EMA/172882/2021

Conbriza

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
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/03/2021		PL	
IB/0053	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2020		SmPC, Annex II, Labelling	

[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).

				and PL	
PSUSA/302/201910	Periodic Safety Update EU Single assessment - bazedoxifene	11/06/2020	n/a		PRAC Recommendation - maintenance
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019		PL	
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019		PL	
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018		PL	
T/0047	Transfer of Marketing Authorisation	11/07/2018	02/08/2018	SmPC, Labelling and PL	
IA/0046/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites	23/05/2018	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/05/2018	02/08/2018	Labelling	
PSUSA/302/201610	Periodic Safety Update EU Single assessment - bazedoxifene	05/05/2017	n/a		PRAC Recommendation - maintenance

IB/0043	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	26/01/2017	n/a		
IA/0042	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/12/2016	n/a		
N/0041	Update of the package leaflet with revised contact details of the local representatives for France, Germany, Italy and Spain. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2016	02/08/2018	PL	
PSUSA/302/201510	Periodic Safety Update EU Single assessment - bazedoxifene	26/05/2016	22/07/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/302/201510.
IB/0039/G	This was an application for a group of variations. 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	08/02/2016	n/a		

II/0038	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	24/09/2015	n/a		
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	26/05/2016	PL	
II/0036	Update of section 4.8 of the SmPC in order to update ADRs frequency categories to align with the Company Core Data Sheet. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder took the opportunity to make minor editorial changes to section 4.2 of the SmPC to bring it in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	26/05/2016	SmPC and PL	Based on the review of frequency analyses of the already labelled ADRs, frequencies of the ADRs retinal vein thrombosis (change from 'rare' to 'uncommon'), oedema peripheral ('common' to 'very common'), rash ('frequency unknown' to 'common'), and pruritus ('frequency unknown' to 'common') have been changed in SPC section 4.8 and PL section 4 has been amended accordingly.
PSUSA/302/201410	Periodic Safety Update EU Single assessment - bazedoxifene	07/05/2015	n/a		PRAC Recommendation - maintenance
PSUV/0034	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
R/0032	Renewal of the marketing authorisation.	18/12/2013	17/02/2014	SmPC, Annex II and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the granting of the initial marketing authorisation, the CHMP considered that the benefit-risk balance of Conbriza in the

					authorised indications remains favourable and therefore recommended the renewal of the marketing authorisation, subject to the conditions as laid down in Annex II to the Opinion. The CHMP considered that the Marketing Authorisation could be granted with unlimited validity. The CHMP recommended amendments to the Annexes I, II and IIIB. These changes do not affect the benefit-risk balance of the product, which remains positive.
II/0033	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	18/12/2013	n/a		
IB/0031	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	22/05/2013	14/08/2013	SmPC	
IA/0030	A.7 - Administrative change - Deletion of manufacturing sites	22/02/2013	n/a		
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
IB/0027	B.I.a.2.e - Changes in the manufacturing process of	30/11/2012	n/a		

	the AS - Minor change to the restricted part of an ASMF				
IB/0026	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	30/11/2012	n/a		
IA/0028	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	14/11/2012	n/a		
A20/0025	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the CHMP further to the concerns raised during a Good Clinical Practice inspection on the conduct of bio-analytical studies by the Cetero Research facilities (Houston, USA), to assess the impact thereof on the risk-benefit balance of Conbriza and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	19/07/2012	01/10/2012		Please refer to the assessment report : EMEA/H/C/913/A-20/0025
IB/0023/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	25/07/2012	n/a		

	packaging, for non-sterile medicinal products 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				
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	08/06/2012	n/a		
IA/0022	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	29/05/2012	n/a		
II/0021	This type II variation concerns an update of SmPC sections 4.4, 4.8 and 5.1 with relevant safety and efficacy data obtained following 7 years of treatment with bazedoxifene in extension II to Study 3068A1-301-WW. In addition, upon request by the CHMP following the assessment of PSUR 4, the MAH proposes the addition of wording in section 5.1 of the SmPC to include the incidences of thyroid cancer and	19/04/2012	25/05/2012	SmPC, Annex II, Labelling and PL	The efficacy and safety data supporting the marketing authorisation for bazedoxifene were based on the multicentre, double-blind, randomized, placebo and raloxifene controlled, Phase 3 study 3068A1-300 GL in postmenopausal women for the prevention of osteoporosis and the 36 month, multicentre, double-blind, randomized, placebo and raloxifene controlled, Phase 3 study 3068A1-301 WW in older, postmenopausal women for the

	ovarian cancer observed in Study 3068A1-301-WW, and the update of sections 4.7 and 4.8 of the SmPC to include information on the ocular adverse events reported and advice regarding the effects of these events on the ability to drive. The Package Leaflet has been updated accordingly. Furthermore, the MAH has taken the opportunity to update the annexes in line with the latest QRD template, version 8, and to update the list of local representatives in the 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				treatment of osteoporosis. The 3 year Core study of 301 WW (CSR 39808) was extended by two 2 year double-blind, placebo-controlled study extensions (Extensions I and II) to assess the long-term efficacy and safety of bazedoxifene in the reduction in fracture incidence in postmenopausal women with osteoporosis. Extension I was a 2-year extension from the end of Year 3 until the end of Year 5 (Month 60); the results of the 5-year period of the Core study and Extension I were presented in CSR-74587. Extension II was the second 2-year extension, from the end of Year 5 until the end of Year 7 (Month 84); the efficacy and safety data for the 7 year period of the Core study and Extensions I and II are presented within this variation application (CSR-81179). A total of 1,732 subjects continued into the second 2-year extension (bazedoxifene 20 mg: n=560, bazedoxifene 40/20 mg: n=582, and placebo: n=590). After 7 years of treatment, the incidence of new vertebral fractures remained lower in the bazedoxifene 20 mg group (7.64%) compared to placebo (9.90%) with a relative risk reduction of 30% (p=0.022). The increases in BMD (bone density) relative to placebo remained statistically significant at the femoral neck, femoral trochanter, and total hip. The increase from baseline in lumbar spine BMD at 7 years in the bazedoxifene 20 mg group was not statistically greater than in the placebo group. After 7 years the rate of VTE (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis) per 1,000 women-years was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group (relative risk 1.51). The rate per 1,000 women-years for ischaemic strokes was the same for the 20 mg bazedoxifene (1.78) and the

					placebo (1.78) groups. The rate per 1,000 women years for TIA was higher for the bazedoxifene 20 mg group (0.96) compared to placebo (0.55). With reference to effects on the uterus, after 7 years of treatment, the endometrial thickness in the bazedoxifene 20 mg group did not change and remained similar to placebo; there were no cases of endometrial cancer in the bazedoxifene 20 mg group compared to 7 cases in the placebo group ($p<0.008$). In the osteoporosis treatment study in 7,492 postmenopausal women (mean age, 66 years), among 1,886 subjects treated with bazedoxifene (20 mg), there were 5 cases of thyroid cancer (0.69 per 1,000) and among 1,885 subjects treated with placebo, there was 1 case of thyroid cancer (0.14 per 1,000) after 7 years of treatment. There were no cases of thyroid cancer in the 40 mg treatment group up to 5 years. Further, there were 5 cases of ovarian cancer (0.69 per 1,000) and among 1,885 subjects treated with placebo, there were 0 cases of ovarian cancer after 7 years of treatment. There was one case of ovarian cancer in the 40 mg treatment group up to 5 years. After 7 years of treatment, there were 13 cases of breast cancer in the bazedoxifene 20 mg group (1.78 per 1,000 women-years) and 11 cases in the placebo group (1.50 per 1,000 women-years). There have been post-marketing reports of ocular events other than retinal vein thrombosis. These reports include visual acuity reduced, blurred vision, photopsia, visual field defect, visual impairment, dry eye, eyelid oedema, blepharospasm, eye pain and eye swelling. The underlying nature of these events is uncertain. If ocular symptoms occur, patients should be advised to seek medical attention

					and should avoid driving or use of machines that requires accurate visual perception until symptoms have resolved, or until they have received medical advice that it safe to do so.
IB/0017/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	21/07/2011	n/a		
IB/0018/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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	08/07/2011	n/a		
IA/0019/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	28/06/2011	n/a		

	B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0015/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	14/06/2011	n/a		
IA/0016	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	12/05/2011	n/a		
WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	14/04/2011		
IA/0014	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	12/04/2011	n/a	Annex II and PL	
IA/0013	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	11/03/2011	n/a		

	changes to an approved test procedure				
II/0010	Update of Summary of Product Characteristics, Annex II and Package Leaflet. Please refer to the scientific discussion "Conbriza/H/C/000913/II/10". C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC, Annex II and PL	This type II variation concerns an update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC to add safety and efficacy information after long-term treatment for up to 5-years from an extension of the pivotal Study 301-WW. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update Annex II with the standard DDPS wording, to update the annexes in line with the current QRD template, version 7.3.1 and the Guideline on Summary of Product Characteristics, revision 2, and to update the list of local representatives in the Package Leaflet.
T/0012	Transfer of Marketing Authorisation	29/11/2010	20/12/2010	SmPC, Labelling and PL	
IB/0011	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	02/12/2010	02/11/2010	SmPC, Labelling and PL	
IA/0008/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.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	23/04/2010	n/a	Annex II	

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
N/0009	Update of 7 local Pfizer representatives in the package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/04/2010	n/a	PL	
IB/0007	IB_33_Minor change in the manufacture of the finished product	05/02/2010	n/a		
IA/0006	IA_13_a_Change in test proc. for active substance - minor change	17/11/2009	n/a		
IA/0005	IA_09_Deletion of manufacturing site	13/10/2009	n/a		
IA/0004	IA_09_Deletion of manufacturing site	13/10/2009	n/a		
IA/0003	IA_13_a_Change in test proc. for active substance - minor change	11/09/2009	n/a		

IA/0002	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	11/09/2009	n/a		
IA/0001	IA_13_a_Change in test proc. for active substance - minor change	14/08/2009	n/a		