Bonviva

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
WS/2451	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC to add information regarding the risk of "Atypical fractures of other long	25/01/2024		SmPC and PL	Atypical fractures of other long bones than the femur, such as the ulna and tibia have been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna

[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).

	bones", and section 4.8 of the SmPC to add "Atypical fractures of long bones other than the femur" as a new ADR with frequency 'not known', based on literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3. The RMP version 3.3 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				fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids. Although the pathophysiology is uncertain, evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains very low. For more information, please refer to the Summary of Product Characteristics.
IAIN/0079	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	07/12/2023	n/a		
WS/2507	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.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	23/11/2023	n/a		
IB/0078	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/06/2023	n/a		
IAIN/0077/G	This was an application for a group of variations.	16/05/2023	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites 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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/1702/ 202106	Periodic Safety Update EU Single assessment - ibandronic acid	24/02/2022	25/07/2022	SmPC and PL	Please refer to Bonviva EMEA/H/C/00501 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0073	A.7 - Administrative change - Deletion of manufacturing sites	03/03/2021	17/06/2021	Annex II and PL	
IA/0072	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	07/01/2021	n/a		
IA/0071	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	07/01/2021	n/a		
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2020	17/06/2021	PL	

IAIN/0069	A.1 - Administrative change - Change in the name and/or address of the MAH	13/08/2020	17/06/2021	SmPC, Labelling and PL	
IAIN/0068	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	11/06/2020	17/06/2021	Annex II and PL	
T/0067	Transfer of Marketing Authorisation	17/04/2019	22/05/2019	SmPC, Labelling and PL	
PSUSA/1702/ 201806	Periodic Safety Update EU Single assessment - ibandronic acid	14/02/2019	n/a		PRAC Recommendation - maintenance
IAIN/0065/G	This was an application for a group of variations. 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 site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	10/07/2018	22/05/2019	Annex II and PL	

	site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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 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 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 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 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				
T/0064	Transfer of Marketing Authorisation	14/03/2018	04/04/2018	SmPC,	

				Labelling and PL	
IA/0063	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	19/01/2018	n/a		
IA/0062	A.7 - Administrative change - Deletion of manufacturing sites	07/12/2017	n/a		
IA/0061	A.7 - Administrative change - Deletion of manufacturing sites	01/06/2017	n/a		
IG/0809	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/05/2017	n/a		
IB/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 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.a - Change in the manufacturing process of the finished or intermediate product - Minor change	10/02/2017	n/a		

	in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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				
WS/0942	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To implement the PRAC recommendation to add patient reminder cards as an additional risk minimisation measure to the ibandronic acid risk management plan, following the PRAC recommendation provided in PSUSA 001702-201506. The MAH is also taking this opportunity to update the RMP to the current template. The requested worksharing procedure proposed amendments to the None and to the Risk Management Plan (RMP). C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/09/2016	n/a		
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2016	04/04/2018	Labelling	

IG/0716	A.7 - Administrative change - Deletion of manufacturing sites	22/07/2016	n/a		
PSUSA/1702/ 201506	Periodic Safety Update EU Single assessment - ibandronic acid	25/02/2016	21/04/2016	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1702/201506.
WS/0870	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add angiogenesis inhibitors as a risk factor for osteonecrosis of the jaw. The Worksharing applicant (WSA) also took the opportunity to implement the PRAC recommendation related to osteonecrosis of the external auditory canal (SDA030 for Bondronat and SDA036 for Bonviva). The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to correct some minor editorial mistakes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/02/2016	21/04/2016	SmPC and PL	Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.
IA/0055/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	10/12/2015	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IB/0053/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	11/11/2015	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
WS/0740	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to update the safety information in regards to severe cutaneous adverse reactions (SCARs) identified in the postmarketing setting. Stevens-Johnson Syndrome, Erythema Multiforme, and Bullous Dermatitis have been added with a very rare frequency. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to address the request of the QRD group from 30 April2014 to revise the dilution instructions for renally impaired patients in the SmPC and PL of Bondronat 2 mg and 6 mg concentrate for solution for infusion. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2015	21/04/2016	SmPC and PL	

IB/0049	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/02/2015	n/a		
IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
IA/0046/G	This was an application for a group of variations. 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.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.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	07/08/2014	n/a		

	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				
IA/0045	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	29/07/2014	n/a		
IB/0043	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	20/03/2014	n/a		
IG/0409	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	21/02/2014	n/a		
R/0039	Renewal of the marketing authorisation.	24/10/2013	18/12/2013	SmPC, Annex II and PL	The efficacy and safety profile of oral and IV Bonviva for the Post Menopausal Osteoporosis indication is well established. It is supported by clinical development program trials and has been confirmed by subsequent studies (including retrospective analyses), literature reviews, and post-marketing surveillance data. Its adverse event profile is as expected for the bisphosphonate (BP) class. The safety profile of IV Bonviva administered every 3 months and of the 150-mg oral tablet administered monthly for PMO has been shown to be consistent with that

					of the 2.5-mg oral formulation administered daily in the clinical development program with respect to potential risks. The safety of long-term BP therapy for the prevention and treatment of osteoporosis is less clear, owing to conflicting study results regarding its possible association with ONJ (osteonecrosis of the jaw), atypical femoral fractures, or esophageal cancer. No cases of ONJ or atypical fracture were reported in the Bonviva trial program over 5 years of treatment. From review of the data on the use of Bonviva in the indication PMO the benefit risk balance remains positive for the use of Bonviva in the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established. The CHMP recommends that the renewal be granted with unlimited validity.
IB/0038/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of	31/07/2013	n/a		

	specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0040/G	This was an application for a group of variations. 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 B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions 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.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 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	11/07/2013	n/a		

IA/0037	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	10/04/2013	n/a		
IG/0256	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/12/2012	n/a		
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
II/0033	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) with information on anaphylactic reaction/shock as follows: - Bonviva 3 mg solution for injection (only): Update of SmPC section 4.4 "Special warnings and precautions for use" of the SmPC and of Package Leaflet section 2 to add a warning and precautions statement regarding anaphylactic reaction/shock. - Bonviva 150 mg film-coated tablets and 3 mg solution for injection: Update of SmPC section 4.8 "Undesirable effects" and of Package Leaflet section 4 to include safety information on anaphylactic reaction/shock. 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	15/11/2012	18/12/2013	SmPC, Annex II, Labelling and PL	The MAH has undertaken an evaluation of a safety signal, taking into account a search for anaphylactic/anaphylactoid shock conditions and anaphylactic reaction in the Roche safety database, containing all serious adverse events from clinical trials of its ibandronate products Bonviva, Bondenza and Bondronat (irrespective of reporter causality assessment) and all spontaneous reports of adverse events from countries where these drugs are marketed. A literature search and search of the UK General Practice Research Database (GPRD) was also performed. Based on analysis of all safety data generated, the MAH proposed to update sections 4.4 "Special warnings and precautions for use"and 4.8 of the Summary of Product Characteristics (SmPC) with information on anaphylactic reaction/shock. In SmPC section 4.4 of the SmPC of the presentations for intravenus administration a warning and precautions statement was added: Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.

	submitted by 6 October 2011." In addition, the product information annexes were aligned with the latest version of the new QRD template (version 8.1) and the SmPC guideline, and editorial corrections as well as linguistic corrections (DK,EL,ES,LV,MT,NL,PL,PT,RO,SK,SL) were implemented. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet. The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Appropriate medical support and monitoring measures should be readily available when intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection and initiate appropriate treatment. In SmPC section 4.8 safety information was added to inform that cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid. The Package leaflet was amended accordingly. The CHMP also accepted the proposed changes to annex II of the product information, the changes to align with the latest version of the new QRD template (version 8.1) and the SmPC guideline, and editorial and linguistic corrections.
IG/0161	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	14/03/2012	n/a		
IG/0125	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	06/12/2011	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2011	n/a	PL	

WS/0143/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. To change specifications for the active substance. To change some test procedures for an active substance and/ or starting material/reagent/intermediate. 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.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.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.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	23/09/2011	23/09/2011		

WS/0141/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. To add a new manufacturing site for the active substance. To introduce minor changes in the manufacturing process of the active substance. To introduce alternative batch sizes in active substance manufacture. To introduce alternative specification parameters and/or limits for raw materials. To introduce alternative test procedures for raw materials. 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	22/09/2011	22/09/2011		

	material/intermediate/reagent - Other variation 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				
IG/0092/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in 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	08/08/2011	n/a		
WS/0144	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SPC section 4.6 "Fertility, pregnancy and lactation" and section 5.3 "Preclinical safety data" and minor editorial changes in SPC, labelling and package leaflet following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC, Annex II, Labelling and PL	Update of SPC section 4.6 "Fertility, pregnancy and lactation" and section 5.3 "Preclinical safety data" to include effects on fertility from reproductive studies in rats; there are no data on the effects on fertility of ibandronic acid from humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility at high daily doses: increased preimplantation losses at dose levels ? 1mg/kg/day. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1mg/kg/day and decreased fertility in males at 1mg/kg/day and in females at 1.2 mg/kg/day. In addition, minor editorial changes in SPC, labelling and package leaflet were agreed.

A20/0024	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-501-RAR-A20-0024-en
WS/0086	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC section 4.8 to include safety information on ocular inflammation events. In addition update of SmPC section 6.6 (special precautions for disposal) and changes in most other sections of the annexes in line with the latest QRD template. The Package Leaflet was 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	17/03/2011	14/04/2011	SmPC, Annex II, Labelling and PL	This application was submitted as a single Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008, mainly to update SmPC section 4.8 to include safety information on ocular inflammation events (uveitis, episcleritis and scleritis). In addition update of SmPC section 6.6 (special precautions for disposal) and changes in most other sections of the annexes to bring the product information in line with the latest QRD template. The Package Leaflet was updated accordingly.

II/0023	Roche - Update of the detailed description of the pharmacovigilance system (version 4.1). Annex II has been updated accordingly. In addition, Annex II has been updated in line with the latest QRD templates and with the RMP version number (2.0) following a recent RMP update. Furthermore details of the local representative for Bonviva in Cyprus have been updated in the Package Leaflet. Update of DDPS (Pharmacovigilance)	18/03/2010	05/05/2010	Annex II and PL	With this variation the MAH submitted a new version of the DDPS (core version 4.1) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed core DDPS. In addition, Annex II has been updated in line with the latest QRD templates and with the RMP version number (2.0) following a recent RMP update. The telephone number of the local representative for Bonviva in Cyprus has been updated in the Package Leaflet.
II/0021	Update of sections 4.3 and 4.4 of the Summary of Product Characteristics to upgrade the safety information on risk of severe oesophageal irritation from section 4.4 "Special warnings and Precautions for use" to section 4.3 "Contraindications" with a strengthening of section 4.4 "Special warnings and Precautions for use". The Package Leaflet has been updated accordingly. Update of the details of the local representative and the new web address of the European Medicines Agency. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	08/02/2010	SmPC and PL	
IB/0022	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	11/12/2009	n/a	SmPC and PL	

II/0018	Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	02/07/2009	SmPC and PL	The objective of this Type II variation was to update section 4.8 of the SPC in order to bring it in line with the SPC guideline, to simplify the text as per QRD comments and to change the MedDRA frequency categories for two adverse events. This was done in response to a commitment given as a part of the renewal adopted in December 2008. In study BM16549, from year one to year two, the relationship of flatulence to the study medication has changed from possibly related to unrelated for one patient. The relationship of fatigue has also changed from possibly related to unrelated for one patient Both adverse events did not reach the 1% level at year 2 and have therefore been listed as uncommon. The Product information was revised to reflect this information.
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2009	n/a	Labelling	
IA/0019	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	04/05/2009	n/a	Annex II and PL	
R/0017	Renewal of the marketing authorisation.	18/12/2008	26/01/2009	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial marketing authorisation, the benefit risk balance of Bonviva remains positive. However the safety profile of Bonviva is to be closely monitored due to the effects of Bisphosphonates as a class, which are currently being assessed by the CHMP. Considering the safety profile of Bonviva and the large number of patients currently enrolled in clinical and post

					marketing studies for the product as well as the ongoing post-marketing obligations and the continued reports of adverse events received by the MAH, the safety profile will continue to be monitored closely and updates will be provided regularly to the CHMP through 1-yearly PSURs. Based on the safety profile of Bonviva in the treatment of osteoporosis in postmenopausal women at increased risk of fracture and considering the requirement of one-yearly PSUR submission, the CHMP recommended one additional renewal for Bonviva.
II/0016	Quality changes	30/05/2008	10/07/2008	SmPC and PL	
N/0015	The MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD templates. Furthermore the MAH took this oportunity to correct minor spelling mistakes in the Czech and Polish PL. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/01/2007	n/a	PL	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2006	n/a	PL	
IB/0013	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	13/10/2006	n/a	SmPC	

IA/0012	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/09/2006	n/a	Annex II and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	Rewording of the indication and update of section 5.1 in accordance with the draft osteoporosis guideline. Section 4.1 Treatment of osteoporosis in post menopausal women at increased risk of fracture. (see section 5.1) A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established. Section 5.1.- addition of the paragraphs below: Independent risk factors, for example, low BMD, age, the existence of previous fractures, a family history of fractures, high bone turnover and low body mass index should be considered in order to identify women at increased risk of osteoporotic fractures. In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronate appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.
IB/0011	IB_37_a_Change in the specification of the finished product - tightening of specification limits	16/08/2006	n/a		
II/0008	Update of Summary of Product Characteristics, Labelling and Package Leaflet	28/06/2006	28/07/2006	SmPC, Annex II, Labelling	The MAH applied for an update of Section 4.4 and 4.8 of the SPC to implement a CHMP class labelling for

				and PL	bisphosphonates of the risk of osteonecrosis of the jaw. The Package Leaflet has been updated accordingly. Furthermore the annexes have been updated to the latest QRD template.
IB/0010	IB_10_Minor change in the manufacturing process of the active substance	05/07/2006	n/a		
IA/0009	IA_13_a_Change in test proc. for active substance - minor change	14/06/2006	n/a		
X/0003	Annex I_2.(e) Change or addition of a new route of administration Annex I_2.(d) Change or addition of a new pharmaceutical form	26/01/2006	29/03/2006	SmPC, Labelling and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2005	n/a	PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2005	n/a	PL	
IA/0004	IA_01_Change in the name and/or address of the marketing authorisation holder	24/10/2005	n/a	SmPC, Labelling and PL	
X/0001	Annex I_2.(c) Change or addition of a new strength/potency	23/06/2005	15/09/2005	SmPC, Labelling and PL	
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	15/10/2004	n/a	SmPC and PL	