



## PritorPlus

### Procedural steps taken and scientific information after the authorisation

| Application number | Scope  | Opinion/ Notification <sup>1</sup> issued on | Commission Decision Issued <sup>2</sup> / amended on | Product Information affected <sup>3</sup> | Summary  |
|--------------------|--|--|--|---|--|
| IG/1549            | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 24/08/2022                                   |  | SmPC and PL                               | To update sections 4.4 and 4.8 of the SmPC and sections 2 and 4 of the PL to implement the wording regarding the adverse event Acute Respiratory Distress Syndrome (ARDS) affecting the medicinal products that contain hydrochlorothiazide. |

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



|           |  |            |            |                       |  |
|-----------|--|------------|------------|-----------------------|--|
| N/0128    | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)   | 06/12/2021 | 29/06/2022 | PL                    |  |
| IG/1448   | A.7 - Administrative change - Deletion of manufacturing sites  | 04/10/2021 | n/a        |                       |  |
| WS/2077   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>To update the PI to align the wording for the excipients lactose, sodium and sorbitol to the "Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668, Rev. 1)", published in Nov. 2019.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p> | 17/06/2021 | 29/06/2022 | SmPC, Annex II and PL |  |
| IG/1262/G | <p>This was an application for a group of variations.</p> <p>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)</p> <p>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</p> <p>B.III.1.a.2 - Submission of a new/updated or</p>                                 | 16/07/2020 | n/a        |                       |  |

|                   |   |            |            |             |                                   |
|-------------------|---|------------|------------|-------------|-----------------------------------|
|                   | deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer  |            |            |             |                                   |
| IG/1259           | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation  | 23/06/2020 | 09/03/2021 | SmPC and PL |                                   |
| IG/1218           | 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   | 10/04/2020 | n/a        |             |                                   |
| WS/1768           | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 19/03/2020 | 09/03/2021 | SmPC and PL |                                   |
| PSUSA/2882/201904 | Periodic Safety Update EU Single assessment - hydrochlorothiazide / telmisartan, telmisartan  | 28/11/2019 | n/a        |             | PRAC Recommendation - maintenance |
| PSUSA/2882/201804 | Periodic Safety Update EU Single assessment - hydrochlorothiazide / telmisartan, telmisartan  | 29/11/2018 | n/a        |             | PRAC Recommendation - maintenance |
| IG/1011           | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation  | 27/11/2018 | 04/11/2019 | SmPC and PL |                                   |
| IG/1002/G         | This was an application for a group of variations.<br><br>B.II.d.1.i - Change in the specification parameters   | 16/11/2018 | n/a        |             |                                   |

|                       |  |            |            |                              |                                   |
|-----------------------|--|------------|------------|------------------------------|-----------------------------------|
|                       | <p>and/or limits of the finished product - Ph. Eur. 2.9.40<br/> uniformity of dosage units is introduced to replace<br/> the currently registered method, either Ph. Eur.<br/> 2.9.5 or Ph. Eur. 2.9.6</p> <p>B.II.d.1.z - Change in the specification parameters<br/> and/or limits of the finished product - Other variation</p> <p>B.II.d.2.a - Change in test procedure for the finished<br/> product - Minor changes to an approved test<br/> procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished<br/> product - Minor changes to an approved test<br/> procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished<br/> product - Minor changes to an approved test<br/> procedure</p> |            |            |                              |                                   |
| IG/0989               | B.III.1.a.2 - Submission of a new/updated or<br>deletion of Ph. Eur. Certificate of Suitability to the<br>relevant Ph. Eur. Monograph - Updated certificate<br>from an already approved manufacturer   | 10/10/2018 | n/a        |                              |                                   |
| T/0115                | Transfer of Marketing Authorisation  | 16/03/2018 | 13/04/2018 | SmPC,<br>Labelling and<br>PL |                                   |
| IG/0904               | A.5.a - Administrative change - Change in the name<br>and/or address of a manufacturer/importer<br>responsible for batch release   | 06/02/2018 | 07/03/2018 | Annex II and<br>PL           |                                   |
| PSUSA/2882/<br>201704 | Periodic Safety Update EU Single assessment -<br>hydrochlorothiazide / telmisartan, telmisartan  | 30/11/2017 | n/a        |                              | PRAC Recommendation - maintenance |

|         |   |            |            |                                  |   |
|---------|---|------------|------------|----------------------------------|---|
| IG/0820 | 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   | 29/06/2017 | n/a        |                                  |   |
| WS/1110 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.5 and 4.8 to align the hydrochlorothiazide component information with that of the originator. The Package Leaflet is updated accordingly.</p> <p>In addition, Worksharing applicant (WSA) took the opportunity of this procedure to bring the PI in line with the latest QRD template, including combining the SmPC of the different strengths, as well as implement minor editorial changes and reformatting of some sections of the SmPC. The details of local representative (Portugal for MicardisPlus and United Kingdom for PritorPlus and Kinzalkomb) in the PL have been updated.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 06/04/2017 | 07/03/2018 | SmPC, Annex II, Labelling and PL | In order to align the information for the Hydrochlorothiazide component with the information from the competitor/originator labels, section 4.8 of MicardisPlus, PritorPlus, and Kinzalkomb SmPCs has been updated with addition of the side effects thrombocytopenia (sometimes with purpura), hypomagnesaemia, hypercalcaemia, hypochloaemic alkalosis, headache, nausea and erythema multiforme. Wording on interaction with Calcium salt in section 4.5 was also updated. The Package Leaflet is updated accordingly. |
| IG/0781 | 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   | 06/03/2017 | n/a        |                                  |   |

|                       |   |            |            |    |                                   |
|-----------------------|---|------------|------------|----|-----------------------------------|
| PSUSA/2882/<br>201604 | Periodic Safety Update EU Single assessment - hydrochlorothiazide / telmisartan, telmisartan  | 01/12/2016 | n/a        |    | PRAC Recommendation - maintenance |
| N/0108                | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)  | 08/07/2016 | 07/03/2018 | PL |                                   |
| IG/0684/G             | This was an application for a group of variations.<br><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 | 25/04/2016 | n/a        |    |                                   |
| PSUSA/2882/<br>201504 | Periodic Safety Update EU Single assessment - hydrochlorothiazide / telmisartan, telmisartan  | 06/11/2015 | n/a        |    | PRAC Recommendation - maintenance |
| N/0105                | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)  | 25/08/2015 | 07/03/2018 | PL |                                   |
| IG/0502               | 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   | 13/11/2014 | n/a        |    |                                   |
| PSUSA/2882/           | Periodic Safety Update EU Single assessment -   | 06/11/2014 | n/a        |    | PRAC Recommendation - maintenance |

|          |  |            |            |             |   |
|----------|--|------------|------------|-------------|---|
| 201404   | hydrochlorothiazide / telmisartan, telmisartan   |            |            |             |   |
| A31/0093 | On 17 April 2013, further to the emergence of new evidence from the scientific literature on dual RAS blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) initiated a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or aliskiren and to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure. | 22/05/2014 | 04/09/2014 | SmPC and PL | For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31 referral - Assessment report. |
| N/0102   | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)   | 14/07/2014 | 07/03/2018 | PL          |   |
| WS/0569  | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Submission of a revised RMP version 9.0 in order to align the RMP with that of telmisartan monotherapy products to ensure consistency. In addition, the RMP was reformatted according to the current  | 26/06/2014 | n/a        |             | N/A   |

|                   |  |            |            |                 |   |
|-------------------|--|------------|------------|-----------------|---|
|                   | <p>requirements of the Guidelines on Good Pharmacovigilance Practice.</p> <p>The requested variation worksharing procedure proposed no amendments to the PI.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>  |            |            |                 |   |
| IG/0388           | A.7 - Administrative change - Deletion of manufacturing sites  | 11/12/2013 | 04/09/2014 | Annex II and PL |   |
| PSUSA/2882/201304 | Periodic Safety Update EU Single assessment - hydrochlorothiazide / telmisartan, telmisartan   | 07/11/2013 | n/a        |                 | PRAC Recommendation - maintenance   |
| WS/0436           | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 5.1 of the SmPC to add information related to the cardiovascular morbidity based on the ONTARGET and TRANSCEND trials following the outcome of the Article 20 procedure for MicardisPlus /PritorPlus /Kinzalkomb (telmisartan/HCTZ).</p> <p>In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.</p> <p>Furthermore, the PI is being brought in line with the latest QRD template version 9.</p> <p>The requested worksharing variation procedure proposed amendments to the Summary of Product</p> | 24/10/2013 | 04/09/2014 | SmPC and PL     | <p>In this type II variation, information related to the cardiovascular morbidity and the ONTARGET and TRANSCEND trials following the Article 20 procedure is provided. The objective was to bring consistent information on the properties of telmisartan regarding cardiovascular prevention for the SmPC of the telmisartan + hydrochlorothiazide medicinal products.</p> <p>The section 5.1 is now in line with the current approved text of the EU SmPC section 5.1 of the telmisartan monocomponent products.</p> |



|         |   |            |            |             |  |
|---------|---|------------|------------|-------------|--|
|         | <p>Characteristics and Package Leaflet.</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>  |            |            |             |  |
| N/0095  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)  | 07/10/2013 | 04/09/2014 | PL          |  |
| IG/0356 | 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   | 23/09/2013 | n/a        |             |  |
| IG/0322 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation  | 19/07/2013 | n/a        |             |  |
| WS/0372 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add a new adverse reaction "acute myopia". The package leaflet is amended accordingly.</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> | 25/04/2013 | 29/05/2013 | SmPC and PL | <p>In a recent procedure WS288, "acute angle-closure glaucoma" was added as a new side effect in section 4.8. Since "acute angle-closure glaucoma" can cause "acute myopia, the WSA is proposing to add this adverse reaction accordingly. The Package Leaflet is proposed to be updated accordingly.</p> <p>Furthermore, the WSA proposed this opportunity to sort out an inconsistency in section 2 of the PILs of MicardisPlus compared to PritorPlus and Kinzalkomb as a different term is used to describe symptoms of acute myopia and acute angle closure glaucoma.</p> <p>The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.</p> |

|         |  |            |            |                                  |   |
|---------|--|------------|------------|----------------------------------|---|
| WS/0362 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.</p> <p>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</p> | 25/04/2013 | 29/05/2013 | SmPC, Annex II, Labelling and PL | <p>For Micardis, Micardis Plus, Kinzalmono, kinzalkomb, Pritor, Pritor Plus</p> <p>Update of sections 4.2, 4.3, 4.4 and 4.5 of the SmPC to implement recommendations regarding the use of telmisartan with aliskiren as requested by the CHMP in the PSUR following the outcome of Article 20 related to aliskiren. In addition, information related to interaction with digoxin is added in section 4.5 of the SmPC. The Package leaflet is updated accordingly.</p> <p>Furthermore, the WSA took the opportunity to sort out a number of inconsistencies in content between SmPCs and PILs for the different products as follows:</p> <p>For Micardis, Micardis Plus, Kinzalmono, kinzalkomb, Pritor, Pritor Plus</p> <ul style="list-style-type: none"> <li>- Inconsistency between SmPC section 4.5 and PIL regarding interaction with alcohol, barbiturates, narcotics or antidepressants</li> <li>- Inconsistency between SmPC section 4.2 and PIL regarding the storage recommendation.</li> </ul> <p>For Twynsta, Onduarp</p> <p>PIL section 4 will be brought in line with SmPC section 4.8 with regard to the side effect hyperglycaemia (amlodipine component)</p> <p>For Micardis Plus, Kinzalkomb, Pritor Plus</p> <p>In the PIL section 2, there is a different wording of telmisartan mono products compared to the telmisartan/HCTZ products for the explanation of cholestasis or biliary obstruction. The MAH proposes to align the wording in the PIL of the telmisartan/HCTZ products so that it is identical with telmisartan mono products.</p> |
|---------|--|------------|------------|----------------------------------|---|

|         |   |            |            |             |  |
|---------|---|------------|------------|-------------|--|
|         |   |            |            |             | <p>Besides, editorial changes are proposed for Twynsta, Onduarp, Micardis, MicardisPlus, Pritor, PritorPlus, Kinzalmono and Kinzalkomb regarding storage recommendations in Annex IIIA in bold characters to bring them in line with the printing style on the actual, marketed products.</p> <p>In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Micardis and Micardis Plus: (Belgium, Bulgaria and Luxembourg, Estonia, Lithuania)</p> <p>Twynsta/Onduarp (Estonia, Belgium and Luxembourg)</p> <p>Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template (Version 9).</p> |
| WS/0288 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.4 of the SmPC in order to add a new warning on acute myopia and angle-closure glaucoma with hydrochlorothiazide and to include acute angle-closure glaucoma as a new ADR in section 4.8 of the SmPC. Sections 2 and 4 of the Package Leaflet are updated accordingly. In addition the MAH is taking the opportunity to make some corrections in the DE, ES, FR, IT and LT Annexes for MicardisPlus, DE and IT Annexes for PritorPlus and Kinzalkomb.</p> <p>C.I.4 - Variations related to significant modifications</p> | 20/09/2012 | 24/10/2012 | SmPC and PL | <p>This type II variation concerns an update of section 4.4 of the telmisartan/HCT SmPC to include a new warning on acute myopia and angle-closure glaucoma with HCT and to include acute angle-closure glaucoma as a new ADR in section 4.8 of the telmisartan/HCT SmPC, with consequential changes to the PL.</p>  |

|           |   |            |            |             |   |
|-----------|---|------------|------------|-------------|---|
|           | of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data   |            |            |             |   |
| IG/0208   | 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   | 22/08/2012 | n/a        |             |   |
| WS/0247   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of Summary of Product Characteristics and Package Leaflet.</p> <p>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</p> | 24/05/2012 | 28/06/2012 | SmPC and PL | <p>This type IB variation concerns an update of section 4.6 of the SmPC and package leaflet. The present worksharing variation application is submitted to update the relevant sections of SmPC and PL according to a harmonised wording concerning the use of hydrochlorothiazide in combination with angiotensin II receptor antagonists during pregnancy and breast-feeding as per the recommendation and wording agreed by PhVWP and CHMP in June 2011.</p> <p>In particular, with this variation the MAH added information on the limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. In addition the MAH added that hydrochlorothiazide crosses the placenta and its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. The updated of the SmPC includes that hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p> |
| IG/0181/G | <p>This was an application for a group of variations.</p> <p>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the</p>  | 25/05/2012 | n/a        |             |   |

|         |   |            |            |                                  |   |
|---------|---|------------|------------|----------------------------------|---|
|         | <p>major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD</p> <p>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</p> <p>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</p>   |            |            |                                  |   |
| WS/0221 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Following the assessment of PSUR 10 and PSUR 11 for telmisartan, update to section 4.4 of the SmPC to include a warning for diabetic patients when treated with insulin or oral antidiabetics and to include a warning on RAAS blockage in patients with uncontrolled blood pressure, and update to section 4.8 of the SmPC to include "cough", "somnolence" and "interstitial lung disease" as new ADR and consequential changes to section 4 of the PL. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for MicardisPlus only. Furthermore, the PI is being brought in line with the latest QRD template version 8. Finally the MAH took the opportunity to make</p> | 19/04/2012 | 25/05/2012 | SmPC, Annex II, Labelling and PL | <p>This type II variation concerns an update of sections 4.4 and 4.8 of the SmPC, upon request by CHMP following the assessment of PSUR 10 and 11 for telmisartan, to include a warning for diabetic patients when treated with insulin or oral antidiabetics and to include a warning on RAAS blockage in patients with uncontrolled blood pressure, and to add "cough", "somnolence" and "interstitial lung disease" as new ADR. Post-marketing experience with telmisartan has identified "somnolence", "cough" and "interstitial lung disease" as new side effects. Regarding "diabetic patients", as several patients that developed hypoglycemia were treated with antidiabetics or insulin, the MAH was requested to include a warning to be added in section 4.4 of SmPC in order to advise caution in patient diabetic treated with antidiabetics or insulin. Based on the cases from post marketing experience, the MAH was requested to discuss if an additional recommendation, regarding the dual blockade of the renin angiotensin.</p> |

|         |  |            |     |  |  |
|---------|--|------------|-----|--|--|
|         | <p>some corrections in the BG, CZ, DA, DE, ES, ET, FI, FR, HU, IS, IT, LV, MT, NL, NO, PL, PT, SE, SK, SL Annexes for PritorPlus and BG, CZ, DA, DE, ES, ET, FI, HU, IS, IT, LV, MT, NL, NO, PL, PT, SE, SK, SL Annexes for Kinzalkomb.</p> <p>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</p> |            |     |  |  |
| IG/0165 | <p>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</p>   | 10/04/2012 | n/a |  |  |
| WS/0175 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>To tighten the specification limits of the finished product.</p> <p>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits</p>   | 15/12/2011 | n/a |  |  |
| IG/0105 | <p>B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur.</p>   | 06/10/2011 | n/a |  |  |

|           |  |            |            |                                  |  |
|-----------|--|------------|------------|----------------------------------|--|
|           | Monograph - Updated certificate from an already approved manufacturer  |            |            |                                  |  |
| IG/0094/G | <p>This was an application for a group of variations.</p> <p>A.1 - Administrative change - Change in the name and/or address of the MAH</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release</p>   | 25/08/2011 | n/a        | SmPC, Annex II, Labelling and PL |  |
| WS/0104   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of Summary of Product Characteristics, Annex II and Package Leaflet.</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> | 17/02/2011 | 02/05/2011 | SmPC, Annex II and PL            | <p>This type II variation concerns an update of section 4.8 of the SPC to include the ADRs 'angioedema (also with fatal outcome)' and 'Exacerbation of activation of Systemic Lupus erythematosus'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SPC and section 4 of the Package Leaflet, to update the contact details of the Spanish local representative in the Package Leaflet and to update annex II with standard wording concerning the pharmacovigilance system.</p> <p>This application was submitted as a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> |
| WS/0087/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>To add a new alternative manufacturer for the active substance.</p>  | 14/04/2011 | 14/04/2011 |                                  |  |

|         |  |            |            |                       |  |
|---------|--|------------|------------|-----------------------|--|
|         | <p>To increase the batch size of the active substance.</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size</p>                                  |            |            |                       |  |
| WS/0039 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of Summary of Product Characteristics and Package Leaflet.</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> | 20/01/2011 | 21/02/2011 | SmPC, Annex II and PL | <p>This type II variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 9, to add further information about 'liver disorder' and to add the ADR 'hypoglycaemia' under post-marketing experience.</p> <p>Most cases of abnormal liver function / liver disorder from post-marketing experience occurred in Japanese patients. The product information has now been updated to reflect the fact that Japanese patients are more likely to experience these adverse reactions.</p> <p>Post-marketing experience with telmisartan has identified hypoglycaemia as a new side effect which occurs mainly in diabetic patients and patients with abnormal glucose tolerance. Based on the statistically significant number of hypoglycaemia reports from pooled clinical trials in hypertensive patients suffering from diabetes, and the cardiovascular outcome trial TRANSCEND, a direct causal relationship between the occurrence of hypoglycaemia in diabetic patients and the therapeutic use of telmisartan cannot be excluded.</p> |



|           |   |            |     |  |  |
|-----------|---|------------|-----|--|--|
|           |   |            |     |  | <p>In addition, the MAH took the opportunity to update Annex II with the standard DDPS wording and to make changes to the SPC to bring it in line with the latest version of the SPC guideline. The Package Leaflet has been updated accordingly.</p> <p>This application was submitted as a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> |
| IG/0045/G | <p>This was an application for a group of variations.</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</p> <p>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database</p> <p>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</p> | 08/02/2011 | n/a |  |  |
| IG/0010/G | <p>This was an application for a group of variations.</p> <p>B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions</p> <p>B.II.b.3.a - Change in the manufacturing process of</p>  | 30/06/2010 | n/a |  |  |

|         |  |            |            |             |  |
|---------|--|------------|------------|-------------|--|
|         | <p>the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions</p> <p>B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test</p> <p>B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)</p>  |            |            |             |  |
| IA/0076 | <p>To adjust the net weights of active pharmaceutical ingredients Telmisartan, Hydrochlorothiazide and Telmisartan Spray Dried Granulate intermediate.</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions</p>  | 04/06/2010 | n/a        |             |  |
| II/0074 | <p>Update of Summary of Product Characteristics and Package Leaflet</p> <p>This type II variation concerns an update of section 4.4 of the SPC to include a warning on the use of dual RAAS blockade and section 4.5 of the SPC to include information on the interaction with ramipril. Further, a minor change has been made to section 4.8 of the SPC to delete the term 'ineffectiveness of telmisartan'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the</p> | 18/03/2010 | 29/04/2010 | SmPC and PL | <p>Dual blockade of the renin-angiotensin-aldosterone system: As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal</p> |

|           |   |            |     |  |  |
|-----------|---|------------|-----|--|--|
|           | <p>SPC and Package Leaflet and to update the list of local representatives in the Package Leaflet.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>  |            |     |  | <p>function.</p> <p>Inteaction with ramipril:<br/>In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.</p> <p>The term 'drug ineffective' currently labelled as an adverse drug reaction observed with telmisartan mono therapy is not substantiated from clinical trial data or from post marketing experience, and has therefore been deleted from section 4.8 of the SPC.</p> |
| IA/0075/G | <p>This was an application for a group of variations.</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site</p> | 26/03/2010 | n/a |  |  |
| IA/0073   | <p>To delete a manufacturing site for an intermediate product.</p> <p>IA_09_Deletion of manufacturing site</p>  | 08/12/2009 | n/a |  |  |
| IA/0072   | <p>IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold</p>   | 03/12/2009 | n/a |  |  |

|         |   |            |            |                     |   |
|---------|---|------------|------------|---------------------|---|
| IA/0071 | IA_09_Deletion of manufacturing site  | 03/12/2009 | n/a        |                     |   |
| IB/0070 | IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)  | 02/12/2009 | n/a        |                     |   |
| IA/0069 | IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer   | 19/10/2009 | n/a        |                     |   |
| II/0064 | Update of Detailed Description of the Pharmacovigilance System<br><br>Update of DDPS (Pharmacovigilance)  | 24/09/2009 | 14/10/2009 | Annex II            | The Detailed Description of the Pharmacovigilance System has been updated (Version 9.7) to notify changes to the DDPS performed since the last approved version, e.g. introduction of a safety management team. Consequently, Annex II has been updated with the new version number of the agreed DDPS. |
| IA/0068 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 01/09/2009 | n/a        |                     |   |
| IA/0067 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 01/09/2009 | n/a        |                     |   |
| IA/0066 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure  | 12/08/2009 | n/a        |                     |   |
| II/0057 | Update of SPC section 4.8 and 5.1 as well as PL section 4 to add information regarding "sepsis" as new side effect. In addition, the MAH took the                   | 23/04/2009 | 27/05/2009 | SmPC, Labelling and | In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of  |

|         |  |            |            |                                  |   |
|---------|--|------------|------------|----------------------------------|---|
|         | <p>opportunity to update the List of Local Representatives.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>   |            |            | PL                               | <p>sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known. The term "sepsis including fatal outcome" was therefore added to SPC section 4.8 with the frequency unknown and the package leaflet was updated accordingly.</p> |
| T/0061  | Transfer of Marketing Authorisation  | 17/04/2009 | 06/05/2009 | SmPC, Annex II, Labelling and PL | <p>The MAH applied for the transfer of the Marketing Authorisation of PritorPlus from Bayer Healthcare AG to Bayer Schering Pharma AG.</p> <p>The transfer will take place on 15 August 2009.</p>   |
| IA/0062 | IA_05_Change in the name and/or address of a manufacturer of the finished product  | 17/04/2009 | n/a        | Annex II and PL                  |   |
| IA/0063 | IA_05_Change in the name and/or address of a manufacturer of the finished product  | 15/04/2009 | n/a        |                                  |   |
| II/0058 | <p>Update of Detailed Description of the Pharmacovigilance System</p> <p>Update of DDPS (Pharmacovigilance)</p>                                      | 19/03/2009 | 07/04/2009 | Annex II                         | <p>The Detailed Description of the Pharmacovigilance System has been updated (Version 9.5) to reflect the integration of the companies' pharmacovigilance systems (Bayer and Schering AG). Consequently, Annex II has been updated with the new version number and date of the agreed DDPS.</p>   |
| II/0059 | The MAH applied for an update of the SPC sections 4.3 and 4.6 as well as PL section 2 to implement the CHMP recommendation on a harmonised labelling | 19/02/2009 | 17/03/2009 | SmPC and PL                      | <p>Available data regarding use of AIIRAs during lactation have been assessed. There are no concrete data to support the contraindication of use of AIIRAs during breast-feeding.</p>   |

|         |  |            |            |             |  |
|---------|--|------------|------------|-------------|--|
|         | <p>relating to the use of Angiotensin II Receptor Antagonists during pregnancy and lactation. Furthermore, minor typographical changes have been introduced to SPC section 4.4.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>  |            |            |             | <p>All AIIRA agents were found in the milk of lactating rats but no human data about their transfer into breast milk are available. There is only a theoretical presumption of low transport according to their high plasma protein binding and low oral availability. A harmonised wording recommending an alternative treatment with better established safety profiles during breast-feeding, especially while nursing a newborn or preterm infant, has been included in the section 4.6 of the SPC and section 2 of the PL.</p> <p>Consequently, the existing contraindication for lactation has been deleted.</p>   |
| II/0054 | <p>Update of the SPC section 4.8 in order to update the information based on a re-calculation of the frequencies for the undesirable effects taking into account adverse drug reactions instead of adverse events. In addition, SPC section 4.9 is proposed to be updated with regard to the information on overdose and information regarding photosensitivity with the component hydrochlorothiazide has been included in SPC section 4.4. The respective sections of the PL have been amended accordingly. Furthermore, the MAH took the opportunity to introduce minor revisions to the PI including an update of the list of local representatives.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 18/12/2008 | 27/01/2009 | SmPC and PL | <p>The revision of the EU SPC Guideline in October 2005 necessitated a re-calculation of the frequencies of undesirable effects taking into account adverse drug reactions instead of adverse events. Furthermore, the basis for the frequency estimation (i.e. the number of patients treated in eligible clinical trials with telmisartan/hydrochlorothiazide) has continuously grown since 2005. For the calculation of frequencies clinical trials have been included with a minimum treatment duration of 8 weeks. Therefore all randomised and double-blind clinical trials (placebo or active controlled) meeting this pre-requisite and which listed adverse events and reactions by individual patients (i.e. patient by patient basis) were identified and 9 clinical trials served as the basis for the frequency estimation of side effects of telmisartan + hydrochlorothiazide.</p> <p>Regarding SPC section 4.9 the information so far stated that "no data are available for telmisartan with regard to overdose in humans". However, several mostly</p> |

|         |   |            |            |             |   |
|---------|---|------------|------------|-------------|---|
|         |   |            |            |             | spontaneous reports of overdoses had been received by the MAH, and consequently SPC section 4.9 has been revised.   |
| IA/0056 | IA_39_Change/addition of imprints, bossing or other markings  | 25/11/2008 | n/a        | SmPC and PL |   |
| IA/0055 | IA_39_Change/addition of imprints, bossing or other markings  | 25/11/2008 | n/a        | SmPC and PL |   |
| N/0053  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)  | 04/08/2008 | n/a        | PL          |   |
| II/0047 | <p>The MAH applied for an update of the SPC sections 4.3, 4.4, and 4.6 as well as PL section 2 to implement the CHMP recommendation on a harmonised labelling relating to the use of ACE inhibitors and Angiotensin II Receptor Antagonists during pregnancy.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 24/04/2008 | 02/07/2008 | SmPC and PL | <p>Cooper's study published in the NEJM in June 2006 identified a signal of increased risk of congenital malformations, particularly cardiac defects after exposure to ACE inhibitors during the first trimester of pregnancy. Since the role of confounding factors such as diabetes and hypertension cannot be accurately defined based on the available data, the teratogenic potential of ACE inhibitors is not demonstrated, even though data suggest that such exposure cannot be considered as safe and should be avoided.</p> <p>There are fewer data regarding the risks associated with first trimester exposure to Angiotensin II receptor antagonists (AIIRAs) than for ACE inhibitors. Nevertheless, there is no evidence that the risk is lower for AIIRAs, and it is considered that any conclusions on ACE inhibitors are also valid for AIIRAs.</p> <p>Therefore, the existing contraindication for the 2nd and 3rd trimester of pregnancy remained, but a harmonised wording regarding pregnancy across the class was</p> |

|         |  |            |            |                              |            |
|---------|--|------------|------------|------------------------------|------------|
|         |  |            |            |                              | introduced |
| IA/0052 | IA_09_Deletion of manufacturing site   | 28/05/2008 | n/a        |                              |            |
| IA/0051 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site   | 28/05/2008 | n/a        |                              |            |
| IA/0050 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site   | 28/05/2008 | n/a        |                              |            |
| IA/0049 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site   | 28/05/2008 | n/a        |                              |            |
| IA/0048 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site   | 09/04/2008 | n/a        |                              |            |
| X/0042  | Annex I_2.(c) Change or addition of a new strength/potency   | 24/01/2008 | 01/04/2008 | SmPC,<br>Labelling and<br>PL |            |
| II/0045 | Changes to the manufacturing process for the finished product<br><br>Change(s) to the manufacturing process for the finished product | 24/01/2008 | 29/01/2008 |                              |            |
| IB/0046 | IB_38_c_Change in test procedure of finished product - other changes   | 07/01/2008 | n/a        |                              |            |
| N/0043  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)                                     | 20/08/2007 | n/a        | Labelling and<br>PL          |            |



|         |  |            |            |                                  |   |
|---------|--|------------|------------|----------------------------------|---|
| IA/0044 | IA_05_Change in the name and/or address of a manufacturer of the finished product  | 10/08/2007 | n/a        |                                  |   |
| R/0040  | Renewal of the marketing authorisation.  | 22/02/2007 | 14/05/2007 | SmPC, Labelling and PL           | <p>Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of PritorPlus continues to be favourable.</p> <p>The CHMP is of the opinion that the renewal can be granted with unlimited validity.</p>   |
| II/0033 | <p>Update of Sections 4.4 and 4.5 of the SPC further to a follow-up measure requested by CHMP. The Package Leaflet has been updated accordingly. Furthermore, the MAH has taken the opportunity to implement the latest QRD template (7.2).</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p> | 24/01/2007 | 28/02/2007 | SmPC, Annex II, Labelling and PL | <p>The following statement with regards to interaction between NSAIDs and angiotensin II antagonists has been added to section 4.5 of the SPC:</p> <p>"NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics and the antihypertensive effects of angiotensin II antagonists. In some patients with compromised renal function (eg dehydrated patients or elderly patients with compromised renal function) the co-administration of angiotensin II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to</p> |

|         |   |            |            |             |   |
|---------|---|------------|------------|-------------|---|
|         |   |            |            |             | <p>monitoring of renal function after initiation of concomitant therapy and periodically thereafter."</p> <p>In addition, minor changes have been introduced in the wording of the subsections on "lithium", "medicinal products that may increase potassium levels or induce hyperkalaemia", "alcohol and antidepressants."</p> <p>Regarding section 4.4, a number of cross-references have been introduced, as well as the following sentence on fructose intolerance, in line with the Guideline on Excipients:</p> <p>Sorbitol: Patients with hereditary problems of fructose intolerance should not take PritorPlus.</p> |
| II/0038 | <p>Change(s) to the manufacturing process for the active substance</p> <p>Change(s) to the manufacturing process for the active substance</p> | 24/01/2007 | 31/01/2007 |             |   |
| II/0034 | <p>Update of SPC (4.8) and implementation of MedDRA terminology.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>  | 16/11/2006 | 08/01/2007 | SmPC and PL | Update Section 4.8 of the SPC to add "acute renal failure, blood creatine phosphokinase increased and hyperkalaemia". The changes are based either on pharmacological mechanisms and/or on data mining of the company safety database.  |
| IB/0041 | IB_33_Minor change in the manufacture of the finished product   | 15/12/2006 | n/a        |             |   |

|         |  |            |            |                              |  |
|---------|--|------------|------------|------------------------------|--|
| IB/0039 | IB_10_Minor change in the manufacturing process of the active substance                          | 09/11/2006 | n/a        |                              |  |
| IA/0037 | IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size          | 17/10/2006 | 17/10/2006 | SmPC,<br>Labelling and<br>PL |  |
| IA/0036 | IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size          | 17/10/2006 | 17/10/2006 | SmPC,<br>Labelling and<br>PL |  |
| IA/0035 | IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms       | 15/10/2006 | n/a        |                              |  |
| N/0032  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 22/06/2006 | n/a        | PL                           |  |
| IA/0031 | IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer          | 12/06/2006 | n/a        |                              |  |
| N/0029  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 16/05/2006 | n/a        |                              |  |
| IA/0030 | IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer          | 12/05/2006 | n/a        |                              |  |
| IA/0028 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold                 | 05/05/2006 | n/a        |                              |  |
| IA/0027 | IA_36_b_Change in shape or dimensions of the container/closure - other pharm. forms              | 28/03/2006 | n/a        |                              |  |

|         |   |            |            |                              |  |
|---------|---|------------|------------|------------------------------|--|
| T/0025  | Transfer of Marketing Authorisation   | 24/02/2006 | 22/03/2006 | SmPC,<br>Labelling and<br>PL | Transfer of MAH from Glaxo Group Limited to Bayer HealthCare AG. |
| IA/0026 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing  | 20/03/2006 | n/a        | Annex II and<br>PL           |  |
| II/0022 | Quality changes   | 23/02/2006 | 28/02/2006 |                              |  |
| IA/0023 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing  | 06/02/2006 | n/a        | Annex II and<br>PL           |  |
| IA/0024 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 03/02/2006 | n/a        |                              |  |
| IA/0021 | IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size   | 29/11/2005 | 29/11/2005 | SmPC,<br>Labelling and<br>PL |  |
| IA/0019 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 11/10/2005 | n/a        |                              |  |
| II/0018 | Quality changes   | 23/06/2005 | 30/06/2005 |                              |  |
| II/0015 | Quality changes   | 26/05/2005 | 30/06/2005 |                              |  |
| IB/0017 | IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient   | 13/04/2005 | n/a        |                              |  |

|         |  |            |            |      |  |
|---------|--|------------|------------|------|--|
| IB/0016 | IB_42_a_01_Change in shelf-life of finished product<br>- as packaged for sale  | 13/04/2005 | n/a        | SmPC |  |
| IB/0013 | IB_31_b_Change to in-process tests/limits during<br>manufacture - addition of new tests/limits   | 10/11/2004 | n/a        |      |  |
| IA/0014 | IA_11_a_Change in batch size of active substance or<br>intermediate - up to 10-fold<br>IA_11_b_Change in batch size of active substance or<br>intermediate - downscaling | 08/11/2004 | n/a        |      |  |
| N/0012  | Minor change in labelling or package leaflet not<br>connected with the SPC (Art. 61.3 Notification)  | 23/07/2004 | n/a        | PL   |  |
| IB/0011 | IB_14_a_Change in manuf. of active substance<br>without Ph. Eur. certificate - change in manuf. site   | 02/04/2004 | n/a        |      |  |
| I/0010  | 11_Change in or addition of manufacturer(s) of<br>active substance   | 18/07/2003 | 22/07/2003 |      |  |
| I/0008  | 14_Change in specifications of active substance<br>24_Change in test procedure of active substance   | 21/07/2003 | 22/07/2003 |      |  |
| I/0009  | 24a_Change in test procedure for starting<br>material/intermediate used in manuf. of active<br>substance   | 04/07/2003 | 08/07/2003 |      |  |
| I/0007  | 12a_Change in specification of starting<br>material/intermediate used in manuf. of the active<br>substance   | 20/06/2003 | 26/06/2003 |      |  |

|        |  |            |            |    |  |
|--------|--|------------|------------|----|--|
| I/0006 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance                                   | 20/06/2003 | 26/06/2003 |    |  |
| I/0005 | 01_Change in the name of a manufacturer of the medicinal product<br>11a_Change in the name of a manufacturer of the active substance | 20/05/2003 | 26/05/2003 |    |  |
| I/0002 | 11_Change in or addition of manufacturer(s) of active substance  | 04/03/2003 | 13/03/2003 |    |  |
| N/0003 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)                                     | 27/01/2003 | 06/03/2003 | PL |  |
| N/0001 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)                                     | 19/07/2002 | 22/08/2002 | PL |  |