Zoely

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
T/0047	Transfer of Marketing Authorisation	04/12/2018	31/01/2019	SmPC, Labelling and PL	
IAIN/0048	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/01/2019		SmPC and PL	
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	23/01/2019	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).

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PSUSA/2182/201801	Periodic Safety Update EU Single assessment - estradiol / nomegestrol acetate	04/10/2018	n/a		PRAC Recommendation - maintenance
IA/0045/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/07/2018	23/01/2019	Annex II and PL	
IAIN/0043	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/02/2018	n/a		
IA/0042	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	27/02/2018	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2017	23/01/2019	PL	
IAIN/0040/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.5.a - Administrative change - Change in the name	08/12/2017	23/01/2019	Annex II and PL	

	and/or address of a manufacturer/importer responsible for batch release B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
II/0038	Update of sections 4.4 and 4.5 of the SmPC concerning Hepatitis C and the risk of elevated ALT due to treatment with the HCV combination regimen ombitasvir/paritaprevir/ritonavir co-administered with ethinylestradiol-containing products. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/02/2017	03/10/2017	SmPC and PL	During clinical trials with the Hepatitis C virus (HCV) combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, alanine aminotransferase (ALT) elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Women using medications containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir.
II/0037	Update of sections 4.4 and 4.5 of the SmPC with revised information regarding interactions with concomitant medications and risk of reduced efficacy. Further, the current paragraph 'laboratory tests' was moved from section 4.5 to section 4.4 of the SmPC. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/02/2017	03/10/2017	SmPC and PL	The efficacy of COCs may be reduced in the event of use of concomitant medicinal products that decrease the plasma concentrations of nomegestrol acetate and/or estradiol. Hepatic metabolism: Interactions can occur with substances that induce CYP450 enzymes, resulting in reduced concentrations of sex hormones and decreased effectiveness of combined oral contraceptives, including Zoely. These substances are represented mostly with anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate); anti-infective drugs (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort;

					bosentan and HIV or Hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non nucleoside reverse transcriptase inhibitors (e.g. efavirenz). Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days. A barrier contraceptive method should also be used during the concomitant use of an enzyme inducer, and for 28 days after its discontinuation. In case of long-term treatment with hepatic enzyme-inducing substances another method of contraception should be considered. If concomitant drug administration runs beyond the end of the active tablets in the current blister pack, the next blister pack should be started right away without the usual placebo tablet interval. Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestogens.
IAIN/0039	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	16/12/2016	03/10/2017	Annex II	
II/0035	Update of section 4.2 of the SmPC to implement minor changes to the existing missed pill advice and section 4.4 of the SmPC with additional information regarding Inflammatory Bowel Disease (Crohn's disease and Ulcerative Colitis). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to align the annexes with the latest QRD	15/09/2016	03/10/2017	SmPC, Labelling and PL	N/A

	template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0036	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	20/07/2016	n/a		
R/0032	Renewal of the marketing authorisation.	25/02/2016	21/04/2016	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 Zoely in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: During the last years there has been an increase of the exposure of Zoely in women above 35 years. This increase raised concerns because age above 35 years is a risk factor of venous thromboembolic events. There is an ongoing imposed post-authorisation study to better characterize the safety profile of the contraceptive combination nomegestrol/estradiol. This study compares the risk of nomegestrol/estradiol use with the risk of levonorgestrel-containing combined oral contraceptive use. The main clinical outcomes are venous thromboembolism events especially deep vein thrombosis of the lower extremities and pulmonary embolism.
N/0034	Update of the package leaflet with revised contact details of local representative for Croatia.	07/04/2016	03/10/2017	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	10/12/2015	21/04/2016	Annex II and PL	
IB/0031	B.I.d.1.b.1 - Stability of AS - Change in the storage conditions - Change to more restrictive storage conditions of the AS	13/10/2015	n/a		
PSUSA/2182/ 201501	Periodic Safety Update EU Single assessment - estradiol / nomegestrol acetate	10/09/2015	n/a		PRAC Recommendation - maintenance
IAIN/0030	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	04/08/2015	n/a		
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/06/2015	21/04/2016	PL	
II/0027	Update of section 4.2 of the SmPC in order to change the missed pill window from 12 to 24 hours. The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2015	21/04/2016	SmPC and PL	
IB/0026	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	12/11/2014	n/a		

IB/0025	To update the Risk-Management Plan (RMP, version 8.0) to include the outcomes of the approved Article 31 referral on VTE risks. The RMP has been updated to reflect changes to the approved EU SmPC and Patient Leaflet of the referral, including the classification of ATE as an important identified risk. Also, the agreed DHPC to communicate the risk of blood clots has been incorporated. Furthermore, information regarding the amended PASS protocol is provided and the RMP is updated with exposure data on an ongoing clinical study. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	30/10/2014	n/a		
PSUSA/2182/ 201401	Periodic Safety Update EU Single assessment - estradiol / nomegestrol acetate	11/09/2014	n/a		PRAC Recommendation - maintenance
T/0023	Transfer of the Marketing Authorisation. Transfer of Marketing Authorisation	08/08/2014	01/09/2014	SmPC, Labelling and PL	Transfer of the Marketing Authorisation from Theramex S.r.l. to Teva B.V.
IB/0024	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	12/08/2014	n/a		
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2014	01/09/2014	PL	
IAIN/0019/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release	08/05/2014	01/09/2014	Annex II and PL	

	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.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				
IA/0018/G	This was an application for a group of variations. 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 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	02/05/2014	n/a		
PSUV/0017	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
A31/0010	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/1213/0010

IB/0016	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/11/2013	n/a		
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/10/2013	16/01/2014	SmPC, Annex II and PL	
IAIN/0015	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	03/10/2013	n/a		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2013	16/01/2014	PL	
IB/0012/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	24/04/2013	16/01/2014	Annex II and PL	

	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 B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
IAIN/0011	B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	05/03/2013	n/a		
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2012	11/06/2013	PL	
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
IB/0006/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements	02/08/2012	29/10/2012	Annex II and PL	

	and quality control testing of the FP - Including batch control/testing B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing 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 B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
IB/0007/G	This was an application for a group of variations. 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 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	21/06/2012	29/10/2012	SmPC, Labelling and PL	
IB/0005	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/03/2012	n/a		
IG/0138	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	02/02/2012	n/a		

N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/12/2011	29/10/2012	Labelling and PL	
IG/0126/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.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	14/12/2011	n/a		
T/0001	Transfer of Marketing Authorisation	29/09/2011	10/11/2011	SmPC, Labelling and PL	Transfer of Marketing Authorisation from Merck Serono Europe to Theramex S.r.l.