Evista

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/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/06/2022		PL	
IAIN/0089	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	02/05/2022	n/a		

[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).

	new manufacturer (replacement or addition)				
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2022		PL	
IA/0087	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	14/10/2021	n/a		
IB/0086/G	This was an application for a group of variations. B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition	07/07/2021	01/04/2022	SmPC and PL	

	of inks used for product marking - Changes in imprints, bossing or other markings 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.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2021	01/04/2022	PL	
IAIN/0084/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	08/04/2021	n/a		
IAIN/0083	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	30/03/2021	01/04/2022	Annex II and PL	
N/0082	Minor change in labelling or package leaflet not	17/02/2021	01/04/2022	PL	

	connected with the SPC (Art. 61.3 Notification)				
IAIN/0081/G	This was an application for a group of variations. 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	20/11/2020	n/a		
T/0080	Transfer of Marketing Authorisation	07/07/2020	31/07/2020	SmPC, Labelling and PL	
PSUSA/2603/ 201812	Periodic Safety Update EU Single assessment - raloxifene	11/07/2019	n/a		PRAC Recommendation - maintenance
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/05/2019	31/07/2020	PL	
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2019	n/a		
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2018	31/07/2020	PL	
IB/0075	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	01/08/2018	n/a		

IA/0074	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	06/06/2018	n/a		
IAIN/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/11/2017	29/10/2018	SmPC, Annex II, Labelling and PL	
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2016	29/10/2018	PL	
IAIN/0071	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	28/05/2015	n/a		
IA/0070/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/10/2014	n/a		
IA/0069	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/09/2014	n/a		

PSUSA/2603/ 201312	Periodic Safety Update EU Single assessment - raloxifene	11/09/2014	n/a		PRAC Recommendation - maintenance
IA/0067	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	09/01/2014	n/a		
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/09/2013	29/10/2018	PL	
II/0063	Update of section 4.8 of the SmPC to include information about the ADR 'fatal strokes'. Further, section 4.8 of the SmPC has been updated to ensure consistency with section 4.4, and the frequency calculation for already listed ADRs in section 4.8 has been revised to reflect all available post-marketing pharmacovigilance data. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the annexes in line with the latest SmPC guideline and QRD template (version 8.1). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	30/08/2012	SmPC and PL	As requested by the CHMP following the assessment of the latest PSUR, the MAH has added a paragraph with information regarding 'fatal strokes' in patients using raloxifene versus patients who received placebo to subsection c of SmPC section 4.8: In the Raloxifene Use for The Heart 'RUTH' study, raloxifene did not affect the incidence of stroke, compared to placebo. However, there was an increase in death due to stroke in women assigned to raloxifene. The incidence of stroke mortality was 2.2 per 1000 women per year for raloxifene versus 1.5 per 1000 women per year for placebo (see section 4.4). During an average follow-up of 5.6 years, 59 (1.2%) raloxifene-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women. The ADR 'fatal strokes' has also been added as an 'uncommon' adverse reaction in the ADR table in SmPC section 4.8. Further, the MAH has recalculated the frequencies of the adverse reactions arising in the post-marketing setting

					based on the raloxifene clinical trials Multiple Outcomes of Raloxifene Evaluation 'MORE' and 'RUTH'. Furthermore, the adverse reactions observed in these clinical trials and reported in the post-marketing setting have now been merged into a single combined table in the SmPC. These changes are acceptable and are in line with the SmPC guideline. The Package Leaflet has been revised to reflect these recalculations. Changes were also made to the SmPC and Package Leaflet to bring the product information in line with the current QRD template (version 8.1), which were reviewed and accepted by the CHMP.
IB/0062	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	16/12/2011	n/a		
N/0061	The MAH took this opportunity to update Annex IIIB amending the details for the local representatives in Bulgaria. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2011	n/a	PL	
IA/0060	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	18/01/2011	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/02/2010	n/a	PL	

IB/0058	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	02/02/2010	n/a		
IB/0057	IB_10_Minor change in the manufacturing process of the active substance	02/02/2010	n/a		
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/10/2009	n/a	PL	
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2008	n/a	PL	
IA/0055	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/11/2008	n/a		
T/0053	Transfer of Marketing Authorisation	24/07/2008	22/08/2008	SmPC, Labelling and PL	
R/0049	Renewal of the marketing authorisation.	30/05/2008	08/08/2008	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Evista continues to be favourable.
IB/0052	IB_10_Minor change in the manufacturing process of the active substance	09/04/2008	n/a		
IA/0051	IA_09_Deletion of manufacturing site	19/02/2008	n/a		
IA/0050	IA_09_Deletion of manufacturing site	19/02/2008	n/a	Annex II and PL	

IB/0047	IB_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	08/02/2008	n/a		
IB/0046	IB_30_b_Change in supplier of packaging components - replacement/addition	08/02/2008	n/a	SmPC	
IB/0045	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	05/12/2007	n/a		
IB/0044	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	21/09/2007	n/a		
IB/0042	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	26/04/2007	n/a	SmPC	
II/0040	Update of the Summary of Product Characteristics (SPC) as follows: a) Update of section 4.8 with adverse events from clinical trial RUTH. b) Update of section 5.1 with information on vertebral fracture, Bone Mineral Density (BMD), cardiovascular risk and risk of breast cancer from RUTH and CORE clinical trials. Relevant sections of the Package Leaflet (PL) were updated accordingly. The latest QRD version has been implemented in the	22/02/2007	28/03/2007	SmPC, Labelling and PL	The MAH submitted in this type II variation the final results of three clinical trials (CORE, RUTH and STAR) assessing the effects of raloxifene on the incidence of invasive breast cancer and cardiovascular events. The CORE trial was a follow-up to the MORE registration trial of 7,705 postmenopausal women with osteoporosis. The CORE study was a multinational, double-blind trial that enrolled women who had been randomized in the MORE osteoporosis treatment trial for an additional 4 years of follow-up. The primary objective was to compare the long-term effect of raloxifene versus placebo on the reduction in incidence of invasive breast cancer. A secondary objective was to assess the effect of raloxifene on the incidence of

	whole product information and the labelling has been updated with Braille. Update of Summary of Product Characteristics, Labelling and Package Leaflet				new non-vertebral fractures over 8 years. The RUTH study was a multinational, double-blind, randomized, placebo controlled trial conducted in postmenopausal women at risk for major coronary events. A total of 10,101 women were enrolled and randomized to one of two therapy groups. The active treatment phase ended after the last randomized patient had been followed for 5 years. The primary objectives of this study were to assess whether treatment with raloxifene, compared with placebo, reduced the incidence of: 1) the combined endpoint of coronary death, nonfatal (including silent) myocardial infarction (MI), or hospitalized acute coronary syndrome (ACS) other than MI; and 2) invasive breast cancer. Secondary endpoints included: Cardiovascular (CV) death, nonfatal (including silent) MI, hospitalized ACS other than MI, myocardial revascularization, and stroke, assessed separately and as a combined endpoint, coronary death, all-cause mortality, hospitalized ACS, all-cause hospitalization, non-coronary arterial revascularization or nontraumatic lower extremity amputation, all breast cancer, fractures and venous thromboembolism (VTEs). Then STAR trial, which included 19,747 postmenopausal women at increased risk of invasive b
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/02/2007	n/a	Labelling	

N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/01/2007	n/a	PL	
IB/0038	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	05/12/2006	n/a		
II/0036	The Marketing Authorisation Holder has applied for an update in the sections 4.4, 4.8, 4.9 of the Summary of Product Characteristics (SPC) and 2, 4 of the Package Leaflet (PL) as requested by the CHMP on 27 April 2006 following the assessment of the early preliminary findings from the RUTH trial. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	16/11/2006	SmPC and PL	The MAH submitted a variation to update the benefit/risk profile of raloxifene based on the CORE, STAR trials and preliminary results of the RUTH trial. As the final study report for the RUTH trial was not available at time of the submission of this variation, the main focus of the current evaluation was to assess the clinical significance of the increased incidence of fatal stroke observed in the RUTH study based on a further analysis of the preliminary data on fatalities due to stroke in raloxifene and placebo groups. Hence the MAH has submitted a cumulative review of their global safety database for spontaneous raloxifene cases reporting stroke or death, including death due to stroke in addition to clinical trial data from the CORE, RUTH and STAR trials. Overall, the CHMP considers that the benefit/risk assessment of raloxifene remains favorable based on the available data from the CORE and STAR trials and the preliminary results of the RUTH trial. Regarding the risk of stroke mortality an amendment to the section 4.4 of the SPC was proposed by the CHMP and implemented accordingly by the MAH. The sections 4.8 and 4.9 have also been updated according to new post-marketing data on adverse reactions (blood and lymphatic disorders, peripheral oedema and vascular disorders) and overdose respectively.

N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2006	n/a	PL	
IB/0035	IB_10_Minor change in the manufacturing process of the active substance IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	24/07/2006	n/a		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2006	n/a	Labelling and PL	
IA/0033	IA_47_c_Deletion of a pack size(s)	12/04/2006	n/a	SmPC	
IB/0032	IB_10_Minor change in the manufacturing process of the active substance	05/04/2006	n/a		
IB/0031	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	21/03/2006	n/a	SmPC, Labelling and PL	
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2005	n/a	PL	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/10/2004	n/a	PL	
IB/0028	IB_38_c_Change in test procedure of finished product - other changes	28/09/2004	n/a		
IB/0026	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	30/06/2004	n/a		

IA/0027	IA_05_Change in the name and/or address of a manufacturer of the finished product	21/06/2004	n/a		
N/0024	The Marketing Authorisation Holder (MAH) applied for the inclusion of additional local representatives of the MAH for all new Member States. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/06/2004	n/a	PL	
IA/0025	IA_09_Deletion of manufacturing site	15/06/2004	n/a		
R/0020	Renewal of the marketing authorisation.	22/05/2003	28/07/2003	SmPC, Annex II, Labelling and PL	
II/0018	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	
I/0022	04_Replacement of an excipient with a comparable excipient	14/05/2003	15/05/2003		
I/0021	04_Replacement of an excipient with a comparable excipient	14/05/2003	15/05/2003		
I/0019	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	14/01/2003	14/02/2003	Annex II and PL	
I/0015	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	09/11/2002	13/11/2002		

N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/10/2002	20/11/2002	PL	
II/0009	Change(s) to the manufacturing process for the active substance	17/10/2002	28/10/2002		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2002	07/11/2002	PL	
I/0014	08_Change in the qualitative composition of immediate packaging material	02/10/2002	n/a		
I/0013	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	11/09/2002	16/09/2002		
I/0010	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/04/2002	18/04/2002		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	27/06/2001	31/10/2001	SmPC and PL	
I/0008	12_Minor change of manufacturing process of the active substance	13/07/2001	n/a		
I/0007	26_Changes to comply with supplements to pharmacopoeias	18/05/2001	01/06/2001		
I/0005	03_Change in the name and/or address of the marketing authorisation holder	25/01/2001	06/03/2001	SmPC, Labelling and PL	

I/0004	16_Change in the batch size of finished product	07/07/2000	02/08/2000		
II/0001	Extension of Indication	18/09/1999	24/03/2000	SmPC, Labelling and PL	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	23/09/1999	31/01/2000	SmPC and PL	