Bondronat

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.
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/0091/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/05/2023		Annex II and PL	

	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				
IA/0088	A.7 - Administrative change - Deletion of manufacturing sites	03/03/2021	16/07/2021	Annex II and PL	
IA/0087	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/0086	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/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/12/2020	16/07/2021	PL	
IAIN/0084	A.1 - Administrative change - Change in the name and/or address of the MAH	13/08/2020	16/07/2021	SmPC, Labelling and PL	
IAIN/0083	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	16/07/2021	Annex II and PL	
T/0082	Transfer of Marketing Authorisation	24/04/2019	20/05/2019	SmPC, Labelling and PL	
PSUSA/1702/ 201806	Periodic Safety Update EU Single assessment - ibandronic acid	14/02/2019	n/a		PRAC Recommendation - maintenance
IAIN/0080/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	10/07/2018	20/05/2019	Annex II and PL	

	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 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.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 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/0079	Transfer of Marketing Authorisation	14/03/2018	04/04/2018	SmPC, Labelling and PL	
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/0077/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 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	30/03/2017	n/a		
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	15/09/2016	n/a		

	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				
N/0076	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	25/04/2016	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	11/02/2016	25/04/2016	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

	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				chronic ear infections.
IA/0073/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	10/12/2015	n/a		
IB/0071/G	This was an application for a group of variations. 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	11/11/2015	n/a		

	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 changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
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	28/05/2015	25/04/2016	SmPC and PL	

	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				
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		
IB/0066	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		
II/0064	Update of SmPC section 4.8 and PL Section 4 to include "asthma exacerbation" in the adverse drug reaction section. Furthermore the PI is brought in line with the latest QRD template version 9 and	20/03/2014	26/03/2015	SmPC, Annex II, Labelling and PL	The MAH has updated the Company Core Data Sheet (CDS) for all Ibandronic acid products, including Bondronat to include "asthma exacerbation". The data for the Bondronat indications are very sparse as among the 76 identified

	changes to harmonize the package leaflet with the SmPC and to enhance the readability of the annexes were agreed. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				cases, the treatment indication in only 4 cases was oncology related, the indication was related to osteoporosis for 56 cases, and in 16 cases the product was used for an unknown indication. The CHMP accepted addition of asthma exacerbation provided that it was added in section 4.8 of the SmPC as an adverse event with unknown frequency. The benefit-risk assessment for oral and IV formulations of Bondronat (ibandronic acid in the oncology setting) remains unchanged.
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		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2013	26/03/2015	PL	
IA/0062/G	This was an application for a group of variations. 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	10/04/2013	n/a		
IG/0256	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	21/12/2012	n/a		

	changes to an approved test procedure				
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
II/0059	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) with information on anaphylactic reaction/shock as follows: - Bondronat 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion (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. - Bondronat 50 mg film-coated tablets and 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion : 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 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 (in BG, DK, EL, ES, IS, LV, NL, PT, RO, SL) were	15/11/2012	03/12/2013	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. 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

	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				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.
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	23/09/2011	23/09/2011		

	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/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	22/09/2011	22/09/2011		

	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/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2011	n/a	PL	
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.	23/06/2011	26/07/2011	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

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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.
IB/0054/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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	15/07/2011	n/a		
IB/0053/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.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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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	06/07/2011	n/a		

	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				
A20/0051	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-101-RAR-A20-0051_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.	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.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/03/2011	n/a	PL	
II/0050	Update of SPC section 4.2 to add dosing recommendations for patients with moderate renal impairment. Furthermore, the MAH proposes to amend SPC section 5.2 with information for patients with different grades of renal impairment. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	25/01/2010	SmPC and PL	Results of a pharmacokinetic open-label, single centre, non-randomised, parallel group study in subjects with varying degrees of renal function were submitted. In subjects with mild renal impairment no clinically meaningful increase in exposure was found. In subjects with moderate and severe renal impairment, AUC exposure increased by 86 and 110%, respectively. The i.v. data were extrapolated (based on the estimation of cumulative AUC's assuming a 40% increase in AUC according to a regression model) to provide dosing recommendations for the oral formulation. The SPC posology section (4.2) is amended to add a recommendation for dose reduction in patients with moderate renal impairment: - from 6 mg to 4 mg (concentrate for solution for infusion) - from one 50 mg film-coated tablet every day to one 50 mg film-coated tablet every second day Dosing recommendations for patients with severe renal impairment had been previously assessed by the CHMP and remain valid. The SPC section 5.2 and the package leaflet are amended accordingly.
II/0049	Update of the Summary of Product Characteristics (SPC) section 4.3 to add a contraindication for	17/12/2009	25/01/2010	SmPC, Labelling and	Please refer to the Scientific Discussion: Bondronat-H-101-

	"hypocalcaemia" in line with the already existing warning for the oral and IV formulation. Update of SPC section 4.3 to add a new contraindication related to severe oesophageal irritation as well as to further strengthen the already existing warning in SPC section 4.4 in this respect for the oral formulation. Update of SPC 4.2 to clarify the method of administration. The labelling and package leaflet has been updated accordingly. Update of the details of the local representatives and the new web address of the European Medicines Agency in the Package leaflet. Update of Summary of Product Characteristics and Package Leaflet			PL	II-49-SD.
II/0048	Introduction of minor changes in the manufacturing process and in-process controls of Bondronat vials 2mg/2ml and 6mg/6ml, following the addition of a production line at the registered manufacturing site Quality changes	17/12/2009	06/01/2010		
II/0047	Change in the qualitative composition of the rubber stoppers for Bondronat vials 2mg/2ml and 6mg/6ml. Quality changes	17/12/2009	06/01/2010		
IA/0046	IA_08_b_01_Change in BR/QC testing - repl./add.	15/06/2009	n/a	Annex II and	

	manuf. responsible for BR - not incl. BC/testing			PL	
IB/0045	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	10/03/2009	n/a	SmPC	
IB/0044	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	18/09/2007	n/a	SmPC	
II/0042	The MAH applied to reduce the currently approved infusion time for the indication of prevention of skeletal events in patients with breast cancer and bone metastases from 1 hour to 15 minutes. The MAH has also taken the opportunity to update the product information according to the latest QRD template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	06/03/2007	SmPC, Annex II, Labelling and PL	The proposed changes are related to the reduction of the infusion time for intravenous ibandronic acid (6 mg every 3-4 weeks) from 60 minutes to at least 15 minutes in patients with breast cancer and bone metastases. The application is based on the results of one international, randomized, multicenter safety study (ML17632). In this study, ibandronic acid (6 mg) was administered either as a 15 minute infusion (n=101) or as an infusion over 60 minutes (n=26) every 3-4 weeks for 6 months. The safety profile of patients who received the 15 minute infusion was compared with that of the known safety profile for ibandronic acid. Renal safety of ibandronic acid was determined based on the change from baseline of a number of biochemical indicators of renal function Only two patients experienced an increase in serum creatinine of 3 44.2 mmol/L from baseline. Although both patients were receiving the 15 minute infusion of ibandronic acid, their previous medical history or concurrent disease status were the most likely underlying reasons for the observed elevations in serum creatinine. The overall adverse event profile of ibandronic acid following the 15 minute infusion was consistent with the known safety profile over longer infusion times and no new

					safety concerns were identified relating to the use of a 15 minute infusion of 6 mg i.v. ibandronic acid in the metastatic breast cancer setting. However, patients included in ML17632 all had normal renal function or mild renal impairment and as a consequence of the lack of information on the renal safety profile of the 15 minute infusion in patients with moderate or severe renal impairment, the proposal to shorten the recommended infusion time for 6 mg i.v. ibandronic acid applies only to metastatic breast cancer patients with normal renal function or mild renal impairment.
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	15/12/2006	n/a	Annex II and PL	
IB/0040	IB_10_Minor change in the manufacturing process of the active substance	07/07/2006	n/a		
R/0038	Renewal of the marketing authorisation.	27/04/2006	26/06/2006	SmPC, Annex II, Labelling and PL	
IA/0039	IA_13_a_Change in test proc. for active substance - minor change	23/06/2006	n/a		
IA/0037	IA_01_Change in the name and/or address of the marketing authorisation holder	09/11/2005	n/a	SmPC, Labelling and PL	
IB/0036	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	21/06/2005	n/a	SmPC, Labelling and PL	

IA/0035	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	04/05/2005	n/a	SmPC and PL	
IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	23/03/2005	n/a		
II/0029	Change(s) to container	16/09/2004	22/10/2004	SmPC, Labelling and PL	
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/06/2004	n/a	PL	
IB/0031	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	17/06/2004	n/a	SmPC and PL	
IB/0026	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/01/2004	n/a	SmPC	
II/0022	Extension of Indication	24/07/2003	07/11/2003	SmPC and PL	
II/0025	New presentation(s)	24/07/2003	31/10/2003	SmPC, Labelling and PL	
X/0023	X-3-iv_Change or addition of a new pharmaceutical form	24/07/2003	24/10/2003	SmPC, Annex II, Labelling and PL	
I/0021	25_Change in test procedures of the medicinal product	30/08/2002	10/09/2002		

X/0017	X-3-iii_Addition of new strength	29/03/2001	13/09/2001	SmPC, Annex II, Labelling and PL	
R/0018	Renewal of the marketing authorisation.	27/04/2006	12/09/2001	SmPC, Annex II, Labelling and PL	
II/0020	Update of Summary of Product Characteristics	25/04/2001	12/09/2001	SmPC	
II/0019	Update of Summary of Product Characteristics	25/04/2001	12/09/2001	SmPC	
I/0016	30_Change in pack size for a medicinal product	23/02/2001	23/04/2001	SmPC, Labelling and PL	
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/05/2000	27/06/2000	PL	
I/0013	20_Extension of shelf-life as foreseen at time of authorisation	05/08/1999	16/11/1999	SmPC and PL	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/1999	16/11/1999	PL	
I/0012	11_Change in or addition of manufacturer(s) of active substance 01_Change in the name of a manufacturer of the medicinal product	09/02/1999	11/05/1999	Annex II and PL	
T/0011	Transfer of Marketing Authorisation	09/02/1999	29/03/1999	SmPC, Labelling and	

				PL	
I/0010	25_Change in test procedures of the medicinal product	21/12/1998	n/a		
I/0009	25_Change in test procedures of the medicinal product	18/12/1998	n/a		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/07/1998	18/09/1998	Labelling and PL	
I/0007	12_Minor change of manufacturing process of the active substance 14_Change in specifications of active substance	10/06/1998	n/a		
II/0004	New presentation(s)	16/04/1997	27/08/1997	SmPC, Labelling and PL	
I/0006	13_Batch size of active substance	26/05/1997	n/a		
I/0005	12_Minor change of manufacturing process of the active substance	26/05/1997	n/a		
I/0001	15_Minor changes in manufacture of the medicinal product	12/02/1997	n/a		
I/0002	25_Change in test procedures of the medicinal product	10/10/1996	n/a		