



Optruma

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/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2023		PL	
N/0078	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/01/2022	29/06/2022	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).



IB/0077	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	13/09/2021	n/a		
IAIN/0076/G	This was an application for a group of variations. A.3 - Administrative change - Change in name of the AS or of an excipient 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.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	18/06/2021	29/06/2022	SmPC, Annex II, Labelling and PL	
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2019	29/06/2022	PL	
PSUSA/2603/201812	Periodic Safety Update EU Single assessment - raloxifene	11/07/2019	n/a		PRAC Recommendation - maintenance
IB/0073	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	22/05/2018	n/a		

IG/0898	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	12/02/2018	19/07/2018	Annex II	
IAIN/0071	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/08/2017	19/07/2018	SmPC, Annex II, Labelling and PL	
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	08/02/2017	SmPC, Labelling and PL	
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2015	08/02/2017	PL	
IA/0068/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/0067	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/0065	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	20/12/2013	n/a		
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
II/0062	<p>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 contact details of the local representatives in the Package Leaflet and to update the annexes in line with the latest SmPC guideline and QRD template (version 8.1).</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	19/07/2012	30/08/2012	SmPC and PL	<p>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:</p> <p>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.</p> <p>The ADR 'fatal strokes' has also been added as an 'uncommon' adverse reaction in the ADR table in SmPC section 4.8.</p> <p>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</p>

					<p>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.</p> <p>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.</p>
IB/0061	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	16/12/2011	n/a		
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	06/01/2011	n/a		
IB/0059	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	02/02/2010	n/a		
IB/0058	IB_10_Minor change in the manufacturing process of the active substance	02/02/2010	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2009	n/a	PL	
IA/0056	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/11/2008	n/a		

R/0052	Renewal of the marketing authorisation.	30/05/2008	11/08/2008	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 Optruma continues to be favourable.
IB/0055	IB_10_Minor change in the manufacturing process of the active substance	09/04/2008	n/a		
IA/0053	IA_09_Deletion of manufacturing site	22/02/2008	n/a	Annex II and PL	
IA/0054	IA_09_Deletion of manufacturing site	20/02/2008	n/a		
IB/0050	IB_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	08/02/2008	n/a		
IB/0049	IB_30_b_Change in supplier of packaging components - replacement/addition	08/02/2008	n/a	SmPC	
IB/0048	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	05/12/2007	n/a		
IB/0047	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/0045	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	03/05/2007	n/a	SmPC	
II/0043	Update of the Summary of Product Characteristics	22/02/2007	27/03/2007	SmPC,	The MAH submitted in this type II variation the final results

	<p>(SPC) as follows:</p> <p>a) Update of section 4.8 with adverse events from clinical trial RUTH.</p> <p>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.</p> <p>Relevant sections of the Package Leaflet (PL) were updated accordingly.</p> <p>The latest QRD version has been implemented in the whole product information and the labelling has been updated with Braille.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>			<p>Labelling and PL</p>	<p>of three clinical trials (CORE, RUTH and STAR) assessing the effects of raloxifene on the incidence of invasive breast cancer and cardiovascular events.</p> <p>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 new non-vertebral fractures over 8 years.</p> <p>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:</p> <ol style="list-style-type: none"> 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. <p>Secondary endpoints included: Cardiovascular (CV) death,</p>
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					<p>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).</p> <p>Then STAR trial, which included 19,747 postmenopausal women at increased risk of invasive b</p>
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/02/2007	n/a	Labelling	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/01/2007	n/a	PL	
IB/0041	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	05/12/2006	n/a		
II/0039	<p>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.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	18/10/2006	22/11/2006	SmPC and PL	<p>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</p>

					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/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2006	n/a	PL	
IB/0038	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/0037	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/0036	IA_47_c_Deletion of a pack size(s)	12/04/2006	n/a	SmPC	
IB/0035	IB_10_Minor change in the manufacturing process of the active substance	05/04/2006	n/a		
IB/0034	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	21/03/2006	n/a	SmPC, Labelling and	

				PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2005	n/a	PL	
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/10/2004	n/a	PL	
IB/0031	IB_38_c_Change in test procedure of finished product - other changes	28/09/2004	n/a		
IB/0029	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	30/06/2004	n/a		
IA/0030	IA_05_Change in the name and/or address of a manufacturer of the finished product	21/06/2004	n/a		
N/0027	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/0028	IA_09_Deletion of manufacturing site	15/06/2004	n/a		
R/0023	Renewal of the marketing authorisation.	22/05/2003	28/07/2003	SmPC, Annex II, Labelling and PL	
II/0020	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	

I/0026	04_Replacement of an excipient with a comparable excipient	14/05/2003	15/05/2003		
I/0025	04_Replacement of an excipient with a comparable excipient	14/05/2003	15/05/2003		
I/0022	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	
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/01/2003	31/01/2003	PL	
I/0018	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	09/10/2002	13/11/2002		
II/0010	Change(s) to the manufacturing process for the active substance	17/10/2002	28/10/2002		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2002	07/11/2002	PL	
I/0017	08_Change in the qualitative composition of immediate packaging material	02/10/2002	n/a		
I/0016	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	11/09/2002	16/09/2002		
I/0013	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/04/2002	18/04/2002		

II/0007	Update of Summary of Product Characteristics and Package Leaflet	27/06/2001	31/10/2001	SmPC and PL	
I/0009	12_Minor change of manufacturing process of the active substance	13/07/2001	n/a		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2001	26/07/2001	PL	
I/0008	26_Changes to comply with supplements to pharmacopoeias	18/05/2001	01/06/2001		
I/0006	03_Change in the name and/or address of the marketing authorisation holder	25/01/2001	06/03/2001	SmPC, Labelling and PL	
I/0005	16_Change in the batch size of finished product	07/07/2000	n/a		
II/0003	Extension of Indication	18/11/1999	24/03/2000	SmPC, Labelling and PL	
II/0004	Update of Summary of Product Characteristics and Package Leaflet	23/09/1999	31/01/2000	SmPC and PL	
I/0001	02_Change in the name of the medicinal product (either invented name or common name)	13/01/1999	11/06/1999	SmPC, Annex II, Labelling and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/1999	11/05/1999	PL	