# Instanyl

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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| T/0084 | Transfer of Marketing Authorisation | 02/08/2024 | 22/08/2024 | SmPC, Labelling and PL | |
| PSUSA/1369/ 202304 | Periodic Safety Update EU Single assessment - fentanyl (transmucosal route of administration) | 25/01/2024 | 27/03/2024 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for |

[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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| II/0082 | Submission of the final report from study Instanyl-5002 listed as a category 3 study in the RMP. This is a non-interventional PASS study with title "Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL Off-Label Use". The RMP version 20.0 has also been submitted.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 11/01/2024 | n/a | | Submission of the final report from study Instanyl-5002 listed as a category 3 study in the RMP. |
| IA/0079/G | This was an application for a group of variations.<br><br>B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 15/09/2023 | n/a | | |
| II/0077 | Update of section 4.8 of the SmPC in order to add hypersensitivity, anaphylactic reaction and anaphylactic shock to the list of adverse drug reactions (ADRs) with frequency not known based on a cumulative review on safety databases, clinical trials data, fentanyl labels and scientific literature. The Package Leaflet is updated accordingly. | 14/09/2023 | 27/03/2024 | SmPC and PL | Hypersensitivity, anaphylactic reaction and anaphylactic shock are added in section 4.8 based on a cumulative review of safety databases, clinical trials data, fentanyl labels and scientific literature, in order to complete the list of adverse drug reactions (ADRs) under the immune system disorders System Organ Class (SOC) with a not known frequency.<br>The PL have been updated accordingly. For more |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | information, please refer to the Summary of Product Characteristics |
| II/0075 | B.IV.z - Quality change - Change in Medical Devices - Other variation | 14/04/2023 | n/a | | |
| IA/0076 | 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 | 14/02/2023 | n/a | | |
| IB/0074 | C.I.3.z - 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 - Other variation | 16/01/2023 | 15/09/2023 | SmPC and PL | |
| IB/0071/G | This was an application for a group of variations.<br><br>C.I.3.z - 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 - Other variation<br>C.I.3.z - 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 - Other variation | 07/12/2022 | 15/09/2023 | SmPC and PL | C.I.3.z – To update sections 4.4 and 4.5 of the SmPC to add a warning about the concomitant use of benzodiazepine and Instanyl, following the CMDh advice on Concomitant use of benzodiazepines/benzodiazepine like products and opioids (CMDh/372/2018). The PL has been updated accordingly.<br>C.I.3.z – To update section 4.5 of the SmPC to include a warning about the interaction between fentanyl and gabapentinoids. The PL has been updated accordingly. |
| IA/0073/G | This was an application for a group of variations.<br><br>B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an | 22/11/2022 | n/a | | |

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| | alternative method is already authorised<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 | | | | |
| IB/0070/G | This was an application for a group of variations.<br><br>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process<br>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing<br>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<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 16/09/2022 | 15/09/2023 | Annex II and PL | |
| IB/0069 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 12/09/2022 | 15/09/2023 | PL | |
| IA/0068 | A.7 - Administrative change - Deletion of manufacturing sites | 21/03/2022 | 02/06/2022 | Annex II and PL | |

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| IB/0067 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 25/02/2022 | 02/06/2022 | Labelling and PL | To add the definition of a patient at risk of misuse and abuse to the Product Information for Instanyl nasal spray, solution, Instanyl nasal spray, solution in single dose container, Instanyl nasal spray, solution (DoseGuard) following the assessment of EMEA/H/C/000959/LEG/30.1 where this amendment was requested.<br><br>In addition the MAH has taken the opportunity to amend the contact details of the local representatives in Cyprus, Malta, Netherlands and Ireland. |
| IB/0066/G | This was an application for a group of variations.<br><br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation | 20/01/2022 | n/a | | |
| IA/0065 | B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) | 02/12/2021 | 02/06/2022 | SmPC, Labelling and PL | |
| IB/0064/G | This was an application for a group of variations.<br><br>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation<br>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 02/12/2021 | n/a | | |

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| IB/0063/G | This was an application for a group of variations.<br><br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation | 05/11/2021 | n/a | | |
| IA/0062/G | This was an application for a group of variations.<br><br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<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 | 04/08/2021 | n/a | | |
| IAIN/0061/G | This was an application for a group of variations.<br><br>A.1 Change in the name and/or address of the marketing authorisation holder<br>A.7 Deletion of manufacturer responsible for batch release<br><br>A.1 - Administrative change - Change in the name and/or address of the MAH<br>A.7 - Administrative change - Deletion of manufacturing sites | 19/05/2021 | 02/06/2022 | SmPC, Annex II, Labelling and PL | |

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| PSUSA/1369/202004 | Periodic Safety Update EU Single assessment - fentanyl (transmucosal route of administration) | 28/01/2021 | 07/04/2021 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1369/202004. |
| IB/0059/G | This was an application for a group of variations.<br><br>B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product<br>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) | 05/02/2021 | 02/06/2022 | SmPC, Labelling and PL | |
| IA/0058 | 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 | 05/11/2020 | n/a | | |
| IB/0055 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 14/10/2020 | 07/04/2021 | SmPC, Annex II and PL | |
| IB/0056/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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>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- | 30/07/2020 | 16/11/2020 | Annex II and PL | |

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| | release, batch control, primary and secondary packaging, for non-sterile medicinal products<br>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing | | | | |
| IAIN/0054 | B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale | 17/06/2020 | 16/11/2020 | SmPC | |
| II/0052 | Please refer to the Recommendations section above.<br><br>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 | 12/03/2020 | 16/11/2020 | Annex II | The Risk Management Plan version 19.6 has been updated to include a greater emphasis for off-label use and the serious risks of misuse and abuse in the educational materials. |
| 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 | 13/02/2020 | 16/11/2020 | Annex II and PL | |
| II/0051 | Update of section 4.8 to include "dyspnoea". The MAH has also taken the opportunity to include editorial changes in Patient Leaflet. | 10/10/2019 | 16/11/2020 | SmPC and PL | Addition of "dyspnoea" in section 4.8 has been approved based on literature references and post-marketing cases. This addition is consistent with section 4.4 of the product |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | SmPC, and the information included in the SmPC of the other transmucosal fentanyl products.<br>Addition in the patient leaflet of further information and visual guide regarding the correct handling and use of the spray is also endorsed. |
| R/0049 | Renewal of the marketing authorisation. | 26/04/2019 | 01/07/2019 | SmPC | |
| II/0047/G | This was an application for a group of variations.<br><br>Update of section 4.4. to revise the risks of respiratory depression and the risks in patients with Chronic Obstructive Pulmonary Disease based on cumulative safety data respectively. Update of section 4.5 with regards interactions with others CNS depressants and skeletal muscle relaxants based on literature data. Update of section 4.8 to add loss of consciousness. Update of section 4.3 and 4.5 to reflect the contraindication with sodium oxybate.<br>The PL is updated accordingly. The MAH took this opportunity to update the labelling in line with QRD latest templates.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 17/01/2019 | 05/03/2019 | SmPC, Labelling and PL | The contraindication of Instanyl with sodium oxybate is included in section 4.3 and 4.5 of the SmPC.<br>The concomitant use of other central nervous system depressants and skeletal muscle relaxants may produce additive depressant effects: hypoventilation, hypotension, profound sedation, coma or death may occur. Therefore, the use of any of these medicinal products concomitantly with Instanyl requires special patient care and observation. This information has been updated in section 4.5.<br>Loss of consciousness is added in section 4.8 based on literature reference and post-marketing cases, as well as change of SOC for PT term “Neonatal withdrawal syndrome”.<br>The Labelling, PL have been updated accordingly. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| IA/0050 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 15/02/2019 | n/a | | |
| IA/0048 | 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 | 17/10/2018 | n/a | | |
| PSUSA/1369/201704 | Periodic Safety Update EU Single assessment - fentanyl (transmucosal route of administration) | 22/02/2018 | 08/05/2018 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1369/201704. |
| IA/0046 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 16/04/2018 | n/a | | |
| N/0045 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 22/11/2017 | 08/05/2018 | PL | |
| IB/0043 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 07/03/2017 | 23/10/2017 | SmPC and PL | |
| IA/0042 | 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) | 29/11/2016 | n/a | | |

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| IA/0041/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits<br>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 | 19/10/2016 | 23/10/2017 | SmPC, Annex II, Labelling and PL | |
| II/0040 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 13/10/2016 | n/a | | |
| X/0030/G | This was an application for a group of variations.<br><br>B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP<br>B.II.e.5.d - Change in pack size of the finished product - Change in the fill weight/fill volume of nonparenteral multi-dose (or single-dose, partial use) products<br>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits<br>B.II.e.5.d - Change in pack size of the finished | 01/04/2016 | 22/09/2016 | SmPC, Annex II, Labelling and PL | |

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| | product - Change in the fill weight/fill volume of nonparenteral multi-dose (or single-dose, partial use) products<br>B.II.e.5.d - Change in pack size of the finished product - Change in the fill weight/fill volume of nonparenteral multi-dose (or single-dose, partial use) products | | | | |
| IB/0039 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 12/05/2016 | n/a | | |
| IB/0037 | B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale | 18/02/2016 | 22/09/2016 | SmPC | |
| IG/0652 | 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 | 22/01/2016 | n/a | | |
| IB/0036 | B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product | 17/09/2015 | 22/09/2016 | SmPC, Labelling and PL | |
| IB/0035 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 18/06/2015 | n/a | | |
| IB/0034 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 20/03/2015 | n/a | | |

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| PSUSA/1369/201404 | Periodic Safety Update EU Single assessment - fentanyl (transmucosal route of administration) | 18/12/2014 | 05/03/2015 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1369/201404. |
| IA/0033 | 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 | 05/02/2015 | n/a | | |
| N/0032 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 23/01/2015 | 22/09/2016 | PL | |
| II/0028 | 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 | 18/12/2014 | n/a | | |
| IAIN/0031 | 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 | 07/11/2014 | 05/03/2015 | Annex II and PL | |
| IAIN/0029/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 | 22/09/2014 | 05/03/2015 | SmPC, Labelling and PL | |

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| | A.7 - Administrative change - Deletion of manufacturing sites | | | | |
| IB/0026/G | This was an application for a group of variations.<br><br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>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 | 28/08/2014 | n/a | | |
| IA/0025/G | This was an application for a group of variations.<br><br>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<br>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>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<br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non- | 27/06/2014 | n/a | | |

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| | significant specification parameter (e.g. deletion of an obsolete parameter) | | | | |
| R/0022 | Renewal of the marketing authorisation. | 20/02/2014 | 23/04/2014 | SmPC, Annex II, Labelling and PL | Reviewing the efficacy and safety data available for Instanyl since the granting of the marketing authorisation revealed no new major safety concerns. From the clinical perspective, the CHMP considered that the overall benefit-risk balance of Instanyl remained unchanged and was positive. However, an additional five-year year renewal was required based on pharmacological grounds mainly driven by the high level of off label use, for which the safety profile remains uncertain. |
| PSUSA/1369/ 201304 | Periodic Safety Update EU Single assessment - fentanyl (transmucosal route of administration) | 19/12/2013 | 28/02/2014 | SmPC and PL | Refer to the Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation for PSUSA/1369. |
| IG/0401 | 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 | 11/02/2014 | n/a | | |
| II/0019 | Submission of the final clinical trial report for the trial FT-1301-032-SP (Nose-400). In this study the nasal tolerability of all dose strengths of Instanyl was investigated.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 21/11/2013 | n/a | | The results of the nasal tolerability study do not impact the benefit/risk balance of Instanyl for the treatment of breakthrough pain in cancer patient.<br><br>According to the results from the nasal tolerability study, a very few number of patients were reported with mucosa signs or abnormalities worsening. However, due especially to the low number of patients included in that study, a risk of local effect and nasal perforation with the product could not be excluded. Therefore nasal tolerability remains of concern and the MAH should continue to monitor cases of |

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| | | | | | nasal effects and should seek to identify risk factors associated to nasal effects and the delay to onset of these effects. |
| IAIN/0021/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.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing | 18/10/2013 | 28/02/2014 | Annex II and PL | |
| IAIN/0020/G | This was an application for a group of variations.<br><br>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)<br>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) | 11/10/2013 | n/a | | |
| IB/0016 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 13/08/2013 | n/a | | |
| IB/0015 | B.II.e.6.z - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Other variation | 13/08/2013 | n/a | | |
| IAIN/0018/G | This was an application for a group of variations. | 24/07/2013 | 28/02/2014 | SmPC, Annex | |

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| | 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 responsible for batch release<br>A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release | | | II, Labelling and PL | |
| IA/0017/G | This was an application for a group of variations.<br><br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 24/07/2013 | n/a | | |
| N/0014 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 19/07/2013 | 28/02/2014 | PL | |
| IG/0293 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 23/04/2013 | n/a | | |
| II/0012 | Update of section 4.8 of the SmPC in order to add "nasal septum perforation" as an adverse reaction, following a previous PSUR assessment. The Package Leaflet was updated accordingly.<br>In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. | 21/03/2013 | 28/02/2014 | SmPC, Annex II and PL | Following conclusions of a PSUR assessment, the MAH complied with the request of the CHMP to update the Product Information by adding the "nasal septum perforation" as a side effect. The following information was included in the Package Leaflet:<br>"There have been reports of patients developing a hole in the septum of the nose – the structure, which separates |

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| | Furthermore, minor editorial changes were introduced in the PI and the Annex II was brought in line with the latest QRD template version 8.3.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | | | | the nostrils." |
| IG/0219 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 25/09/2012 | n/a | | |
| IB/0010/G | This was an application for a group of variations.<br><br>B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer<br>B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 09/08/2012 | n/a | | |
| IB/0009/G | This was an application for a group of variations.<br><br>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)<br>B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other | 09/08/2012 | 25/10/2012 | SmPC | |

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| | variation | | | | |
| N/0008 | The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 28/11/2011 | 27/02/2012 | PL | The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB. |
| IB/0007/G | This was an application for a group of variations.<br><br>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)<br>B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation | 09/08/2011 | n/a | SmPC | |
| IB/0004 | C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH | 20/07/2011 | n/a | SmPC, Annex II, Labelling and PL | Update of section 4.8 of the Summary of Product Characteristics" to add "hallucination" in a new table column titled "Not known". The Package Leaflet has been amended accordingly.<br>The Product Information was also updated according to the latest QRD guidelines. |
| IA/0006 | C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV | 01/07/2011 | n/a | | |
| X/0002 | Annex I_2.(d) Change or addition of a new pharmaceutical form | 14/04/2011 | 29/06/2011 | SmPC, Labelling and PL | |

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| N/0001 | "The Marketing Authorisation Holder (MAH) took this opportunity to shorten the Braille and remove "mcg/dose". The MAH also made minor changes to the name of the local representative in Austria.<br><br>Additionally minor linguistic changes to the Finnish, Latvian, Polish and Dutch Package Leaflets and to the Czech labelling."<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 30/11/2009 | n/a | Labelling and PL | |