Esmya

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
A20/0043	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 30 November 2017 the opinion of the European Medicines Agency after serious cases of liver injury associated with the use of Esmya were reported, including few cases which lead to liver transplantation. The PRAC was requested to assess the impact thereof on the benefit-risk balance of Esmya and to give its recommendation whether the	31/05/2018	26/07/2018	SmPC, Annex II, Labelling and PL	Please refer to the assessment report: Esmya - EMEA/H/A-20/1460/C/2041/0043

[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).

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	marketing authorisation of this product should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.				
PSUSA/9325/ 201702	Periodic Safety Update EU Single assessment - ulipristal acetate (treatment of moderate to severe symptoms of uterine fibroids)	12/10/2017	08/12/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9325/201702.
R/0040	Renewal of the marketing authorisation.	15/09/2016	14/11/2016	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 Esmya in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0041	To update the RMP following completion of the PASS PGL10-014 (Premya) study: a prospective multicentre non-interventional study of women treated with Esmya as pre-operative treatment of moderate to severe symptoms of uterine fibroids. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	n/a		
PSUSA/9325/ 201602	Periodic Safety Update EU Single assessment - ulipristal acetate (treatment of moderate to severe	02/09/2016	n/a		PRAC Recommendation - maintenance

	symptoms of uterine fibroids)				
IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/04/2016	n/a		
II/0037	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on the results of phase III study (PGL11-024). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	14/11/2016	SmPC	This variation resulted in updating the safety information in sections 4.8 and 5.1 of SmPC for Esmya, based on results from the completed long-term study PGL11-024. The study evaluated the efficacy and safety in women who received 8 courses of a 10 mg dose of ulipristal. A total of 64 women started the treatment, 53 of which completed the study. There were no new safety findings and the efficacy was comparable to what had been previously reported. The incidence of endometrial hyperplasia with this increased exposure did not increase in 43 women who received up to 8 courses of ulipristal acetate 10 mg.
PSUSA/9325/ 201502	Periodic Safety Update EU Single assessment - ulipristal acetate (treatment of moderate to severe symptoms of uterine fibroids)	10/09/2015	n/a		PRAC Recommendation - maintenance
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/08/2015	n/a		
IB/0035	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2015	n/a		
II/0028	Extension of the indication to include intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age;	23/04/2015	27/05/2015	SmPC, Annex II and PL	This variation extends the use of Esmya to include intermittent treatment of moderate to severe symptoms of uterine fibroids based on data from two phase III studies.

	consequently, the sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the key elements of the educational material in Annex II have been revised. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				In that context, safety information has also been updated with recommendations for periodic monitoring of the endometrium and information on the management of altered bleeding (inter-menstrual bleeding) and hyperplasia (with and without atypia). Please refer to Scientific Discussion 'Esmya-H-C-2041-II-28'
PSUSA/9325/ 201408	Periodic Safety Update EU Single assessment - ulipristal acetate (treatment of moderate to severe symptoms of uterine fibroids)	12/03/2015	n/a		PRAC Recommendation - maintenance
IB/0031	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	22/12/2014	n/a		
IA/0033	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/12/2014	n/a		
IA/0030	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/12/2014	n/a		
IB/0029/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	11/12/2014	n/a		

	re-test period/storage period supported by real time data B.I.d.1.b.1 - Stability of AS - Change in the storage conditions - Change to more restrictive storage conditions of the AS B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
PSUV/0025	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IAIN/0027	B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	12/08/2014	n/a		
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/07/2014	n/a		
II/0023	To introduce a new post approval change management protocol related to the finished product. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	22/05/2014	n/a		
IAIN/0024/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	11/04/2014	16/03/2015	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IAIN/0022	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	14/03/2014	16/03/2015	SmPC, Labelling and PL	
PSUV/0021	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0019	Update of sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC based on two completed studies which investigated the safety and efficacy of up to four 3-month treatment courses of ulipristal acetate 10 mg. The limitation of a single 3-month treatment course has been removed and the prescription of a second 3-month treatment course has been allowed. In addition, “alopecia” and “dry skin” have been included in the “uncommon” category of section 4.8 of the SmPC. The Package Leaflet was proposed to be updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.6.b - Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication	21/11/2013	18/12/2013	SmPC, Annex II and PL	Further to the results of PGL09-027 and PGL09-026 studies (respectively PEARL III extension and PEARL III) the limitation of a single 3-month treatment course was removed and a second 3-month treatment course is allowed if deemed appropriate by the treating physician. This second 3-month treatment course should be separated from the first treatment course by a drug-free interval to allow return of menstruation and shedding of the endometrium. The treatment should not exceed two treatment courses of 3 months due to the lack of long term safety data. Sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC were updated to reflect the new data. The PL was updated accordingly. In addition, the key elements of the educational material were amended to reflect a) the revised posology: 5 mg tablet once daily for up to 3 months. This 3-month treatment course can be repeated once. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion. Treatments should always be started during the first week of menstruation, and b) absence of safety data on the endometrium for continuous treatment longer than 3

					months
II/0014	Update of sections 4.4, 4.5 and 5.3 of the SmPC based on one clinical study conducted to assess potential drug-drug interactions with rifampicin, one pharmacokinetic study to assess the pharmacokinetics of ulipristal acetate in subjects with moderate hepatic impairment and two non-clinical carcinogenicity studies. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.1 and to assign a new pharmaco-therapeutic group for the medicinal product according to WHO. The requested variation proposed amendments to the Summary of Product Characteristics 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	24/10/2013	18/12/2013	SmPC and PL	Based on the studies submitted by the MAH, section 4.4 of the SmPC was amended to state that the concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended. Section 4.5 of the SmPC was amended to state that administration of the potent CYP3A4 inducer rifampicin (300 mg twice daily for 9 days) to healthy female volunteers markedly decreased Cmax and AUC of ulipristal acetate and its active metabolite by 90 % or more and decreased ulipristal acetate half-life by 2.2-fold corresponding to an approximately 10-fold decrease of ulipristal acetate exposure. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, StJohn´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended. Section 5.3 of the SmPC was amended to include information related to carcinogenicity studies (in rats and mice) showing that ulipristal acetate is not carcinogenic. Finally, the PI was brought in line with the latest QRD template version 9.1 and a new pharmaco-therapeutic group was assigned for the medicinal product, according to WHO.

IAIN/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/07/2013	n/a		
IB/0017	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	22/05/2013	n/a		
IB/0016	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	22/05/2013	n/a		
IB/0015/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/05/2013	n/a		
II/0013	Update of sections 4.4, 4.5, 4.6 and 4.8 and 5.2 of the SmPC based on two clinical studies conducted to assess potential drug-drug interactions with ketoconazole and fexofenadine, one pharmacokinetic	21/03/2013	18/12/2013	SmPC, Annex II and PL	Based on the studies submitted by the MAH, section 4.4 of the SmPC was amended to state that co administration of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, nefazodone,

	study to assess excretion of ulipristal acetate in human breast milk and one open-label clinical study. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.3 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				itraconazole, telithromycin, clarithromycin) CYP3A4 inhibitors and ulipristal acetate is not recommended. Section 4.5 of the SmPC was amended to state that after administration of the potent CYP3A4 inhibitor ketoconazole (400 mg once daily for 7 days) to healthy female volunteers, Cmax and AUC of ulipristal acetate increased 2 and 5.9 fold, respectively; the AUC of the active metabolite of ulipristal acetate increased 2.4 fold while the Cmax of the active metabolite decreased (0.53 fold change). In vitro data also indicate that ulipristal acetate may be an inhibitor of P gp at clinically relevant concentrations in the gastrointestinal wall during absorption. Simultaneous administration of ulipristal acetate and a P gp substrate has not been studied and an interaction cannot be excluded. In vivo results show that ulipristal acetate (administered as a single 10 mg tablet) 1.5 hour before administration of the P gP substrate fexofenadine (60 mg) has no clinically relevant effects on the pharmacokinetic of fexofenadine. It is therefore recommended that co-administration of ulipristal acetate and P gp substrates (e.g. dabigatran etexilate, digoxin, fexofenadine) should be separated in time by at least 1.5 hours. Section 4.6 of the SmPC was amended to include reference to the fact that the effect on newborn/infants has not been studied, whilst section 5.2 of the SmPC noted that ulipristal acetate and its active mono N demethylated metabolite are excreted in breast milk with a mean AUCt milk/plasma ratio of 0.74 ± 0.32 for ulipristal acetate.

					The list of adverse events was updated with the frequency of AEs, following the additional open-label phase III study conducted (Study PGL09-026). Finally, the PI was brought in line with the latest QRD template version 8.3.
II/0012	To extend shelf-life of the finished product from 2 years to 3 years. B.II.f.1.b.4 - Stability of FP - Extension of the shelf life of the finished product - Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines	21/02/2013	18/12/2013	SmPC and Annex II	
II/0004/G	This was an application for a group of variations. - Addition of a new amanufacturer of the active substance - Changes in control methods of the active substance B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	13/12/2012	n/a		

	or addition) for the AS or a starting material/intermediate 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				
IB/0011	B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	09/11/2012	n/a		
IB/0010/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.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.z - Change in the specification parameters and/or limits 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)	21/09/2012	n/a		

IB/0009	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	05/09/2012	29/10/2012	SmPC, Labelling and PL	
T/0003	Transfer of Marketing Authorisation	04/07/2012	26/07/2012	SmPC, Labelling and PL	Transfer of MAH from PregLem France SAS to Gedeon Richter Plc.
IB/0002/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.3.z - Change in the manufacturing process 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)	08/05/2012	n/a		