

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/0083 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 25/09/2024 | | Labelling and PL | |
| IA/0084 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 28/08/2024 | 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).



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| PSUSA/2603/202312 | Periodic Safety Update EU Single assessment - raloxifene | 11/07/2024 | n/a | | PRAC Recommendation - maintenance |
| IG/1620 | B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information | 01/08/2023 | n/a | | |
| IB/0080/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>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)</p> | 27/06/2023 | n/a | | |
| N/0079 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 23/01/2023 | | PL | |

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| 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 | |
| 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 | <p>This was an application for a group of variations.</p> <p>A.3 - Administrative change - Change in name of the AS or of an excipient</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>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</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold</p> | 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 | 22/05/2018 | n/a | | |

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| | re-test period/storage period supported by real time data | | | | |
| 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 | <p>This was an application for a group of variations.</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> | 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 | | |

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| 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</p> |

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| | | | | | 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/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 | | |

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| 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 (SPC) as follows: | 22/02/2007 | 27/03/2007 | SmPC, Labelling and | The MAH submitted in this type II variation the final results of three clinical trials (CORE, RUTH and STAR) assessing |

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| | <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> | | PL | <p>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, nonfatal (including silent) MI, hospitalized ACS other than</p> |
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| | | | | | 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/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 | 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 | 22/11/2006 | 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 |

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| | | | | | 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 | |

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| 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 | 14/05/2003 | 15/05/2003 | | |

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| | excipient | | | | |
| 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 | |

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| 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 | |