BRAND NAME: PROLIA / XGEVA

PROPER NAME: Denosumab

MANUFACTURER: Amgen, Inc.

INDICATION: Xgeva is a RANK ligand (RANKL) inhibitor indicated for:

- Prevention of skeletal-related events 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.

DESCRIPTION: Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

REGULATORY MILESTONES:

US Approval	June 01, 2010
EU Approval	July 13, 2011
Health Canada Approval	May 10, 2011
Japanese Ministry of Health, Labor and Welfare (MHLW) Approval	February 18, 2012
TGA	September 08, 2011

ADVISORY COMMITTEE:

An Advisory Committee meeting was held during the first review cycle on August 13, 2009, to discuss the four biologic licensing applications/indications for denosumab. The advisory

committee unanimously voted for the approval of denosumab for the indication "treatment of postmenopausal osteoporosis.

MANUFACTURING:

PARAMETER	DATA	REFERENCE
Manufacturer	Amgen, Inc.	
Indication	Xgeva is a RANK ligand (RANKL) inhibitor indicated for: • Prevention of skeletal-related events 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.	1
Cell Substrate	Chinese hamster ovary (CHO) cells	3
Manufacturing platform	Denosumab is manufactured by a batch-wise cell culture process in the production bioreactor followed by a harvest process using conventional unit operations (centrifugation and membrane filtration), and a purification process employing several chromatography steps (protein A, cation exchange and hydrophobic interaction), a viral inactivation step and a viral removal step. Finally, formulation is made by means of ultrafiltration/diafiltration.	3
Dose in vial/final container	120 mg/1.7 mL (70 mg/mL) single-use vial	1
Dose to patient	• **Bone Metastasis from Solid Tumors:** Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen. • **Giant Cell Tumor of Bone:** Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.	1

1. Package insert - Xgeva
2. EPAR full - Xgeva
3. EPAR quality - Xgeva: EPAR - Public assessment report

4. FDA Review - Prolia (denosumab) Injection

CLINICAL TRIALS:

NCT	TRIAL PHASE	NO OF PATIENTS ENROLLED	TITLE	COUNTRIES
Primary Phase 3 trials Reviewed in original BLA				
NCT00089791	3	7808	A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis	
NCT00091793	3	332	Study to Evaluate AMG 162 in the Prevention of Postmenopausal Osteoporosis	
NCT00089661	3	252	AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Aromatase Inhibitor Therapy for Non-metastatic Breast Cancer	
NCT00089674	3	1468	AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Androgen-Deprivation Therapy for Non-metastatic Prostate Cancer	
Key trials with the new data in CR safety update				
NCT00523341	3	4550	Extension Study to Evaluate the Long-Term Safety and Efficacy of Denosumab in the Treatment of Osteoporosis	
NCT00325468	3	200	An Open-label, Single-arm Extension Study to Evaluate the Long-term Safety of Denosumab Administration in Postmenopausal Women with Low Bone Mineral Density	
NCT00518531	3	250	Denosumab Adherence Preference Satisfaction Study	
NCT00887965	2	15	A Transiliac Crest Bone Histology and Histomorphometry Study in Postmenopausal Women with Low Bone Mass or Osteoporosis Previously Treated with Denosumab	

POST APPROVAL CHANGES

DATE	TYPE OF CHANGE	DESCRIPTION	LINK