# Targretin

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 |
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| IA/0062 | B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer | 08/10/2021 | 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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| IA/0061/G | This was an application for a group of variations.<br><br>B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer<br>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 | 17/08/2021 | n/a | | |
| IA/0060 | A.6 - Administrative change - Change in ATC Code/ATC Vet Code | 12/05/2021 | 21/06/2021 | SmPC, Annex II and PL | |
| PSUSA/404/202009 | Periodic Safety Update EU Single assessment - bexarotene | 06/05/2021 | n/a | | PRAC Recommendation - maintenance |
| IA/0059/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites | 02/03/2021 | 21/06/2021 | Annex II and PL | |
| IG/1263 | B.II.b.2.c.1 - Change to importer, batch release | 24/06/2020 | 21/06/2021 | Annex II and | |

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| | 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 | | | PL | |
| IG/1260/G | This was an application for a group of variations.<br><br>A.1 - Administrative change - Change in the name and/or address of the MAH<br>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release<br>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 | 24/06/2020 | 21/06/2021 | SmPC, Labelling and PL | |
| IA/0055/G | This was an application for a group of variations.<br><br>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<br>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 | 13/12/2019 | n/a | | |
| IA/0054 | 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 | 11/12/2019 | n/a | | |

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| | control/testing takes place | | | | |
| IAIN/0053/G | This was an application for a group of variations.<br><br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>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 | 30/01/2019 | n/a | | |
| IG/1008 | 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 | 30/11/2018 | 07/11/2019 | Annex II and PL | |
| T/0050 | Transfer of Marketing Authorisation | 30/08/2018 | 17/09/2018 | SmPC, Labelling and PL | |
| A31/0043 | Pursuant to Article 31 of Directive 2001/83/EC, the United Kingdom triggered on 7 July 2016 a referral resulting from pharmacovigilance data, and requested the PRAC to review the routine risk minimisation in place for the oral and topical retinoids to ensure the available data and the risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed within the product | 22/03/2018 | 21/06/2018 | SmPC, Annex II and PL | Please refer to the assessment report: Targretin EMEA/H/A-31/1446/C/000326/0043 |

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| | information where appropriate and justified by data. Furthermore, the PRAC was requested to review any additional risk minimisation measures to ensure that these are optimal in terms of provision of information and delivery of effective risk management that is subject to appropriate monitoring. The PRAC was called upon to assess the impact of the above concerns on the benefit-risk balance of retinoid-containing medicinal products and issue a recommendation on whether the products should be maintained, varied, suspended or revoked.<br><br>As the request resulted from the evaluation of data resulting from pharmacovigilance activities, the PRAC issued a recommendation to the Committee for Medicinal Products for Human Use (CHMP). | | | | |
| PSUSA/404/201709 | Periodic Safety Update EU Single assessment - bexarotene | 17/05/2018 | n/a | | PRAC Recommendation - maintenance |
| N/0048 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 15/11/2017 | 21/06/2018 | PL | |
| IA/0047 | 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) | 24/08/2017 | n/a | | |
| IB/0045/G | This was an application for a group of variations. | 06/01/2017 | n/a | | |

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| | 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<br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier<br>B.II.f.1.e - Stability of FP - Change to an approved stability protocol | | | | |
| IAIN/0044 | B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site | 19/10/2016 | n/a | | |
| N/0042 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 31/08/2015 | 21/06/2018 | PL | |
| PSUSA/404/201409 | Periodic Safety Update EU Single assessment - bexarotene | 26/03/2015 | 27/05/2015 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/404/201409. |
| N/0040 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/10/2014 | 13/04/2015 | PL | |

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| N/0039 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 03/06/2014 | 13/04/2015 | PL | |
| IA/0038 | 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 | 25/04/2014 | n/a | | |
| IA/0037 | 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) | 07/02/2014 | n/a | | |
| IAIN/0036 | B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product | 14/01/2014 | n/a | | |
| IG/0345 | 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 | 03/09/2013 | n/a | | |
| IAIN/0034 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 30/04/2013 | n/a | | |
| II/0033 | Update of section 5.2 of the SmPC in order to add information on pharmacokinetics in special populations. In addition, the MAH took the | 21/02/2013 | 13/04/2015 | SmPC, Annex II, Labelling and PL | The following information resulting from an overview of the pharmacokinetics of bexarotene in patients with various cancer indications across 11 clinical trials was included in |

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| | opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.3.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | the Summary of Product characteristics, section 5.2: Pharmacokinetic Properties.<br>Pharmacokinetics in Special Populations<br>Age: Based on the population pharmacokinetic analysis of data for 232 patients aged ≥ 65 years and 343 patients aged < 65 years, age has no statistically significant effect on bexarotene pharmacokinetics.<br>Body Weight and Gender: Based on the population pharmacokinetics analysis of data for 614 patients with a weight range of 26 to 145 kg, the bexarotene apparent clearance increases with increasing body weight. Gender has no statistically significant effect on bexarotene pharmacokinetics.<br>Race: Based on the population pharmacokinetic analysis of data for 540 Caucasian and 44 Black patients, bexarotene pharmacokinetics are similar in Blacks and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of bexarotene for other races.<br>In addition changes were introduced to bring the text in line with approved templates and changes to the contact details of local representatives were made. |
| IA/0032/G | This was an application for a group of variations.<br><br>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<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | 05/07/2012 | n/a | | |

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| | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | | | | |
| N/0031 | The MAH revised the list of local representatives contact details.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 25/04/2012 | 13/04/2015 | PL | |
| IB/0030/G | This was an application for a group of variations.<br><br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 26/08/2011 | n/a | | |
| IA/0029/G | This was an application for a group of variations.<br><br>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 | 21/07/2011 | n/a | | |

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| | 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<br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer<br>B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State | | | | |
| IA/0028 | IA_01_Change in the name and/or address of the marketing authorisation holder | 06/04/2009 | n/a | SmPC, Labelling and PL | |
| IA/0027 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing | 05/02/2009 | n/a | Annex II and PL | |
| N/0026 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 14/10/2008 | n/a | PL | |
| II/0025 | Update of or change(s) to the pharmaceutical documentation | 24/07/2008 | 25/08/2008 | SmPC and PL | |
| IA/0024 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 20/12/2007 | n/a | | |

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| II/0023 | Update of Summary of Product Characteristics | 15/11/2007 | 11/12/2007 | SmPC | This type II variation was submitted by the MAH upon request by the CHMP following the assessment of FU2 006.2, and concerns an update of section 4.5 of the SPC with information regarding combination with CYP3A4 substrates with a narrow therapeutic margin.<br>In the absence of detailed information, caution must be advised in case of combination with CYP3A4 substrates having a narrow therapeutic margin i.e. immunosuppressive agents (ciclosporine, tacrolimus, sirolimus) as well as CYP3A4-metabolised cytotoxics, i.e. cyclophosphamide, etoposide, finasteride, ifosfamide, tamoxifen, vinca-alcaloïds. |
| T/0022 | Transfer of Marketing Authorisation | 16/03/2007 | 11/04/2007 | SmPC, Labelling and PL | The MAH applied for a transfer of the Marketing Authorisation from 'Ligand Pharmaceuticals UK Ltd' to 'Eisai Ltd'. |
| IB/0020 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 21/12/2006 | n/a | | |
| IA/0021 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 20/12/2006 | n/a | Annex II and PL | |
| IB/0018 | IB_10_Minor change in the manufacturing process of the active substance | 11/08/2006 | n/a | | |
| IA/0019 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 03/08/2006 | n/a | | |
| IA/0017 | IA_13_a_Change in test proc. for active substance - minor change | 02/08/2006 | n/a | | |

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| IB/0016 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 04/07/2006 | n/a | SmPC and PL | |
| R/0015 | Renewal of the marketing authorisation. | 23/02/2006 | 24/04/2006 | SmPC, Annex II, Labelling and PL | |
| N/0014 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 28/10/2005 | n/a | PL | |
| N/0013 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 11/02/2005 | n/a | Annex II and PL | |
| N/0012 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 26/11/2004 | n/a | PL | |
| N/0011 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 29/09/2004 | n/a | PL | |
| IA/0010 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 11/08/2004 | n/a | | |
| IA/0009 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 11/08/2004 | n/a | | |
| IA/0008 | IA_19_a_Change in specification of an excipient - tightening of specification limits | 11/08/2004 | n/a | | |
| N/0007 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 14/06/2004 | n/a | Labelling and PL | |

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| IA/0006 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 23/03/2004 | n/a | Annex II and PL | |
| N/0005 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 15/05/2003 | 04/06/2003 | PL | |
| I/0004 | Addition of Gelita Group, Eberbach, Germany (production sites: DGF Stoess AG, Eberbach and Göpingen, Germany; Kind and Knox Gelatine Inc, Sergeant Buff, Iwo, USA) as additional supplier for Gelatin used as excipient.<br><br>04_Replacement of an excipient with a comparable excipient | 19/12/2002 | 07/01/2003 | | |
| II/0002 | Update of Summary of Product Characteristics and Package Leaflet | 27/06/2002 | 17/10/2002 | SmPC and PL | |
| I/0003 | 03_Change in the name and/or address of the marketing authorisation holder | 11/06/2002 | 11/07/2002 | SmPC, Labelling and PL | |