
Novartis Pharmaceuticals Corporation

59 Route 10

East Hanover, NJ 07936

**Appendix 4:
ONJ in Clinical Studies**

Zometa[®] (zoledronic acid) Injection

and

Aredia[®] (pamidronate disodium) Injection

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Table 1 - Pivotal bone metastases studies included in the search for terms related to ONJ using MedDRA terms

Phase I Study No.	Indication	No. patients	Study duration	Zol 0.4/8 mg	Zol 2/8 mg	Zol 4/8 mg	Zol/Aredia 90 mg	Aredia 90 mg
CZOL4460007+E ¹⁾	BCa, MM	288	9mo/21mo	62	62	59	30	75

Phase III randomized Study No.	Indication	No. patients	Study duration	Treatment Groups (No. patients)			
				Zol 4 mg	Zol 8mg/4 mg	Aredia 90 mg	Placebo
ZOMETETA studies							
CZOL4460010+E	MM, BCa	1648	25 mo	564	526	558	NA
CZOL4460011+E	Solid tumors (except BCa+PCa)	773	21 mo	257	266	NA	250
CZOL4460039+E	PCa	643	24 mo	214	221	NA	208
CZOL4460704	PCa	405	38.7 mo ²⁾	49	155	NA	201
Total Zometa studies		3,469		1,084	1,168	558	659
AREDIA studies							
CARD233AP12	MM	392	21 mo	NA	NA	203	189
CARD233AP18	BCa	371	24 mo	NA	NA	182	189
CARD233AP19	BCa	382	24 mo	NA	NA	185	197
Total Aredia studies		1,145				570	575
TOTAL (Z+A Phase III)		4,614		1,084	1,168	1,128	1,234

¹⁾ After the 9 month core study patients who entered the extension study were switched from lower Zometa doses to 8 mg Zometa or Aredia. Patients in the Aredia group continued to receive Aredia.

²⁾ Study was terminated earlier. The maximum duration on study was 38.7 months.

Table 2 – Pivotal Zometa hypercalcemia studies included in the search for terms related to ONJ using MedDRA

Phase I Study No.	Indication	No. patients	Study duration	Zol 0.002 mg/kg	Zol 0.005 mg/kg	Zol 0.01 mg/kg	Zol 0.02 mg/kg	Zol 0.04 mg/kg
CHJC1 ¹⁾	Cancer	33	5 weeks	3	3	4	5	18

Phase II Study No.	Indication	No. patients	Study duration	Zol 4 mg	Zol 8 mg	Aredia 90 mg
CZOL446036 ²⁾	Cancer	144	Max. 3 mo	46	48	50
CZOL446037 ²⁾	Cancer	138	Max. 3 mo	40	47	51
Total Phase 2		282		84	95	101

¹⁾Single infusion

²⁾Hypercalcemia of malignancy (HCM) study: patients received a single dose of Zometa 4 mg or 8 mg or Aredia. Patients with HCM that was refractory or had relapsed after the first dose received a second infusion of Zometa 8 mg

Table 3 – Non-pivotal bone metastases studies included in the search for terms related to ONJ using MedDRA

Phase I –III Study No.	Indication	No. patients	Study duration	Zol ≤ 2 mg	Zol 4 mg	Zol 8/4 mg	Zol 8 mg	Zol 16 mg	Are 90 mg	Placebo
CZOL4460001 ¹⁾	M. Paget	16	14 d	16	NA	NA	NA	NA	NA	NA
CZOL4460002 ¹⁾	M. Paget	175	3 mo	140	NA	NA	NA	NA	NA	35
CZOL4460003+E	Cancer	59	3mo/48mo	45	7	NA	7	NA	NA	NA
CZOL4460035+E	NSCLC, PCa	42	2mo/ max. 31.6 mo	16	8	NA	8 ²⁾	10 ³⁾	NA	NA
CZOL4460503+E	Cancer	36	1 mo/~3 y	NA	12	NA	12	12	NA	NA
CZOL4460506+E	Cancer	19	3 mo/2 yrs	NA	19	NA	NA	NA	NA	NA
CZOL4460510	MM, PCa	20	6 mo/1 y	Core: 1x4 mg, 2x8mg, 2x12 mg, 1x4mg sequentially Extention: 4 mg (investigator may decide to					NA	NA

Phase I –III Study No.	Indication	No. patients	Study duration	Zol ≤ 2 mg	Zol 4 mg	Zol 8/4 mg	Zol 8 mg	Zol 16 mg	Are 90 mg	Placebo
				give 8 or 12 mg)						
CZOL4460705	PCa	106	12 mo	NA	55	NA	NA	NA	NA	51
CZOL446IA03	MM, BCa	240	15-20 weeks	NA	NA	115	NA	NA	125	NA
Total		713		217	101⁴⁾	115⁴⁾	27⁴⁾	22⁴⁾	125	86

Phase IV Single Arm Study No.	Indication	Zometa 4 mg No. of Patients	Study Duration
CZOL446EDE02	Cancer	604	36-48 weeks (follow-up until week 60)
CZOL446EIT01	BCa	312	48 weeks
CZOL446EAU05	PCa	184	36-48 weeks
CZOL446EAU07	MM	11	16 weeks
CZOL446GAU09	MM	2	12 months
CZOL446EGB01	BCa	101	9 months
CZOL446EIN01	Cancer	73	3 months
CZOL446EPH01	BCa, PCa, MM	70	6 months
CZOL446GFR02	BCa	102	12 months
CZOL446EUS24	PCa	257	12 months
Total	1,716		

¹⁾Zometa administered as single dose

²⁾After the 8-26 months 5 patients switched from 8 mg Zometa to 4 mg Zometa

³⁾2 patients from the 16 mg Zometa group switched to Aredia after 18 months

⁴⁾Patient numbers of study CZOL4460510 are not included due to non-uniform dose regimen

Table 4 – Osteonecrosis/osteomyelitis cases (related to jaw or with unknown location) reported in pivotal bone metastases and hypercalcemia trials

Center/ Subject	Indication	Treatment Group	No. inf. ¹⁾	Date First Infusion	Diagnosis / Location	Start/end date	AE reporting/ study drug relationship	Possible risk factors ²⁾
CZOL446G0007 (n=288)								
609/2023	Multiple myeloma	Zol 0.4 mg/ Aredia 90 mg ³⁾	28 (10+18)	4Nov1996	Aseptic necrosis bone / mandible	Mar 1999/ Data not available	Not serious / not suspected	Chemotherapy; cortico- steroids; candidal infection (4Dec1996); tooth abscess (12Aug1997)
627/2382	Multiple myeloma	Zol 4/8mg	17 (10+7)	24Oct1996	Osteomyelitis (tenderness) / mandible ⁴⁾	9Apr1998/ continued	Not serious / not suspected	Chemotherapy; cortico- steroids; 1 cm radiolucency at mandible seen on a radiograph of the skull (31Jul1997); jaw infection (start date unknown); osteoarthritis (medical history/ongoing)
CZOL446G0010 (n=1648)								
2264/11160	Multiple myeloma	Zol 4 mg	28	10May1999	Osteomyelitis ⁵⁾ / Jaw	5Mar2001/ continued	Not serious / not suspected	Chemotherapy; cortico- steroids; ulcer mouth (Oct2000); cyst under chin (Apr2000); infection of the gum and teeth, lesions in the mandible (not related to myeloma, no exposed bone (5Mar2001)
2346/10594	Multiple myeloma	Zol 8/4 mg	12 (12+0)	27May1999	Osteonecrosis, bone necrosis / not specified ⁶⁾	17Apr2000/ continued	Not serious / not suspected	Chemotherapy; cortico- steroids
2346/20593	Breast cancer	Zol 8/4 mg	22 (14+8)	14Jun1999	Osteoradionecrosis / jaw	18Dec2000/ continued	Not serious / not suspected	Radiation (date unknown); tooth extraction (16Apr1999); mouth sores (Jul1999);

Center/ Subject	Indication	Treatment Group	No. inf. ¹⁾	Date First Infusion	Diagnosis / Location	Start/end date	AE reporting/ study drug relationship	Possible risk factors ²⁾
								periodontal disease (28Jan00); chemotherapy; corticosteroids
CZOL446G0704 (n=398)								
0521/0002	Prostate cancer	Zol 8/4 mg	20 (7+13)	29Dec1999	Osteomyelitis / jaw	26Mar2002/ continuing	Not serious / not suspected	Dental abscess (8Nov2001), tooth extraction (date unknown); oral fistula (26Mar2002); arthritis (1994, active problem); hormone therapy
CARD233AP12 (n=392)								
M6596P/6	MM	Aredia 90 mg	14	20Aug1991	Osteomyelitis / jaw	21Oct1992/ ongoing	Not serious / not suspected	Chemotherapy; corticosteroids; dentition poor (10Jul1992); denuded bone in posterior aspect of mandible (15Sep1992)
CARD233AP19 (n=380)								
M7488U/101	BCa	Placebo	3	7Oct1992	Osteomyelitis / not specified	30Nov1992/29Dec1992	Not serious / not suspected	Chemotherapy; hormone therapy; sepsis (19Oct1992)
CZOL4460037 (Hypercalcemia)								
M1694E/1303	SSC Head&Neck	Zometa 8 mg	1	16Jul1992	Osteonecrosis / Maxilla (cancer related)	28Jul1999/ ongoing	Not serious/ not suspected	Chemotherapy

¹⁾Number of infusions received before diagnosis of osteomyelitis/necrosis

²⁾In medical history or as current condition

³⁾The patient received 10 infusions of Zometa 0.4 mg before switching to Aredia (18 infusions)

⁴⁾Excision of right mandibular bone and soft tissue mass (26.Apr.2001)

⁵⁾Term not identified in CRF

⁶⁾No adverse events indicating jaw involvement

Table 5 – ONJ cases reported in ongoing bone metastases studies

Center/ Subject	Indication	Treatment	No. inf. ¹⁾	Date First Infusion	Diagnosis / Location	Start/end date	AE reporting/ study drug relationship	Possible risk factors ²⁾
CZOL446G2408 (ongoing, 1036 patients enrolled, 6Jan2005)								
1/100055	Breast cancer	Zometa 4 mg	Max. 4	26Jan04	Osteonecrosis / jaw	May2004	Serious / suspected	Chemotherapy; corticosteroids; gingival infection (9Feb2004); dental extraction (16Feb2004)
CZOL446EDE07 (ongoing, 309 patients enrolled, 14Jan2005)								
20/9	Prostate cancer	Zometa 4 mg	Max. 9	25Feb03	Osteomyelitis / jaw	Already present at study entry	Serious / not suspected	Preexisting osteomyelitis of the jaw
CZOL446EDEKR02 (ongoing, 40 patients enrolled Jan2005)								
1/11	Breast cancer	Zometa 4 mg	Max. 4	25Jul03	Osteomyelitis / jaw	After 6Jan2004	Serious / not suspected	Chemotherapy; chronic gingivitis (6Jan2004); sequestrectomy (20Apr2004)
CZOL446EDE01 (ongoing, 101 patients enrolled, 14Jan2005)								
?	Multiple myeloma	Zometa 4 mg	?	?	Osteonecrosis / jaw	?	Not serious / ?	?