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
PSUSA/2182/ 202401	Periodic Safety Update EU Single assessment - estradiol / nomegestrol acetate	19/09/2024	14/02/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2182/202401.
IA/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	24/09/2024		Annex II 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).

	manufacturing sites B.III.1.a.4 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Deletion of certificates (in case multiple certificates exist per material)				
IA/0063	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)	06/12/2022	n/a		
A31/0060	Pursuant to Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, on 22 September 2021, the ANSM requested the European Medicines Agency to assess the risk of meningioma associated with nomegestrol acetate or chlormadinone acetate use. The PRAC was requested to assess the impact thereof on the benefit-risk balance of Zoely and to give its recommendation whether the marketing authorisation of this product should be varied. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion was adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.	01/09/2022	28/11/2022	SmPC and PL	Please refer to the assessment report: Zoely EMEA/H/A-31/1510/C/1213/60
IA/0062	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	31/10/2022	n/a		

	from an already approved manufacturer				
IAIN/0061	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)	17/06/2022	n/a		
SW/0058	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0032 - Variation	14/10/2021	16/12/2021	SmPC, Annex II and PL	The study eliminated a 1.5-fold risk of venous thromboembolism (VTE) for NOMAC-E2 (nomegestrol acetate/estradiol) compared to COCLNG (combined hormonal contraceptive containing levonorgestrel). The results of the study show that nomegestrol acetate/estradiol (Zoely) may have a risk of VTE in the same range as observed with COCLNG. Therefore, in view of available data regarding the PASS final study report, the PRAC considers that changes to the product information are warranted.
PSUSA/2182/ 202101	Periodic Safety Update EU Single assessment - estradiol / nomegestrol acetate	14/10/2021	16/12/2021	SmPC and PL	In view of available data on the risks from clinical trials, the literature and in view of a plausible mechanism of action, as well as previous PSUSA outcomes, the PRAC considers a causal relationship for the drug-drug interaction between estradiol / nomegestrol acetate and glecaprevir/pibrentasvir is at least a reasonable possibility. The PRAC concluded that the sections 4.4. and 4.5 of the SmPC of product information of products containing estradiol / nomegestrol acetate should be amended accordingly. In addition, in view of a literature data, a plausible mechanism of actions and previous PSUSA outcomes, the PRAC considers a causal relationship between estradiol / nomegestrol acetate and the exacerbation of symptoms of

					hereditary and acquired angioedema is at least a reasonable possibility. The PRAC concluded that the product information of products containing estradiol / nomegestrol acetate should be amended accordingly.
IB/0059	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	09/09/2021	n/a		
IB/0056/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/05/2021	n/a		
R/0055	Renewal of the marketing authorisation.	25/02/2021	10/05/2021	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 and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0054	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)	24/09/2020	n/a		
IA/0053/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	03/09/2020	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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 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 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 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				
II/0050	Update of sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, upon request by PRAC following the assessment of Post-authorisation measure LEG 014. The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Netherlands and Portugal in the Package Leaflet. Update of RMP to version 11.0 in order to and add meningioma as an important potential risk in the list of safety concerns and to introduce a specific	30/04/2020	09/06/2020	SmPC and PL	The SmPC sections 4.3 and 4.4 were updated in order to add a new contraindication and a new warning regarding meningioma. The Package Leaflet has been updated accordingly.

	adverse reaction follow-up questionnaire on meningioma. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				
IB/0052/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.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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 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)	10/01/2020	n/a		

II/0051	To update the RMP to version 9.1 as requested in the outcome of the imposed PASS protocol adopted by the PRAC in June 2019 for a prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the risk of VTE in users of combined oral contraceptives (COCs)-containing levonorgestrel, including the change of the due date from June 2020 to April 2021. The RMP is also updated in line with GVP V revision 2. As a consequence, annex II is updated. The MAH also took the opportunity to amend the package leaflet in order to update the list of local representatives. 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	28/11/2019	04/02/2020	Annex II and PL	
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	04/02/2020	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	

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	15/09/2016	03/10/2017	SmPC, Labelling and PL	N/A

	took the opportunity to align the annexes with the latest QRD 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	07/04/2016	03/10/2017	PL	

	details of local representative for Croatia. 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	12/11/2014	n/a		

	compared to the originally approved batch size				
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 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	08/05/2014	01/09/2014	Annex II and PL	
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	21/11/2013	16/01/2014	SmPC and PL	Please refer to the assessment report: EMEA/H/A-31/1356/C/1213/0010

	venous thromboembolism.				
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	24/04/2013	16/01/2014	Annex II and PL	

	site 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				
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	02/08/2012	29/10/2012	Annex II and PL	

	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 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.