Adrovance

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/2696	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of an updated RMP version 8.1 following the assessment outcome from procedure WS/2467 to	31/10/2024	n/a		not applicable

[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).

	reclassify the risk of atypical femoral fracture from "important potential risk" to "important identified risk" and to extend the risk of "atypical femoral fracture" to "atypical fractures of long bones". Further, the MAH took the opportunity to update the information in the RMP regarding important identified risks and missing information. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IG/1756	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	16/07/2024	27/09/2024	Annex II and PL	
WS/2699	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	06/06/2024	n/a		
IG/1711/G	This was an application for a group of variations.	27/02/2024	n/a		

	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.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
WS/2467	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 in order to include information on the risk of 'atypical fractures of other bones' (than the femur), and update of section 4.8 to add 'atypical fractures of other bones' as a new ADR with frequency 'not known' and to include further information about the risk of 'atypical subtrochanteric and diaphyseal femoral fractures', based on post-marketing case reports and literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes and to bring the product information in line with the latest QRD template and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	30/11/2023		SmPC, Labelling and PL	Although the pathophysiology is uncertain, consistent 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 rare. Atypical fractures of other bones, such as the ulna and tibia have also 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 fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids. For more information, please refer to the Summary of Product Characteristics.

	data				
IG/1634/G	This was an application for a group of variations. 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.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	04/10/2023		Annex II and PL	
IG/1488	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	14/03/2022	n/a		
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2021		PL	
PSUSA/79/2020/2101	Periodic Safety Update EU Single assessment - alendronic acid / colecalciferol, alendronic acid / calcium / colecalciferol	02/09/2021	n/a		PRAC Recommendation - maintenance
T/0047	Transfer of Marketing Authorisation	17/03/2021	21/04/2021	SmPC, Labelling and	

				PL	
IG/1353	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/02/2021	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/01/2021	21/04/2021	PL	
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2020	21/04/2021	PL	
WS/1857	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/09/2020	21/04/2021	SmPC, Labelling and PL	
IG/1266	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	14/07/2020	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2020	21/04/2021	PL	
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2018	21/04/2021	PL	
T/0039	Transfer of Marketing Authorisation	13/06/2018	06/07/2018	SmPC,	

				Labelling and PL	
IG/0764	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	31/01/2017	n/a		
R/0036	Renewal of the marketing authorisation.	21/07/2016	19/09/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Adrovance in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/79/201601	Periodic Safety Update EU Single assessment - alendronic acid / colecalciferol, alendronic acid / calcium / colecalciferol	02/09/2016	n/a		PRAC Recommendation - maintenance
WS/0862	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/04/2016	02/06/2016	SmPC and PL	
IG/0632	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2015	n/a		
WS/0752	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	24/09/2015	02/06/2016	SmPC and PL	

	Update of the SmPC section 4.4 to add 'angiogenesis inhibitors' as another example of a risk factor for ONJ. The Package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/06/2015	02/06/2016	SmPC, Annex II, Labelling and PL	
IG/0516	A.7 - Administrative change - Deletion of manufacturing sites	21/01/2015	n/a		
WS/0657/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. Type IB (B.I.a.2.e) – To introduce a minor change in the manufacturing process of the active substance to the restricted part of an Active Substance Master File. Type IA (B.I.b.1.c) – To introduce a specification parameter of a reagent used in the manufacturing process of the active substance Type IA (A.4) – To change the company name of the drug substance manufacturer from BASF Health & Nutrition A/S to BASF A/S Type IAIN (B.III.1.a.3) – To submit a new Ph. Eur. certificate of suitability from a new manufacturer for	18/12/2014	n/a		

	cholecalciferol. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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 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.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
IB/0030	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/12/2014	n/a		
IG/0481	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	29/09/2014	n/a		
IG/0366	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	08/11/2013	n/a		

	(including contact details) and/or changes in the PSMF location				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2013	02/06/2016	PL	
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
WS/0212/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling	19/04/2012	19/04/2012		
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/01/2012	02/06/2016	PL	
R/0013	Renewal of the marketing authorisation.	22/09/2011	21/11/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Adrovance remains positive, but considers that its safety profile is to be closely monitored for the following reasons: There are a number of ongoing safety issues for alendronate for which post-marketing studies are ongoing or planned, the results of which are expected to yield important new safety data which could impact on the

					benefit-risk balance of the product. These studies pertain to oesophageal adverse effects and atypical femoral fractures Therefore, based upon the safety profile of Adrovance, which requires the submission of 3-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IG/0112	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	11/10/2011	n/a		
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2011	n/a	PL	
A20/0012	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-759-RAR-A20-0012-en
IG/0060/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished	27/04/2011	n/a	SmPC, Labelling and PL	

	product formulation - Change that affects the product information				
WS/0095	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 to re-structure section 4.8 (and corresponding section in the PL) in accordance with the current SPC Guideline and QRD guidance, as agreed during the assessment of the FOSAVANCE Renewal. In addition the MAH requested changes in Section 6 of the PL in the details of local representatives and a minor change in Annex II (deletion of DDPS version number). This application was submitted as a Type II variation 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	17/02/2011	18/03/2011	SmPC, Annex II and PL	The information in section 4.8 of the SPC is restructured according to QRD guidance and the Guideline on Summary of Product Characteristics Rev.2 (September 2009). The previous separate tables for adverse reactions reported during clinical studies and/or post-marketing use with defined frequency, and adverse reactions reported during post-marketing experience with unknown frequency, have been consolidated into one single tabulated list of adverse reactions. Additionally, the frequency category for the adverse reactions that had been added to the label based on post-marketing data was re-assessed according to EU SmPC Guideline. In addition the MAH details of the local representatives in Section 6 of the PL were amended and the version number of the DDPS was deleted from Annex II .
IG/0040	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	18/01/2011	n/a		
WS/0038	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/10/2010	29/11/2010	SmPC and PL	This variation concerns an update of the SPC, further to a cumulative review by the MAH of spontaneous reports describing osteonecrosis of the jaw (ONJ), to add

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				"smoking" as a risk factor for ONJ in section 4.4 of the SPC. The application was submitted as a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. As the information about ONJ in the Product Information did not fully reflect the key messages regarding the risk minimisation measures for ONJ as identified in the Article 5(3) Referral on bisphosphonates and ONJ, additional wording fully reflecting those key messages were implemented in SPC section 4.4. The description of ONJ in SPC section 4.8 was shortened. The PL was amended accordingly, informing patients about the symptoms of ONJ and what action to take; advising on the need for patients to maintain good oral hygiene, to receive routine dental check ups and to report any oral symptoms such as dental mobility, pain or swelling; advising on the possible need for patients to have a dental check- up before starting treatment with the medicinal product. In addition, the PL section 2 was reformatted for FOSAVANCE/ADROVANCE/VANTAVO to make it consistent with FOSAMAX; the details of the Dutch local representative in Section 6 were amended; the ADROVANCE and VANTAVO annexes were harmonised with the annexes of Fosavance as agreed during the Fosavance Renewal (QRD changes).
IG/0027/G	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	10/11/2010	n/a	Annex II	

	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				
IG/0020	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/09/2010	n/a		
IG/0003	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	06/05/2010	n/a	Annex II and PL	
II/0011	Update of section 4.4 'Special warnings and precautions for use' of the SPC to list Barrett's oesophagus as one of the oesophageal diseases requiring caution when alendronate therapy is administered, following a request from the CHMP. Update of section 2 'Before you take Adrovance' of the PL accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	29/10/2009	SmPC and PL	Following the assessment of the MAH's cumulative review of alendronate and oesophageal carcinoma, the CHMP concluded that Barrett's oesophagus is a potentially premalignant condition of the oesophagus and a significant marker for the development of oesophageal cancer. Although the data are currently inconclusive and further investigation is required, the possibility that alendronate use may be associated with an increased risk of oesophageal cancer can not be excluded. Therefore Barrett's oesophagus was included as a warning in section 4.4 of the SPC.
II/0010	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 6.0. Annex II has been updated to reflect the version number of the DDPS.	25/06/2009	16/07/2009	Annex II	The MAH updated its DDPS and submitted therefore this type II variation. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements and is considered acceptable.

	Update of DDPS (Pharmacovigilance)				
II/0009	To update section 4.2, 4.4, 4.5, 4.7 and 4.8 of the SPC following the outcome of the final assessment for nationally authorised Alendronate containing medicinal products under the PSUR Work-sharing Agreement procedure. Sections 2, 3 and 4 of the PL have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	02/07/2009	SmPC and PL	The present variation introduced the following changes: Clarification on the need to swallow the tablet as a whole, in section 4.2 and clarification on the known risk in increasing bone mineral, decreases in serum calcium and phosphate especially in patients taking glucocorticoids was introduced in section 4.4. In addition, section 4.7 was updated following certain adverse drug reactions which may affect ability to drive. Furthermore, section 4.5 was updated to include that caution should be used during concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) with alendronate due to an increased risk of serious upper GI complications in patients taking NSAIDs and alendronate concomitantly, and in section 4.8 dysgeusia was added as side effect. The PL has been updated accordingly.
II/0008	To update sections 4.4 and 4.8 of the SPC with low energy stress fractures and to update the post-marketing experience in section 4 of the PL accordingly as requested by CHMP in December 2008. The MAH also took the opportunity to correct the numbering of sections 1 and 3 of the PL in the annexes of Adrovance 70 mg/5600 IU tablets and to correct minor editorial errors in section 6 of the PL for both Adrovance 70 mg/2800 IU tablets and Adrovance 70 mg/5600 IU tablets. Update of Summary of Product Characteristics and	19/02/2009	07/04/2009	SmPC and PL	For further information please refer to the Scientific Discussion: Adrovance-H-759-II-08-AR.

	Package Leaflet				
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/11/2008	n/a	PL	
II/0006	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) with the term "alopecia" based on a review of spontaneously reported adverse events. The section 4 "possible side effects" of the Package Leaflet (PL) is updated accordingly. In addition, the MAH takes the opportunity to update the PL with new contact details for Iceland. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	31/07/2008	SmPC and PL	From the time of market introduction of alendronate (16 July 1993) to 31 January 2008 the Marketing Authorisation Holder has received a total of 1720 spontaneous adverse reaction reports of alopecia in association with alendronate. A total of 224 reports had evidence of recovery/recovering upon discontinuation of alendronate therapy, including 23 reports in which patients restarted alendronate therapy and the condition recurred. The reported adverse events were generally characterised by diffuse loss of scalp hair 1-2 months after initiation of alendronate therapy. As an improvement or full recovery upon discontinuation of alendronate therapy was observed in some of the cases, the CHMP considered that a causal relationship between alopecia and alendronate therapy cannot be excluded and agreed to include the term 'alopecia' in section 4.8 of the SPC and accordingly in the PL.
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/01/2008	n/a	PL	
II/0003	To add periodontal disease as a risk factor for osteonecrosis of the jaw (ONJ) in association with bisphosphonates in section 4.4 of the SPC. Update of Summary of Product Characteristics	20/09/2007	31/10/2007	SmPC	Evidence from the literature and spontaneous reports indicated that periodontal disease is a risk factor for Osteonecrosis of the jaw (ONJ) associated with bisphosphonates. Periodontal disease was found in a subset of the patients in a review of spontaneous cases reported with alendronate. A total of 147 spontaneous reports of ONJ in association with alendronate sodium and

					alendronate sodium/colecalciferol were identified. In 48 of these reports the patients had periodontal disease and/or other concurrent oral conditions including gum disorders and ill-fitting dentures. The CHMP therefore agreed to update the SPC to include periodontal disease as a risk factor for ONJ.
X/0001	This application consists in the increase of the strength of vitamin D (colecalciferol) contained within the combination with alendronate 70mg from 2800 IU to 5600 IU per tablet to be taken once a week in order to further reduce the risk of vitamin D deficiency in risk patient groups including the elderly. The overall risk-benefit is considered to be favourable. Given the importance of adequate vitamin D status in osteoporotic patients, and the evidence of a high incidence of vitamin D insufficiency in osteoporotic patients, this treatment would simplify therapy and help to prevent vitamin D insufficiency in this group. Furthermore, the satisfactory safety profile of the combination tablet, in both baseline vitamin D sufficient and insufficient subjects, would make it suitable for patients without the need for prior assessment of vitamin D status. The Product Information of the 70 mg/5600 IU tablets reflects also that this tablet should be given to patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency. Annex I_2.(c) Change or addition of a new strength/potency	19/07/2007	02/10/2007	SmPC, Labelling and PL	This application consists in the increase of the strength of vitamin D contained within the combination of alendronate 70mg/ colecaliferol (Vitamin D) from 70 2800 IU to 5600 IU per tablet to be taken once a week in order to further reduce the risk of vitamin D deficiency in risk patient groups including the elderly. The overall risk-benefit is considered to be favourable. Given the importance of adequate vitamin D status in osteoporotic patients, and the evidence of a high incidence of vitamin D insufficiency in osteoporotic patients, this treatment would simplify therapy and help to prevent vitamin D insufficiency in this group. Furthermore, the satisfactory safety profile of the combination tablet, in both baseline vitamin D sufficient and insufficient subjects, would make it suitable for patients without the need for prior assessment of vitamin D status.

N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/03/2007	n/a	PL	