EVRA

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
IB/0051/G	This was an application for a group of variations. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	13/06/2022		SmPC, Labelling and PL	

[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).

	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				
IAIN/0050/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary 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	20/09/2021		Annex II and PL	
II/0048/G	This was an application for a group of variations. B.II.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	02/09/2021	n/a		
T/0049	Transfer of Marketing Authorisation	06/08/2021	20/08/2021	SmPC, Labelling and PL	
PSUSA/1311/ 201911	Periodic Safety Update EU Single assessment - ethinylestradiol / norelgestromin	09/07/2020	n/a		PRAC Recommendation - maintenance

II/0046/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add anaphylactic reaction to the list of adverse drug reactions (ADRs) with frequency rare, following the update of the company's core data sheet (CCDS) due to new data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	21/05/2021	SmPC, Annex II and PL	Section 4.8 of the SmPC has been updated in order to add anaphylactic reaction to the list of adverse drug reactions (ADRs) with frequency rare. The Package Leaflet is updated accordingly
IAIN/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	09/12/2019	SmPC and PL	
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	09/12/2019	PL	
IA/0043	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	19/09/2018	n/a		
II/0041	Update of sections 4.3, 4.4, and 4.5 of the SmPC, in	05/05/2017	23/06/2017	SmPC and PL	During clinical trials with patients treated for hepatitis C

	line with the PI wording for a class effect agreed by CMDh, in order to add a contraindication for patients receiving drug combinations with Direct-acting antiviral (DAA) agents that contain paritaprevir/ritonavir, ombitasvir, and/or dasabuvir as these DAAs have the potential for a drug-drug interaction with ethinyl estradiol (EE)-containing combined hormonal contraceptives resulting in ALT elevations. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in the Netherlands in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinyl estradiol-containing medications such as combined hormonal contraceptives (CHCs). Therefore, EVRA-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. EVRA can be restarted 2 weeks following completion of treatment with this combination drug regimen.
IA/0040	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	17/06/2016	n/a		
II/0039	Update of section 4.5 of the SmPC as a result of the CMDh opinion issued in March 2015 on the deletion of interaction between broad spectrum antibiotics and combined oral contraceptives. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.	14/04/2016	06/04/2017	SmPC and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0038/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.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	25/02/2016	n/a		
PSUSA/1311/ 201411	Periodic Safety Update EU Single assessment - ethinylestradiol / norelgestromin	11/06/2015	n/a		PRAC Recommendation - maintenance
IB/0037	To update the annexes to the latest QRD template (version 9). In addition editorial corrections have been made (i.e. local representatives for BE, BG, CZ, DA, ET, FR, IS, CY, LU, MT, NO, PT, RO, SL and FI, and formatting). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/04/2015	30/03/2016	SmPC and PL	
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		

A31/0031	Pursuant to Article 31 of Directive 2001/83/EC, review of the benefit-risk balance of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate at the request of the French medicines agency (ANSM) following concerns about the risk of venous thromboembolism.	21/11/2013	16/01/2014	SmPC and PL	Please refer to the assessment report: EMEA/H/A-31/1356/C/410/0031
IA/0034	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	18/11/2013	n/a		
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0028	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	16/01/2014	SmPC and PL	The SmPC and PIL changes are proposed in section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction. The package leaflet has been amended accordingly.
IB/0030	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	14/02/2013	16/01/2014	SmPC	

IAIN/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2012	n/a		
R/0027	Renewal of the marketing authorisation.	19/04/2012	15/06/2012	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 EVRA for female contraception indication remains positive and therefore recommends the renewal of the marketing authorisation with unlimited validity.
II/0026	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC and PL	To update the sections 2, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2, 5.3, 6.3, 6.5, 6.6 and 10 of the SmPC in order to comply with the EU Guideline on Summary of Product Characteristics (SmPC) (2009) and the inclusion of safety information to include a warning on smoking and age, add "increased appetite" (SOC Metabolism and nutrition disorders) with the frequency uncommon and additional information on a drug interaction with etoricoxib. The Package Leaflet has been updated in accordance.
IB/0024	B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	30/07/2010	n/a		
IA/0023/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.7 - Administrative change - Deletion of	07/04/2010	n/a		

	manufacturing sites				
II/0021	Change to the supplier and/or plant of two excipients of EVRA transdermal patch. Quality changes	17/12/2009	06/01/2010		
II/0022	Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	22/12/2009	SmPC and PL	Following a CCDS revision by the MAH, section 4.5 'Interactions' and section 4.8 'undesirable effects' of the SPC have been updated. Section 4.5 has been completely reworded taking into account products of the same class that were reviewed recently. Further, one adverse drug reaction "abnormal taste" has been added to section 4.8. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet.
IA/0020	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	24/06/2009	n/a		
IA/0019	IA_09_Deletion of manufacturing site	24/06/2009	n/a		
II/0018	The Marketing Authorisation Holder applies to update the expression of the release rate of EVRA patch based on a new study which shows that the average release rates of Ethinyl Estradiol and Norelgestromin onto the skin are respectively 33.9 micrograms per day and 203 micrograms per day. There are no changes to the qualitative and quantitative composition of the patch nor any change to its functional characteristics. This amendment is	20/11/2008	22/12/2008	SmPC, Labelling and PL	

	done only to reflect the amount of active substance released from the patch onto the skin instead of the quantity of active substance measured in the systemic blood circulation as previously. Annexes and embossing of the patch are updated accordingly. Quality changes				
II/0017	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	08/09/2008	SmPC and PL	The hypertension contraindication is further clarified in section 4.3 "Contraindications" of the SPC. Evra is contraindicated in patients with severe hypertension, i.e. with persistent blood pressure values equal or greater of 160 mm Hg for the systolic or equal or greater than 100 mm Hg for the diastolic. Following literature reports referring to a clinical trial as well as the search of the safety database of the MAH, the information of interaction of the combined contraceptives and lamotrigine has been added in section 4.5 "Interactions with Other Medicinal Products and Other Forms of Interaction" of the SPC. Lamotrigine is an anticonvulsant agent. Combined hormonal contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. In addition the Adverse Drug Reaction of "colitis" is added in the section 4.8 of the SPC based on data from the literature and class effect consistent with an ADR in association with norelgestromin/ethinylestradiol

					transdermal system. Finally the Package Leaflet of the medicinal product is updated following the User Readability Testing performed by the MAH as requested during the Renewal procedure of the product.
II/0016	Update of section 4.4 of the SPC with regard to venous thromboembolism (VTE) and section 4.8 'Undesirable effects' was also restructured in accordance to the SPC Guideline. In addition, the MAH amended section 4.5 to include the active substance 'bosentan' as a medicinal product potentially interacting with EVRA. The PL has been updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	20/06/2008	SmPC, Labelling and PL	Following the finalisation of a Boston Collaborative Drug Safety Program (BCDSP) study, the MAH has updated section 4.4 'Special warnings and precautions for use' of the SPC with a warning related to the increased risk of VTE (deep vein thrombosis, pulmonary embolism) with the use of any combined hormonal contraceptive, including EVRA, compared to no use as recommended by the PhVWP and the CHMP. The results of the retrospective cohort analysis suggest, that the incidence rates for overall VTE risk in women who use EVRA are slightly increased in comparison with users of a levonorgestrel-containing Oral Contraceptives. Section 4.8 'Undesirable effects' was also restructured in accordance to the SPC Guideline. In addition, following the assessment of published data, Section 4.5 'Interaction with other medicinal products and other forms of interaction' was amended to include the active substance 'bosentan' as a medicinal product potentially interacting with EVRA. This interaction can result to breakthrough bleeding and hormonal contraceptive failure. The Product Information was also amended in line with the latest QRD template. The PL has been updated accordingly.
R/0015	Renewal of the marketing authorisation.	24/05/2007	07/09/2007	SmPC, Annex II, Labelling	The quality, safety and efficacy of EVRA continue to be adequately and sufficiently demonstrated since the

				and PL	approval of this product. The benefit/risk profile of EVRA remains favourable in the indication for female contraception. The CHMP considers that the benefit-risk balance of EVRA remains positive, but that its safety profile is to be closely monitored in particular with regards to the Thromboembolic events. Based upon the above defined safety issues of EVRA, the CHMP decided that the MAH should continue to submit yearly PSURs. Finally, considering the above, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0014	This variation relates to an update of section 5.2 of the Summary of Product Characteristics (SPC) in relation to pharmacokinetic (PK) profiles and parameters between EVRA and an oral contraceptive containing 250 mcg norgestimate and 35 mcg ethinyl estradiol, following CHMP request further to the assessment of the FUM 033. Update of Summary of Product Characteristics	14/12/2006	25/01/2007	SmPC	Further to the assessment of the FUM 33 (a post-approval commitment to study the pharmacokinetic profile of EVRA transdermal patch in comparison with the pharmacokinetic profile of CILEST, a combined oral contraceptive containing 250mg norgestimate (parent drug of norelgestromin) and 35 micrograms ethinylestradiol), the MAH updated the section 5.2 of the SPC in relation to pharmacokinetic (PK) profiles and parameters between EVRA and the oral contraceptive containing 250 mcg norgestimate and 35 mcg ethinyl estradiol by including differences of Cmax values, and inter-subject variability (%CV) for the PK parameters between transdermal and oral combined hormonal contraceptives.
II/0013	This variation relates to an update of section 4.4 of	14/12/2006	25/01/2007	SmPC and PL	Two epidemiological studies have been performed in the US

	the Summary of Product Characteristics (SPC) concerning an increased risk of Venous Thromboembolic Events (VTE) associated with contraceptive transdermal patches in comparison with oral contraceptives containing norgestimate and 35 mcg of estrogen (ethinyl estradiol). The Package Leaflet (PL) has been updated accordingly. In addition, contact details of Bulgaria and Romania local representatives were also included. Update of Summary of Product Characteristics and Package Leaflet				to assess the risk of thromboembolic disorders (venous and arterial thrombosis) in users of ORTHO EVRA (US patch for transdermal administration that contains 750 mcg of ethinyl estradiol combined with 6 mg of norelgestromin as active substances) compared with users of oral contraceptives containing norgestimate and 35 mcg ethinyl estradiol. One study was conducted by the Boston Collaborative Drug Safety program, the other by the i3 Drug Safety. The results of the two US studies have now become available. According to the data available from these studies, is not possible to exclude a higher risk of VTE with EVRA in comparison with other combined hormonal contraceptives. The current available data (section 4.4 of the SPC and section 2 of the PL) have been updated accordingly.
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2006	n/a	PL	
IB/0011	IB_38_c_Change in test procedure of finished product - other changes	05/01/2006	n/a		
II/0010	Quality changes	14/12/2005	21/12/2005		
II/0009	Quality changes	14/12/2005	21/12/2005		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2005	n/a	PL	
II/0006	Quality changes	23/06/2004	29/06/2004		

N/0007	Marketing Authorisation Holder applied for the inclusion of additional local representatives of the Marketing Authorisation Holder for all new Member States. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
IB/0005	IB_20_b_Change in test procedure for an excipient - minor change (biological excipient)	07/04/2004	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/09/2003	03/10/2003	Labelling and PL	
I/0003	15_Minor changes in manufacture of the medicinal product	21/03/2003	22/04/2003	SmPC and PL	
II/0001	Change(s) to the test method(s) and/or specifications for the finished product	18/12/2002	04/03/2003	SmPC, Labelling and PL	
I/0002	31_Change in container shape	18/12/2002	17/02/2003	SmPC, Labelling and PL	