EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Bondenza

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion / Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
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/0034	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) with information on anaphylactic reaction/shock as follows: - Bondenza 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. - Bondenza 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.	15/11/2012		SPC, 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

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	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." 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, ES, EL, LV, MT, PT, RO, 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				precautions statement was added: Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid. 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		
WS/0143	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission	23/09/2011	23/09/2011		

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	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				
WS/0141	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	22/09/2011	22/09/2011		

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	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 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				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2011	n/a	PL	
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	08/08/2011	n/a		

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	pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
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 Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SPC, Annex II, Labelling, 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 and the MAH took the opportunity to update annex II (Bonviva & Bondenza) with the version number of the latest RMP update agreed by the CHMP.
A20/0025	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. Article 20 Review	14/04/2011	29/06/2011	SPC, Annex II, PL	Please refer to the Assessment Report: H-502-RAR-A20-0025-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	17/03/2011	14/04/2011	SPC, Annex II, Labelling, 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

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	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 Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				bring the product information in line with the latest QRD template. The Package Leaflet was updated accordingly.
II/0024	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. Update of DDPS (Pharmacovigilance)	18/03/2010	05/05/2010	Annex II	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.
II/0022	Update of Summary of Product Characteristics and Package Leaflet	17/11/2009	08/02/2010	SPC, PL	Please refer to the Scientific Discussion: Bondenza-H-502-II-22-SD.
IB/0023	42_a_01_Change in shelf-life of finished product - as packaged for sale	11/12/2009	n/a	SPC, PL	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	02/07/2009	SPC, 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

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					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/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2009	n/a	Labelling	
IA/0020	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, PL	
R/0018	Renewal of the Marketing Authorisation	18/12/2008	20/02/2009	SPC, Annex II, Labelling, PL	Based upon the data that have become available since the granting of the initial marketing authorisation, the benefit risk balance of Bondenza remains positive. However the safety profile of Bondenza 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 Bondenza 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 Bondenza in the treatment of osteoporosis in postmenopausal women at increased risk of fracture, and considering the requirement of one year PSUR submission, the CHMP recommended one additional renewal for Bondenza.
II/0017	Quality changes	30/05/2008	10/07/2008	SPC, PL	
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/09/2007	n/a	PL	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/01/2007	n/a	PL	

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IB/0012	42_a_01_Change in shelf-life of finished product - as packaged for sale	13/10/2006	n/a	SPC	
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2006	n/a	PL	
IA/0011	05_Change in the name and/or address of a manufacturer of the finished product	12/09/2006	n/a	Annex II, PL	
II/0006	The MAH applied for a rewording of Section 4.1 of the SPC. In addition, further information has been provided in Section 5.1 of the SPC. The Package leaflet is updated accordingly. Furthermore the MAH took the opportunity to update the List of Local Representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SPC, PL	The purpose of this Type II variation was to revise the wording of the treatment-indication in section 4.1 of the SPC as, according to the MAH, the current wording caused confusion amongst prescribers. Furthermore, additional information in section 5.1 has been introduced during the procedure together with a review of the Package Leaflet wording of the indication. In addition, minor changes in the addresses of local representatives were introduced by the MAH. The rewording of section 4.1 referred to the treatment indication only. The prevention indication was only approved for the 2.5 mg tablet and was not a subject for this variation. All forms and strengths are approved for the treatment of osteoporosis. No new clinical studies were submitted to support the rationale for the change of the indication wording. The MAH evaluated the understanding of Bondenza's therapeutic indication amongst 200 physicians (general practitioners and specialists) in the UK and Germany. The outcome of this readability test was that only one third of physicians interpreted the indication wording correctly i.e. that Bondenza is indicated for patients with postmenopausal osteoporosis at risk of fractures. The majority of physicians, 67% overall, believed the current statement to indicate that Bondenza should be used specifically for patients with postmenopausal osteoporosis at risk of vertebral fractures. The Product Information was consequently updated to improve the readability.
IB/0010	37_a_Change in the specification of the finished product - tightening of specification limits	16/08/2006	n/a		
II/0007	The MAH applied for an update of Section 4.4 and 4.8 of the SPC to implement a CHMP class labelling for bisphosphonates of	28/06/2006	28/07/2006	SPC, Annex II, Labelling, PL	The Pharmacovigilance Working Party (PhVWP) performed a class review to further investigate a possible causal relationship between bisphosphonates and osteonecrosis of the jaw, the

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	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 Update of Summary of Product Characteristics, Labelling and Package Leaflet				underlying pathophysiology, identify of risk factors and appropriate precautionary measures. Following this review, the CHMP asked the MAH to update the SPC accordingly. In this variation procedure, changes relating to osteonecrosis of the jaw, in line with the wording adopted by the CHMP, were included in the Product Information.
IB/0009	10_Minor change in the manufacturing process of the active substance	05/07/2006	n/a		
IA/0008	13_a_Change in test proc. for active substance - minor change	14/06/2006	n/a		
X/0004	Addition of a new route of administration Change or addition of a new pharmaceutical form The MAH submitted an application for Marketing Authorisation for Bondenza 3mg/3ml solution for injection under Annex II, point 2 iii, iv, v to Commission Regulation (EC) No 1085/2003. X-3-iv_Change or addition of a new pharmaceutical form, X-3-v_Addition of a new route of administration	26/01/2006	29/03/2006	SPC, Labelling, PL	This procedure introduced an i.v. dosing regime of 3mg/3ml ibandronate given every 3rd month for the indication "treatment of postmenopausal osteoporosis" and introduced a pre-filled syringe of 3mg/3ml solution for injection. The rationale for this being the Due to inconvenience associated with dosing of oral bisphosphonates since, particularly for patients with existing GI tract disease or intolerance to oral bisphosphonates, it was considered more convenient to administer drug parenterally. The MAH provided data on quality, clinical efficacy and safety in support of the claim to introduce the solution for injection as a new pharmaceutical form. The CHMP considered that the new formulation represents a very stable, soluble, well characterised and documented i.v. solution containing the active substance and common excipients. The manufacturing process of the finished product is a validated process and stability tests indicated that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. The results from the clinical trials provided demonstrate that both the 2 mg every 2 months and the 3 mg every 3 months IV ibandronate dose regimens were both non-inferior and significantly increased bone mineral density (BMD) relative to the approved oral daily dose regimen. In all ibandronate treatment groups, the mean relative increase in BMD at the lumbar spine and proximal femur was greater after 2 years of treatment than after the first year. Differences between the two i.v. regimens in BMD change were marginal and not clinically relevant. In both

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					Year 1 and Year 2 of the study, serum CTX levels observed post treatment were well within the pre-menopausal range in the vast majority of patients in all three treatment groups. The ibandronate 3 mg every 3 months IV regimen delivers efficacy that is comparable to the 2 mg every 2 months IV Ibandronate regimen, was not associated with an increase in overall adverse events, and offered the additional benefit of patient convenience as a result of fewer patient office visits
IA/0005	01_Change in the name and/or address of the marketing authorisation holder	24/10/2005	n/a	SPC, Labelling, PL	
X/0002	02_iii_Change or addition of a new strength/potency The MAH submitted an application for Marketing Authorisation for Bondenza 150 mg film-coated tablet under Annex II, point 2 iii to Commission Regulation (EC) No 1085/2003. Annex I_2.(c) Change or addition of a new strength/potency	23/06/2005	15/09/2005	SPC, Labelling, PL	Due to the inconveniences associated with intake of oral bisphosphonates (i.e. fasting conditions, frequent upper gastrointestinal intolerance) that may result in poor compliance, the MAH considered it desirable to develop a more convenient drug formulation and a monthly oral regimen was expected to offer greater benefits to postmenopausal women, with respect to therapeutic convenience. The MAH provided data on quality, non-clinical and clinical efficacy and safety in support of the claim to introduce the new pharmaceutical form. New non-clinical studies undertaken to support the 150 mg dose once a month showed that the safety margins were comparable to those observed with other bisphosphonates and/or dosing regimens and suggest that the proposed dosing regimen of 150 mg ibandronic acid p.o. once a month is unlikely to be associated with any significant risk of kidney toxicity. The evaluation of the efficacy of the once monthly treatment of osteoporotic postmenopausal women with ibandronate was based on a single pivotal multicenter, randomised, double-blind, parallel group Phase III study, which was designed to demonstrate non-inferiority, in terms of lumbar BMD changes from baseline, between daily and monthly ibandronate applications. Ibandronate 150 mg once monthly was associated with a significant and robust increase in BMD at the lumbar spine (LS) and proximal femur. This increase was significantly and consistently greater than that seen with the 2.5 mg daily regimen after two years. Furthermore, the mean additional increase in BMD during the second year of treatment was

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					greatest in the 150 mg monthly group (1.6%). The two years clinical safety data from this study provided evidence that the use of a 150 mg once-monthly dose is associated with a generally acceptable safety profile. Especially, there were no indications of nephrotoxicity or any development of aseptic osteonecrosis after 2 years of treatment.
IB/0003	42_a_01_Change in shelf-life of finished product - as packaged for sale	15/10/2004	n/a	SPC, PL	
IB/0001	02_Change in the name of the medicinal product	18/08/2004	n/a	SPC, Labelling, PL	