamidronate (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to zoledronic acid or pamidronate (medical records required) **OR** 3. The patient has an FDA labeled contraindication to BOTH zoledronic acid and pamidronate (medical records required) **OR** 4. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** H. The patient has a diagnosis of systemic mastocytosis and ONE of the following: 1. The patient has renal insufficiency **OR** 2. BOTH of the following: A. The patient has tried zoledronic acid (medical records required) **AND** B. The patient has persistent bone pain **OR** 3. The patient has an intolerance or hypersensitivity to zoledronic acid (medical records required) **OR** 4. The patient has an FDA labeled contraindication to zoledronic acid (medical records required) **OR** 5. The requested agent is a NCCN category 1 preferred agent for the requested diagnosis **OR** I. The patient has another FDA labeled indication for the requested agent and route of administration **OR** J. The patient has another indication supported in compendia for the requested agent and route of administration (i.e., indication must be supported in compendia by ALL requirements [e.g., performance status, disease severity, previous failures, monotherapy vs. combination therapy]) **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: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. BOTH of the following: 1. The requested quantity (dose) exceeds the program quantity limit **AND** 2. The requested quantity (dose) is within FDA labeling or supported in compendia for the requested indication **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2A recommended use **Length of Approval:** 12 months