XGEVA

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0087/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters	06/12/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0086/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol	06/12/2024		SmPC	
II/0084	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/09/2024		SmPC and PL	
IG/1743	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/06/2024		Annex II	
PSUSA/9119/ 202309	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	16/05/2024	n/a		PRAC Recommendation - maintenance
II/0082/G	This was an application for a group of variations. B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product	25/01/2024		SmPC, Labelling and PL	The SmPC sections 1; 2; 4.2; 4.4; 6.1; 6.3; 6.4; 6.5; 6.6; and 8 have been updated as follows to reflect the introduction of the 120 mg/mL solution for injection in pre-filled syringe (EU/1/11/703/004-006), the corresponding change in composition (addition of phenylalanine and reduction in sorbitol concentration),

	B.II.a.5 - Change in concentration of a single-dose, total use parenteral product, where the amount of AS per unit dose (i.e. the strength) remains the same B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				addition of instructions under “Method of administration”, addition of traceability measures and warnings towards Phenylketonuria (PKU). The Labelling and Package Leaflet have been updated accordingly.

	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/07/2022	29/06/2023	SmPC and PL	To update section 4.4 of the SmPC and section 2 of the PL to align the wording for the excipients sorbitol and sodium with the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev. 1*).
WS/2252	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Please refer to the Recommendations section B.I.b.2.d - Change in test procedure for AS or	19/05/2022	n/a		Not applicable

	starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
WS/2159/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Please refer to the Recommendations section B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.b.z - Change in control of the AS - Other variation	22/04/2022	29/06/2023	Annex II	The Annex II has been updated to include the name and address of Immunex Rhode Island Corporation as a manufacturer of the biological active substance The PL have been updated to: -add Northern Ireland to the list of local representative at the end of the package leaflet (in compliance with QRG template V10.2 rev.1), and - update the local representatives for Malta and Germany at the end of the package leaflet, in the package leaflet of Xgeva.
II/0078	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/10/2021	n/a		
WS/2026	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch	08/07/2021	n/a		

	control/testing takes place and any of the test method at the site is a biol/immunol method				
PSUSA/9119/ 202009	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0075	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/11/2020	n/a		
IB/0074	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	28/10/2020	n/a		
II/0072/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/06/2020	17/06/2021	SmPC	
II/0071/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch	14/05/2020	n/a		

	release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0070	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/01/2020	n/a		
II/0069	Update of SmPC sections 4.2, 4.8, 5.1 and 5.2 based on the final analysis from study 20062004; a phase 2, open-label, single-group study to evaluate the safety and pharmacokinetics of denosumab in adult and adolescent subjects with giant cell tumour of bone (GCTB). The final CSR for study 20062004 was previously assessed by CHMP as part of procedure P46 027 and the finalisation of the study addresses the final PIP measure. In addition, the MAH took the opportunity to update the description of ONJ incidence in section 4.8 of the SmPC in order to express events per 100 patient years without a percentage sign. The Package Leaflet has been updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with	17/10/2019	19/11/2019	SmPC and PL	Please refer to Scientific Discussion 'Xgeva-H-C-2173-II-69'

	new additional data submitted by the MAH				
II/0068	Update of section 4.8 of the SmPC based on post-marketing experience to include the new ADR 'lichenoid drug eruptions' with a frequency category of 'uncommon'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Ireland and Portugal in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/04/2019	28/06/2019	SmPC and PL	Lichenoid drug eruptions (e.g. lichen planus-like reactions) have been reported in patients in the post-marketing setting, including multiple cases with positive rechallenged, which supports a conclusion that there may be a causal association with denosumab.
PSUSA/9119/ 201809	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	11/04/2019	n/a		PRAC Recommendation - maintenance
IB/0066	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	04/01/2019	n/a		
II/0065	Update of section 4.8 of the SmPC to modify the frequency category of the ADR Atypical Femoral Fracture (AFF) from 'rare' to 'uncommon' and to add descriptive language regarding latency observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH is taking the opportunity to remove the black triangle and corresponding text from the Annexes as Xgeva is	29/11/2018	28/06/2019	SmPC, Annex II, Labelling and PL	In the clinical trial programme, atypical femoral fractures have been reported uncommonly in patients treated with Xgeva and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

	no longer under additional monitoring, to implement editorial changes in the annexes and to update the contact details of the local representative in Ireland in the Package Leaflet. An updated RMP (version 33) was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/9119/ 201709	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	26/04/2018	25/06/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9119/201709.
IG/0946	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	04/06/2018	28/06/2019	PL	
IB/0062	B.II.z - Quality change - Finished product - Other variation	24/04/2018	n/a		
IB/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/04/2018	n/a		
II/0059	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/04/2018	25/06/2018	SmPC and PL	

II/0055	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/02/2018	27/03/2018	SmPC and PL	Please refer to Scientific Discussion Xgeva-H-C-2173-II-0055
IB/0057	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	05/12/2017	n/a		
IG/0857/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	10/11/2017	27/03/2018	Annex II and PL	
X/0048/G	This was an application for a group of variations. Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	20/07/2017	18/09/2017	SmPC, Annex II, Labelling and PL	

	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0054	Submission of an updated RMP version 25 in order to remove cataracts from the list of potential risks associated with denosumab therapy based on the results of study 20080560 (Multicentre, randomized, double blind, placebo-controlled study in men with nonmetastatic prostate cancer receiving androgen deprivation therapy cataract development and progression study using a slit-lamp-based evaluation system (Lens Opacities Classification System III (LOCS III)). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	01/09/2017	n/a		
II/0051	To update to the Risk Management Plan (RMP) with addition of the important potential risk 'hypercalcemia several months after the last dose in patients with GCTB' and the modification of the	20/07/2017	n/a		

	important identified risk 'hypercalcemia following treatment discontinuation in patients with growing skeletons' to 'hypercalcemia in patients with growing skeletons several months after the previous dose'; the MAH is also taking the opportunity to implement a minor correction to the RMP for correction or to add clarification. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/9119/ 201609	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9119/201609.
IAIN/0053	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/03/2017	16/06/2017	Annex II and PL	
II/0046	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	16/06/2017	SmPC and PL	
IB/0049	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/11/2016	n/a		

IB/0050	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	09/11/2016	n/a		
IA/0047	A.7 - Administrative change - Deletion of manufacturing sites	07/09/2016	16/06/2017	Annex II	
PSUSA/9119/ 201509	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone)	14/04/2016	n/a		PRAC Recommendation - maintenance
R/0042	Renewal of the marketing authorisation.	28/01/2016	04/04/2016	SmPC, Annex II and PL	
IB/0044	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	08/01/2016	n/a		
II/0041	Update of sections 4.2 and 4.4 of the SmPC regarding risk of off-treatment hypercalcaemia following cessation of XGEVA treatment in young patients with growing skeletons. The Package Leaflet has been updated accordingly. Further, the MAH took the opportunity to make minor changes in the Package Leaflet in order to align the text with the SmPC, and to update the contact details of the local representatives in the Package Leaflet. A revised RMP version 17.0 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	04/04/2016	SmPC and PL	Xgeva is not recommended in patients with growing skeletons. Clinically significant hypercalcaemia has been reported in XGEVA-treated patients with growing skeletons weeks to months following treatment discontinuation.

II/0039	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	24/09/2015	n/a		
IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	11/08/2015	n/a		
II/0036/G	This was an application for a group of variations. B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.f.1.e - Stability of FP - Change to an approved stability protocol	23/07/2015	n/a		
WS/0666/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.e - Change to in-process tests or limits	23/07/2015	n/a		

	applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
PSUSA/9119/ 201409	Periodic Safety Update EU Single assessment - denosumab (indicated for skeletal related events	23/04/2015	13/07/2015	SmPC, Annex	Please refer to Xgeva PSUSA-9119-201409 EPAR: Scientific conclusions and grounds recommending the variation to the

	associated with bone metastases and for giant cell tumour of bone)			II and PL	terms of the marketing authorisation
II/0038	Update of section 4.8 of the SmPC in order to update the safety information regarding the risk of osteonecrosis of the jaw (ONJ). In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the SmPC in line with the Package leaflet regarding typographical errors in section 4.2 of the SmPC. An updated RMP (version 13.0) was adopted with this variation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	04/04/2016	SmPC	In a phase III trial in patients with non-metastatic prostate cancer (a patient population for which XGEVA is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment, 3.0% in the second year, and 7.1% per year thereafter.
WS/0660	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	26/03/2015	n/a		
WS/0642/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.b - Changes in the manufacturing process of	26/02/2015	n/a		

	the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.II.h.1.b.2 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier - without modifications of risk assessment				
WS/0589	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change in-process control limits applied during the manufacture of the AS. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	25/09/2014	n/a		To change in-process control limits applied during the manufacture of the AS.
II/0028	Update of the SmPC, upon request by PRAC following the assessment of PSU 014, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal	24/07/2014	01/09/2014	SmPC and PL	Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream. Severe symptomatic hypocalcaemia (including fatal cases) has been reported in patients receiving treatment with XGEVA. During clinical trials, severe hypocalcaemia (corrected serum calcium < 7 mg/dL

	pain as an identified risk in section 4.8 further to post-marketing experience. Further, sections 4.2 and 5.3 of the SmPC have been updated with respect to recommendations for monitoring of calcium levels, and information regarding patients with renal impairment. The Package Leaflet and the RMP have been modified accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				or < 1.75 mmol/L) occurred in 3.1% of patients receiving treatment with XGEVA. Most cases of severe symptomatic hypocalcaemia have occurred in the first weeks of initiating therapy. The risk of developing hypocalcaemia during XGEVA treatment is greater with increasing degree of renal impairment. In a clinical study in patients without advanced cancer, 19% of patients with severe renal impairment (creatinine clearance < 30 ml/min) and 63% of patients receiving dialysis developed hypocalcemia despite calcium supplementation. The overall incidence of clinically significant hypocalcemia was 9%. Patients should be encouraged to report of symptoms indicative of hypocalcaemia. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures, and altered mental status (including coma). Symptoms of hypocalcaemia in clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.
II/0027	Update of the SmPC, upon request by PRAC following the assessment of PSU/014, to revise the warnings in SmPC section 4.4 on osteonecrosis of the jaw (ONJ), and to add information in sections 4.4 and 4.8 of the SmPC on the incidence of ONJ based on duration of exposure. The Package Leaflet and the RMP have been updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	24/07/2014	01/09/2014	SmPC and PL	The new information in the SmPC and Package Leaflet informs prescribers of the risk of ONJ with XGEVA, provides information on the nature of these events, and guides physicians in the recognition and management of this risk. Further, a DHPC has also been agreed as an additional risk minimisation measure in order to inform prescribers of this safety concern and the subsequent changes to the SmPC. In clinical XGEVA trials, the incidence of ONJ was higher with longer duration of exposure. The patient-year adjusted incidence of confirmed ONJ was

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				1.1% during the first year of treatment, 3.7% in the second year and 4.6% per year thereafter. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure were excluded from the clinical trials. Known risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease. Other risk factors for ONJ are advanced malignancies, infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck), smoking and previous treatment with bisphosphonates. While on treatment, patients should avoid invasive dental procedures if possible. In patients with risk factors for ONJ, an individual benefit-risk assessment should be performed before initiating therapy with XGEVA. For patients who develop ONJ during treatment, doctors should create a management plan in close collaboration with a dentist or oral surgeon with ONJ expertise, and a temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible. Patients should be encouraged to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with XGEVA. Patients should also be advised to refer to the Patient Information Leaflet (PIL) for information on

					symptoms of ONJ.
II/0016	Extension of indication to add treatment of giant cell tumour of bone in adults or skeletally mature adolescents. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, section 4.6 of the SmPC was updated with further guidance regarding pregnancy. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to update the contact details for the local representative in Croatia in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/07/2014	01/09/2014	SmPC and PL	For further information, please refer to the scientific discussion 'XGEVA-H-C-2173-II-16'.
IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/07/2014	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/05/2014	01/09/2014	PL	
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	27/05/2014	n/a		
PSUV/0026	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0023	Changes in the upstream manufacturing process of denosumab.	20/02/2014	n/a		

	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol				
IAIN/0025	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	09/12/2013	01/09/2014	SmPC and PL	
IA/0024	A.7 - Administrative change - Deletion of manufacturing sites	13/11/2013	n/a		
II/0011	Update of section 4.8 of the SmPC to delete the ADR cellulitis and the text describing "skin infections (predominantly cellulitis) leading to hospitalisation" and to delete the associated warning in SmPC section 4.4. Further, section 4.8 of the SmPC has been updated with a change in frequency of the ADR drug hypersensitivity from uncommon to rare, and with the addition of text describing symptoms of hypocalcaemia observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	24/10/2013	18/12/2013	SmPC and PL	Patients with castration resistant prostate cancer (CRPC) eventually develop bone metastases and skeletal complications. Denosumab is currently licensed for the prevention of skeletal related events (SRE) in patients with solid tumours and known bone metastases. As part of the current procedure, the MAH initially applied for an extension of indication to add "treatment of castration-resistant prostate cancer at high risk of developing bone metastases as determined by assessment of prostate-specific antigen (PSA). XGEVA prolongs bone-metastasis-free survival by preventing bone metastases". During the procedure, as part of the response to the 2nd CHMP Request for Supplementary Information (RSI), the applicant revised the proposed indication to: "Delay of bone metastases in men with castration-resistant prostate cancer at high risk of developing bone metastases

	modification of an approved one				based on prostate-specific antigen (PSA) doubling time of 6 months or less". Pivotal for this application was a placebo controlled study conducted in patients with CRPC at increased risk for bone metastases based PSA levels ≥8.0 ng/ml or PSA doubling time ≤10 months. As the study was initiated prior to the authorisation of XGEVA for prevention of SRE, study therapy was stopped at the time of diagnosis of bone metastasis. Thus, the benefit of early therapy vs. initiation of therapy at the time of overt bone metastasis cannot not be assessed. The primary endpoint was bone metastasis free survival. Following the assessment of the available data the CHMP concluded that in the full study population, the treatment effect in terms of bone metastasis-free survival has not been convincingly documented statistically. Furthermore, the apparent treatment effect is modest. Thus available data make attempts to undertake a thorough benefit – risk assessment futile in the full study population. In a post hoc identified subgroup where the apparent benefit of treatment is improved without signs of increased treatment related risks, the lack of external data supporting the notion that the activity of denosumab is increased, constitutes a major concern. In conclusion, altogether the benefit – risk balance in the proposed new indication has not been shown to be favourable. Therefore, the CHMP adopted the following major objection during the procedure: "This submission for an extended indication to encompass patients with CRPC is based on a single pivotal trial. In the ITT population, the treatment effect is small and the results are not considered robustly documented from a statistical

					perspective. Post hoc a subgroup of patients was identified with apparent increased benefit of therapy. Most likely, however, the benefit of therapy is overestimated and may not outweigh the risk of ONJ and thus a proper benefit – risk assessment cannot be undertaken." In view of the outstanding major objection above, the MAH informed the CHMP of their decision not to pursue the claimed extension of the indication for XGEVA applied for under the present procedure, but proposed nevertheless to pursue with the application to enable implementation of the safety-related changes to the SmPC and Package Leaflet, and the consequential changes to the risk management plan (RMP) that had been agreed during the CHMP review. The CHMP endorsed the MAH's proposed way forward. In view of the final revised scope of the application, the CHMP concluded that the proposed safety-related changes to the SmPC, Package Leaflet and RMP can be agreed. The benefit/risk balance for XGEVA remains positive in the already approved indication: "Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours." For further information please refer to the Scientific Discussion "XGEVA-H-C-2173-II-11-AR".
IAIN/0022	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	26/09/2013	n/a		

	(including contact details) and/or changes in the PSMF location				
IA/0021/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	27/08/2013	n/a		
II/0019	Update of sections 4.4 and 4.8 of the SmPC to include a new warning to reflect very rare cases of 'atypical femoral fracture' reported in the post-marketing setting. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	18/12/2013	SmPC and PL	Within the current procedure, the MAH has evaluated the potential for atypical femoral fractures in cancer patients treated with denosumab in clinical trials and the post-marketing setting. A causal relationship of atypical femoral fracture with XGEVA cannot be ruled out, and therefore the MAH proposed that the XGEVA SmPC is updated to include atypical femoral fracture in the special warnings and precautions for use and undesirable effects sections. The content of the information in the special warnings and precautions section is the same as that recently agreed for Prolia and informs prescribers of the risk of atypical femoral fracture with XGEVA, provides information on the nature of these events, and guides physicians in the recognition and management of this risk. Atypical femoral fractures have been reported in patients receiving XGEVA (denosumab). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid

					arthiritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of XGEVA therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. During XGEVA treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture. There is no need for further risk minimisation activities. The overall benefit risk profile of XGEVA (denosumab 120 mg Q4W) remains favorable.
II/0018	This type II variation concerns an update of section 4.8 of the SmPC with additional information to reflect the fact that anaphylactic reactions have been reported in the post-marketing setting. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update annex II in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	18/12/2013	SmPC, Annex II and PL	Two cases of anaphylactic reaction in the post-marketing setting were assessed as causally related to XGEVA. The MAH's proposal to include anaphylactic reaction in the undesirable effects sections of the SmPC for XGEVA to inform prescribers is endorsed. The Package Leaflet has been updated accordingly. Changes were also made to the annex II to bring it in line with the current QRD template version 8.3, which were reviewed and accepted by the CHMP. The overall benefit-risk profile of denosumab remains favorable.
II/0017/G	This was an application for a group of variations.	25/04/2013	n/a		

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test				
IAIN/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/03/2013	n/a		
II/0014	Update of sections 4.4, 4.8 and 5.1 to include further information on the incidence of Osteonecrosis of the Jaw (ONJ) after longer term exposure following analysis of data from open label extensions of studies 20050103 and 20050136, and safety follow-up to study 20050244. Further, SmPC section 5.1 has been updated to reflect the content of the latest PIP decision. In addition, the MAH took the opportunity to make editorial changes to the annexes.	17/01/2013	18/12/2013	SmPC	In clinical trials, the incidence of ONJ was higher with longer duration of exposure. The MAH has presented data to show that there are increased proportions of subjects with adjudicated positive ONJ adverse events when comparing denosumab and zoledronic acid groups over the entire durations of studies 20050136 (4.7% versus 3.5%) and 20050103 (3.8% versus 2.2%) and that there are increasing incidences of events of adjudicated positive ONJ adverse events in the denosumab groups in both studies over time (0.9 events/ 100 subject years in the first 12

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				months compared to 3.8 events / 100 subject years in > 12 months in study 20050136 and 1.4 events / 100 subject years in the first 12 months compared to 4.7 events / 100 subject years in > 12 months in study 20050103). The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range: 4 - 53). The data presented justify the proposed labelling changes. Such changes provide adequate information to maintain a positive benefit / risk balance.
IG/0247	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2012	n/a		
II/0013	B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	13/12/2012	n/a		
IAIN/0012/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	03/09/2012	29/10/2012	Annex II and PL	
II/0009	This type II variation concerns an update of sections 4.2, 4.4 and 4.8 of the SmPC to include information about cases of severe symptomatic hypocalcaemia, including fatal cases, reported in the post-marketing setting.	19/07/2012	23/08/2012	SmPC	The risk of severe hypocalcaemia associated with denosumab use is known and is already reflected in the current product information, which includes recommendations on risk minimisation. Severe symptomatic hypocalcalcemia, including fatal cases,

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				has been reported in patients treated with denosumab. Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation. Following receipt of these adverse drug reaction reports, the existing warnings in the product information have been updated to inform prescribers that severe fatal cases have been reported in the post-marketing period. The product information has also been updated with information on the risk of late onset of hypocalcaemia. Hypocalcaemia can occur at any time during therapy with denosumab, although most commonly it occurs within the first 6 month of dosing.
IB/0010	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	22/06/2012	n/a		
IAIN/0008/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	16/05/2012	n/a		
IB/0007	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	14/05/2012	n/a		
II/0003	Update of sections 4.6 and 5.3 of the SmPC to reflect	16/02/2012	21/03/2012	SmPC, Annex	In a study of cynomolgus monkeys dosed with denosumab

	the outcome of Study 112197 with the inclusion of new nonclinical data regarding enhanced pre-postnatal development (ePPND). Further, SmPC section 4.6 has been updated to include information related to the MAH's Pregnancy Surveillance Programme (PSP) and Lactation Surveillance Programme (LSP). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the annexes in line with the latest QRD template (version 8). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II, Labelling and PL	during the period equivalent to the first trimester of pregnancy denosumab doses resulting in 9 times greater systemic exposure than the recommended human dose did not induce maternal toxicity or foetal harm during a period equivalent to the first trimester, although foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at systemic exposures 12-fold higher than the human dose, there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. From a clinical viewpoint, women who become pregnant during Xgeva treatment are encouraged to enrol in the MAH’s Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Information for the user. Similarly, women who are nursing during Xgeva treatment are encouraged to enrol in the MAH’s Lactation Surveillance Program. Contact details are provided in section 6 of the

					Package Leaflet – Information for the user.
II/0005/G	This was an application for a group of variations. Addition of a new manufacturing site for active substance, changes in the specification parameters of buffer used in the manufacture of active substance, change in test methods for the finished product and update of TSE certificates. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	16/02/2012	16/02/2012		
IB/0006	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	27/01/2012	n/a		
IAIN/0004	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	16/12/2011	31/01/2012	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes			PL	
IA/0002	A.7 - Administrative change - Deletion of manufacturing sites	14/10/2011	n/a	Annex II	
IA/0001	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	12/08/2011	n/a		