Zometa

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
II/0103/G	This was an application for a group of variations. B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a	05/09/2024		SmPC, Annex II and PL	

[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).

	manufacturing site for the FP - Secondary packaging site B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
PSUSA/3149/ 202308	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	25/04/2024	17/06/2024	SmPC and PL	
IB/0102/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.2 - Change to importer, batch release	10/01/2024	17/06/2024	Annex II and PL	

	arrangements and quality control testing of the FP - Including batch control/testing B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IB/0100	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	06/09/2022	n/a		
IAIN/0099/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.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	04/06/2021	24/06/2022	Annex II and PL	
PSUSA/3149/ 202008	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	09/04/2021	n/a		PRAC Recommendation - maintenance
T/0098	Transfer of Marketing Authorisation	12/03/2021	26/03/2021	SmPC, Labelling and PL	
IB/0096	C.I.z - Changes (Safety/Efficacy) of Human and	10/11/2020	26/03/2021	SmPC, Annex	

	Veterinary Medicinal Products - Other variation			II, Labelling and PL	
IA/0095/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	14/07/2020	n/a		
IB/0093/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure	04/05/2020	n/a		

	(including replacement or addition)				
PSUSA/3149/ 201908	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	17/04/2020	n/a		PRAC Recommendation - maintenance
II/0091	The SmPC sections 4.4 and 5.1 have been updated. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). A study showed that ONJ was higher in myeloma patients when compared to other cancers. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/04/2020	26/03/2021	SmPC	The SmPC sections 4.4 and 5.1 have been updated. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). A study showed that ONJ was higher in myeloma patients when compared to other cancers.
IA/0094	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/02/2020	n/a		
IB/0090/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	14/06/2019	n/a		
IA/0089	A.7 - Administrative change - Deletion of manufacturing sites	03/05/2019	n/a		

PSUSA/3149/201808	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	11/04/2019	n/a		PRAC Recommendation - maintenance
IB/0087/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/12/2018	n/a		
IA/0086	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/07/2018	25/07/2019	SmPC, Annex II, Labelling and PL	
IG/0950	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)	18/06/2018	n/a		

IA/0084	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	05/06/2018	n/a		
T/0083	Transfer of Marketing Authorisation	20/03/2018	26/04/2018	SmPC, Labelling and PL	
PSUSA/3149/ 201708	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0082/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	05/04/2018	n/a		
IB/0081	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/03/2018	n/a		
IB/0080/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for	05/01/2018	n/a		

	sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the				

	finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
PSUSA/3149/ 201608	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	21/04/2017	15/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3149/201608.
WS/1016/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.z - Changes in the manufacturing process of the AS - Other variation 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which	15/12/2016	n/a		

	does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
IB/0077/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.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.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	16/11/2016	n/a		

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IAIN/0075	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/09/2016	n/a		
IG/0705/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	08/08/2016	n/a		
PSUSA/3149/ 201508	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	28/04/2016	21/06/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3149/201508.
II/0069	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	25/02/2016	n/a		

	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				
IAIN/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/12/2015	21/06/2016	SmPC and PL	
IG/0611	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/09/2015	n/a		
IG/0574/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	13/08/2015	n/a		

PSUSA/3149/ 201408	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	23/04/2015	03/07/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3149/201408.
IG/0578/G	This was an application for a group of variations. 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) 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)	01/07/2015	n/a		
IG/0559	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)	20/05/2015	n/a		
IB/0065	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/02/2015	n/a		
IG/0524	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	10/02/2015	n/a		
IB/0062/G	This was an application for a group of variations.	19/12/2014	n/a		

	B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IAIN/0064	A.1 - Administrative change - Change in the name and/or address of the MAH	16/12/2014	03/07/2015	SmPC, Labelling and PL	
IB/0061/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits	17/11/2014	n/a		

	applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
II/0057/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC to add information on additive effect of hypocalcaemia-causing medicinal products; Update of section 4.6 of the SmPC to add information for women of child-bearing potential; Update of section 4.8 of the SmPC to change frequency of uveitis (from "very rare" to "rare"); and Update of section 5.2 of the SmPC to revise the text on plasma protein binding. Furthermore, editorial changes are made to update	25/09/2014	17/11/2014	SmPC and PL	Caution is advised when Zometa is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5). Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zometa therapy. Patients should be adequately supplemented with calcium and vitamin D. Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics, since both these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

	some adverse reaction terms in section 4.8 of the SmPC according to MedDRA preferred terms. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Women of child-bearing potential should be advised to avoid becoming pregnant while on treatment with Zometa. The frequency of uveitis and cardiac arrhythmia (secondary to hypocalcaemia) as adverse drug reactions of Zometa therapy is 'rare' (may affect up to 1 in 1,000 people - previously 'very rare' [may affect up to 1 in 10,000 people]). In an in vitro study, zoledronic acid showed no low affinity for the cellular components of human blood. The plasma protein binding is low, with the unbound fraction ranging from 60% to 77%.
IG/0443	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)	20/08/2014	n/a		
IAIN/0059/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	25/07/2014	n/a		

	site				
WS/0522	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a new specification parameter and limits to the specification of a solvent used in the manufacturing process of the active substance. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	22/05/2014	n/a		
IB/0058/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change	14/05/2014	n/a		

	to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
PSUSA/3149/ 201308	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for cancer and fractures)	10/04/2014	n/a		PRAC Recommendation - maintenance
IG/0394/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 A.7 - Administrative change - Deletion of manufacturing sites	19/12/2013	n/a		
IA/0052/G	This was an application for a group of variations. 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) B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	13/12/2013	n/a		
II/0051	Update of the Summary of Product Characteristics to add arthritis and joint swelling as symptoms of acute phase reaction in section 4.8 'Undesirable effects'. The Package Leaflet has been updated accordingly. In addition the MAH took the opportunity to update	24/10/2013	17/11/2014	SmPC, Annex II, Labelling and PL	The MAH has performed an extensive and thorough cumulative review of their safety database with respect to "arthritis" and "joint swelling". Based on this review, the proposed inclusion of "arthritis" and "joint swelling" as a manifestation of the acute phase reaction with the

	the list of local representatives in the Package Leaflet (for the Netherlands, Luxembourg and Croatia), and to make linguistic corrections (Swedish translation). Furthermore the MAH took the opportunity to bring the Product Information in line with the latest QRD template version 9. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				frequency "rare" in the SmPC section 4.8 is supported by the CHMP. The results of the review of the safety database do not change the overall benefit - risk balance for Zometa which remains favourable.
II/0049/G	This was an application for a group of variations. This was an application for a group of variations: -To change some specification parameters and/or limits of the finished product. -To introduce some changes in the test procedures for the finished product. The MAH has taken the opportunity to introduce some editorial changes to 3.2.P.5.1. and 3.2.P.5.2. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.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	19/09/2013	n/a		

	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.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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0048/G	This was an application for a group of variations. This was an application for a group of variations: -To introduce some changes in the specification parameters and/or limits of the finished product. -To introduce some changes in the test procedures for the finished product. The MAH has taken the opportunity to introduce	19/09/2013	n/a		

	some editorial changes to 3.2.P.5.1. and 3.2.P.5.2. 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.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.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.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.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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished				

	product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0050/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	02/08/2013	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0045	Update of sections 4.4 and 4.8 of the SmPC further to the assessment of PSUR 13 in order to include additional information in SmPC section 4.4 on severe cases of hypocalcaemia and on risk factors for osteonecrosis and to include in SmPC section 4.8 additional information on interstitial lung disease. The Package Leaflet section 4 was updated in accordance to include additional information on	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	This variation concerns updates to the product information following assessment of PSUR 13 to include additional information in SmPC section 4.4 in order to warn that severe hypocalcaemia, including life-threatening, may be encountered. More extensive information on risk factors for ONJ is added to SmPC section 4.4 mentioning that when evaluating an individual`s risk of developing ONJ, the following risk

	interstitial lung disease. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (Malta). Furthermore, the PI is brought in line with the current QRD template version 8.1. The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II: `The MAH should submit an updated Risk Management Plan reflecting "atypical femoral fractures" as potential risk. The Risk Management plan should be submitted by 6 October 2011.' C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				factors should be considered: potency of the bisphosphonate, route of administration and cumulative dose; cancer, chemotherapy, radiotherapy, corticosteroids, smoking; history of dental disease, poor oral hygiene, invasive dental procedures and poorly fitting dentures. Furthermore interstitial lung disease was included in SmPC section 4.8 in the tabular list of adverse reactions and in the Package Leaflet section 4. The update of the list of local representatives in the Package Leaflet (Malta), and changes to bring the product information in line with the current QRD template version 8.1 were also agreed by the CHMP.
IAIN/0044	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/06/2012	n/a		
IG/0180	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/05/2012	n/a		
IB/0042	Update of SmPC Section 4.5 and 4.8 to implement wording agreed in the context of PSUR 12 on concomitant use of Zometa and anti-angiogenic	16/02/2012	24/10/2012	SmPC and PL	

	medicinal products and additional information on incidence rates of reports of renal impairment by patient cancer type. The Package Leaflet, Section 2, was updated accordingly. The MAH also took the opportunity to make minor editorial and linguistic corrections (Bulgarian, Czech, Danish, German, Greek, Estonian, Finnish, French, Hungarian, Italian, Latvian, Maltese, Polish, Portuguese, Romanian, Slovenian and Swedish). C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
IA/0041/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	16/12/2011	n/a		
IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2011	n/a		

IG/0135/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	16/12/2011	n/a		
IA/0039/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	15/12/2011	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS				
X/0035	Addition of a new pharmaceutical form 4mg/100ml solution for infusion Annex I_2.(d) Change or addition of a new pharmaceutical form	23/06/2011	24/08/2011	SmPC, Labelling and PL	This application was submitted under Article 8(3) of Directive 2001/83/EC as an extension to the licence for Zometa This is an extension of marketing authorisation, as described in Annex I to the Commission Regulation (EC) 1234/2008. The changes requiring an extension application pertinent to this application are according to the point 2(d) of annex I: A new pharmaceutical form: Solution for infusion Zometa 4 mg/100 ml solution for infusion is the same strength as that prepared by dilution of the currently approved/marketed Zometa 4 mg/5 ml concentrate. The excipients contained in the proposed "ready to use" 4 mg/100 ml presentation are the same as in the Zometa 4 mg/5 ml concentrate. The applicant applied for the following indication which is

					the same as for the authorised presentations: - Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. - Treatment of tumour-induced hypercalcaemia (TIH).
A20/0036	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 19 October 2010, the opinion of the CHMP on measures necessary to ensure the safe use of the above mentioned medicinal product further to the CHMP review on the currently available data in relation to the incidence of atypical stress fractures and its impact on the risk-benefit balance.	14/04/2011	29/06/2011	SmPC, Annex II and PL	Please refer to the Assessment Report: H-336-RAR-A20-0036-en
IG/0041/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	08/02/2011	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
II/0031	Update of SPC section 5.1 regarding clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years. SPC sections 4.2, 4.4, 4.8 and 5.2 have been revised as well considering the available data in paediatric patients. Furthermore, SPC section 4.4 has been amended with a warning regarding the concomitant use of Aclasta. In addition, changes to SPC sections 4.3, 4.6, 4.8 have been performed to align with the QRD template. Annex II has been updated with the RMP standard text reflecting the latest agreed version number. The package leaflet has been revised based on the results of a Readability Testing. Extension of Indication	17/12/2009	25/01/2010	SmPC, Annex II and PL	Please see Scientific Discussion Zometa-H-336-II-31-AR.
II/0032	Change to specification of a raw material Change to the test procedure and/or specification of a raw material	24/09/2009	29/09/2009		
II/0033	Update of SPC section 4.8 with the terms " scleritis" and "orbital inflammation" under post-marketing experience. The PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	14/07/2009	SmPC and PL	In the context of the tenth PSUR for Zometa (zoledronic acid) covering the period from 01 September 2007 to 31 August 2008 "scleritis" and "orbital inflammation" were identified as two new relevant safety findings. "Orbital inflammation" and "scleritis" safety findings were observed in 11 and 5 cases over 2.7 million treated

					patients, respectively. In some cases there were co-reports of both events. Therefore, these findings will be considered as very rare events (<1/10,000 cases).
II/0030	The MAH applied for changes in the in-process controls used in the manufacturing of the active substance. Quality changes	19/03/2009	23/03/2009		
IA/0029	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/10/2008	n/a		
II/0028	Update of SPC sections 4.3 and 4.6, i.e. deletion of the contraindication for pregnancy and revision of the breast-feeding wording as well as re-positioning of a statement to section 5.3. Furthermore, update of section 4.8 of the SPC to add "anaphylactic reaction/shock, urticaria" as undesirable effects following the 9th PSUR assessment as well as updates to sections 4.2 and 6.2 of the SPC to align with the company core data sheet. The package leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	04/07/2008	SmPC and PL	The terms "anaphylactic reaction/shock and urticaria" were added under post marketing experience of SPC section 4.8, Undesirable effects. In addition, in SPC section 4.3 the absolute contraindication during pregnancy was deleted considering the use of Zometa in life-threatening diseases and taking into account the discussion paper on contraindications in pregnancy (CPMP/3833/03). The statement in SPC section 4.6 that "Zometa should not be used during pregnancy" is maintained. SPC section 4.6 was revised to state that Zometa is contraindicated during breast-feeding in line with SPC section 4.3. In addition, information on dystocia in rats was moved to SPC section 5.3. Furthermore, minor changes to SPC sections 4.2 and 6.2 were implemented in order to provide also in section 4.2 the information that Zometa must not be mixed with calcium or other divalent cation-containing infusion solutions and should be administered as a single intravenous solution in a separate infusion line.

					Accordingly, these changes were also reflected in section 2, 3 and 6 of the PL.
IB/0027	IB_17_a_Change in re-test period of the active substance	09/04/2008	n/a		
II/0026	Update of section 4.8 of the SPC to add "atrial fibrillation" and update of section 4.9 to include information on overdose, following assessment of PSUR 8 covering the periond from 1 September 2005 to 31 August 2006. The Package Leaflet has also been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	19/10/2007	SmPC and PL	In one 3 year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs. placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (33 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with Zometa (zoledronic acid) 4 mg every 3 4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown. This information is now added in the Summary pof Product Characteristics, under section 4.8. In addition the section 4.9 (Overdose) has been updated to reflect clinical experience with overdose, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. It is recommended that in the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.
II/0024	The MAH has applied to update sections 4.4 and 4.8 of the SPC to include a precaution on renal	26/04/2007	04/06/2007	SmPC and PL	The following changes were implemented: 1) section 4.4, new subsection heading "General", in which the statements

	dysfunction, to revise the warning on osteonecrosis of the jaw and to add "bronchoconstriction" and somnolence", following the assessment of the 7th and 8th PSURs. The Package Leaflet was updated accordingly. Minor editorial changes were also introduced in the SPC. Update of Summary of Product Characteristics and Package Leaflet				are included "overhydration should be avoided in patients at risk of cardiac failure" and "the safety and efficacy of Zometa in paediatric patients have not been established" from other parts of section 4.4. The headlines "renal insufficiency", "hepatic insufficiency", "osteonecrosis of the jaw" and "musculoskeletal pain" are included at relevant paragraphs. Under the heading "renal insufficiency" the statement "renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zometa". 2) section 4.8, post marketing experience, it is stressed that Zometa is included among the biphosphonates, which may cause osteonecrosis. "Somnolence" and "bronchoconstriction" is included under the category of very rare cases. A warning on somnolence was included in the section on driving and use of machines in the Package Leaflet.
IA/0025	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/05/2007	n/a		
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2007	n/a	PL	
II/0018	Update of Summary of Product Characteristics	21/09/2006	19/10/2006	SmPC and Annex II	Update of Section 5.1 of the SPC with the results of a phase III study comparing Zometa to placebo in Japanese patients with breast cancer metastatic to the bone. Minor amendments have also been implemented into the annex II in order to comply with the latest QRD template.
IB/0020	IB_33_Minor change in the manufacture of the finished product	05/09/2006	n/a		

IB/0019	IB_33_Minor change in the manufacture of the finished product	20/07/2006	n/a		
II/0017	Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	01/06/2006	SmPC and PL	Clarifications of the warnings and update the estimated frequency of the "osteonecrosis of the jaw" under sections 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects" of the SPC. The Package Leaflet (Section 4. "Possible Side effects") has also been updated accordingly.
R/0016	Renewal of the marketing authorisation.	23/02/2006	24/04/2006	SmPC, Annex II, Labelling and PL	
II/0013	Update of Summary of Product Characteristics and Package Leaflet	17/11/2005	23/12/2005	SmPC and PL	Update of the SPC to include a warning on severe musculoskeletal pain in section 4.4 (Special warnings and special precautions for use) and to add hypotension , syncope, circulatory collapse in section 4.8 (Undesirable effects) following the assessment of the 6th PSUR. The PL was updated accordingly. In addition, the section "Possible side effects" in the Package Leaflet was amended to specify reactions related to the osteonecrosis of the jaw in detail.
IA/0015	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	14/11/2005	n/a		
IA/0014	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	22/09/2005	n/a		
II/0010	Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	22/03/2005	SmPC and PL	Update of sections 4.2, 4.4 and 6.6 of SPC in order to include dose recommendations in patients with renal impairment. The Package Leaflet has been revised accordingly.

IA/0012	IA_05_Change in the name and/or address of a manufacturer of the finished product	02/02/2005	n/a		
IA/0011	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	02/02/2005	n/a		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	04/11/2004	SmPC and PL	Addition of "uveitis, episcleritis and ostencrosis" in the SPC under section 4.8 Undesirable effects. The Package Leaflet was amended accordingly.
IB/0008	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	16/06/2004	n/a		
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2004	n/a	PL	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	04/06/2003	SmPC and PL	
II/0006	Change(s) to the test method(s) and/or specifications for the active substance	25/04/2003	30/04/2003		
X/0002	X-3-iv_Change or addition of a new pharmaceutical form	18/12/2002	16/04/2003	SmPC, Annex II, Labelling and PL	
I/0004	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	13/12/2002	07/01/2003		
II/0001	Extension of Indication	25/04/2002	19/07/2002	SmPC and PL	