# Irbesartan Hydrochlorothiazide BMS

## Procedural steps taken and scientific information after the authorisation

**MAJOR CHANGES**[1]

| No | Scope | Opinion issued on | Commission Decision Issued/ amended on | Product Information affected[2] | Summary |
|---|---|---|---|---|---|
| II/0029 | Change(s) to the manufacturing process for the active substance<br><br>Change of the manufacturing site of irbesartan and as a consequence a change in the batch size of this active substance. | 24/09/2009 | 30/09/2009 | | |
| II/0022 | Update of Summary of Product Characteristics and Package Leaflet<br><br>Update of SPC sections 2, 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 6.1 as well as the package leaflet to align the Product Information of Irbesartan Hydrochlorotihazide BMS with the Product Information of the reference product Karvezide. | 19/03/2009 | 07/04/2009 | SPC, PL | The SPC and Package Leaflet of Irbesartan Hydrochlorothiazide BMS have been aligned with the Product Information of the reference product Karvezide as approved with the renewal procedure. |
| II/0021 | Update of Summary of Product Characteristics and Package Leaflet<br><br>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 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. | 19/02/2009 | 18/03/2009 | SPC, PL | 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.<br>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.<br>Consequently, the existing contraindication for lactation has been |



[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet)

| No | Scope | Opinion issued on | Commission Decision Issued/ amended on | Product Information affected[2] | Summary |
|---|---|---|---|---|---|
| | | | | | deleted. |
| II/0020 | Changes to QPPV<br>Update of DDPS (Pharmacovigilance)<br><br>Update of Detailed Description of the Pharmacovigilance System | 22/01/2009 | 24/02/2009 | Annex II | The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. |
| II/0013 | Update of Summary of Product Characteristics and Package Leaflet<br><br>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. | 24/04/2008 | 10/06/2008 | SPC, PL | 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.<br>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.<br>Therefore, the existing contraindication for the 2nd and 3rd trimester of pregnancy remained, but a harmonised wording regarding pregnancy across the class was introduced. |
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**MINOR CHANGES[3]**

| No | Scope | Product Information affected[2] | Date[4] |
|---|---|---|---|
| N/0030 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | PL | 09/10/2009 |
| IA/0028 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 08/07/2009 |

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change

| No | Scope | Product Information affected[2] | Date[4] |
|---|---|---|---|
| IB/0024 | 07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release<br>07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | PL | 23/06/2009 |
| IA/0027 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 22/06/2009 |
| IA/0026 | 08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | PL | 10/06/2009 |
| IA/0025 | 32_a_Change in batch size of the finished product - up to 10-fold | | 20/05/2009 |
| IB/0023 | 10_Minor change in the manufacturing process of the active substance | | 17/04/2009 |
| IB/0019 | 10_Minor change in the manufacturing process of the active substance<br>11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 18/08/2008 |
| IA/0018 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 29/07/2008 |
| IB/0015 | 07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release<br>07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms<br>08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | Annex II, PL | 08/05/2008 |
| IB/0017 | 42_a_01_Change in shelf-life of finished product - as packaged for sale | SPC | 07/05/2008 |
| IB/0016 | 10_Minor change in the manufacturing process of the active substance<br>11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 25/04/2008 |
| IA/0014 | 09_Deletion of manufacturing site | | 03/04/2008 |
| IA/0012 | 09_Deletion of manufacturing site | | 13/02/2008 |
| IA/0011 | 09_Deletion of manufacturing site | | 13/12/2007 |
| N/0010 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | PL | 07/12/2007 |
| IB/0008 | 10_Minor change in the manufacturing process of the active substance | | 21/09/2007 |
| IA/0009 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 20/09/2007 |
| N/0007 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | PL | 22/08/2007 |
| IB/0006 | 07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release<br>07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms<br>08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | Annex II, PL | 22/08/2007 |
| IB/0004 | 07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release<br>07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms<br>08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | PL | 07/06/2007 |
| N/0002 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | PL | 07/06/2007 |
| IB/0003 | 33_Minor change in the manufacture of the finished product | | 21/05/2007 |
| IA/0005 | 32_b_Change in batch size of the finished product - downscaling down to 10-fold | | 15/05/2007 |
| IA/0001 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | | 23/03/2007 |
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