Procedural steps taken and scientific information after the authorisation

Posaconazole SP

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0011	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the SPC to reflect the adverse event terms according to MedDRA terminology and to be in compliance with the most recent EU SPC guidance. In addition section 4 of the PL was aligned with the psychiatric disorders events listed in the SPC section 4.8. The MAH took this opportunity to update the contact details of the local representatives in Austria, Bulgaria, Finland and Poland in section 6 of the PL.	23/10/2008	04/12/2008	SPC, PL	Following the assessment of variation II/07 the Marketing Authorisation Holder committed to submit a variation to bring section 4.8 of the SPC in line with the correct EU SPC guidance. Based on data from clinical trials and post marketing surveillance setting, section 4.8 was thus updated in accordance with MedDRA terminology. A single table for all adverse events regardless of source and appropriate cross reference to the warnings section was included. In addition "Sudden behaviour changes, problems with thinking or speech" was added to section 4 of the PL to reflect the psychiatric disorders events listed in section 4.8 of the SPC.
II/0007	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the SPC to include updated wording regarding hepatic events following CHMP assessment of PSUR 3 (covering the period 26.10.2006 - 25.04.2007). The PL has been updated accordingly.	24/01/2008	03/03/2008	SPC, PL	In the framework of the Periodic Safety Update Report (PSUR) 3, a cumulative review of hepatic events was presented by the Marketing Authorisation Holder (MAH). This cumulative review included only serious events and selected 17 cases of 'severe' liver injury out of a total 112 cases for detailed review. Of these, 11 cases had a fatal outcome with 2 outcomes unknown. Further to the assessment of this cumulative review, the CHMP concluded that it could not be excluded that posaconazole was the main contributor to the serious hepatic events and fatal outcome in many cases and the potentially fatal outcome of such events is not currently reflected in the SPC. Additionally, it was noted that the SPC already carries a warning in section 4.4 concerning serious hepatic events and lists several hepatic

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

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					events in section 4.8. However, on the basis of the high case fatality rate associated with serious hepatic events, the CHMP concluded that the SPC should be further amended in sections 4.4 and 4.8 in relation to fatal outcomes and that section 4 of the PL has been amended to reflect the new SPC wording.
II/0004	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.5 of the SPC with interaction data from a clinical study evaluating the effect of posaconazole on the pharmacokinetics of four CYP3A4 substrates (midazolam, sirolimus, efavirenz and boosted atazanavir) in healthy volunteers. The MAH took the opportunity to update the PL with the contact details of the local representatives in Italy, Latvia, Norway and The Netherlands.	20/09/2007	30/10/2007	SPC, PL	This open label study was made of 4 parts corresponding to the 4 CYP3A4 substrates. The study showed that: - Co-administered with oral or intra-venous midazolam, posaconazole increases midazolam blood levels, - Co-administered with sirolimus, posaconazole had a marked effect on plasma levels of sirolimus, - Co-administered with atazanavir, posaconazole had a marked effect on unboosted atazanavir and on ritonavir-boosted atazanavir plasma levels. Furthermore, atazanavir being usually administered with ritonavir in the European Union, posaconazole has a marked effect on ritonavir-boosted atazanavir plasma levels. - Co-administration of oral efavirenz and posaconazole resulted in clinically relevant decreases in posaconazole Cmax and AUC. The Product Information has been updated to reflect that blood levels of posaconazole can be decreased by efavirenz and that posaconazole can increase blood levels of sirolimus, atazanavir and midazolam.
II/0002	Extension of Indication Update of the section 4.1 of the SPC to extend the current approved indications with treatment of oropharyngeal candidiasis (OPC). Consequently sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SPC have been updated. The PL has been updated accordingly.	21/09/2006	30/10/2006	SPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: PosaconazoleSP-H-610-II-02-AR
II/0001	Extension of Indication Update of the section 4.1 of the Summary Products Characteristics (SPC) to extend the	21/09/2006	30/10/2006	SPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: PosaconazoleSP-H-610-II-01-AR

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	current approved indications with prophylaxis of fungal infections in high-risk patients. Consequently sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SPC have been updated. The PL has been updated accordingly. The details of the local representative for Lithuania have also been amended. The MAH took the opportunity to update the annexes according to the latest QRD templates.				

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0015	04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)		06/10/2008
IA/0014	04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)		17/09/2008
IA/0013	04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)		02/09/2008
IB/0009	10_Minor change in the manufacturing process of the active substance		08/02/2008
IA/0008	05_Change in the name and/or address of a manufacturer of the finished product		05/12/2007
IB/0006	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		12/09/2007
IB/0005	10_Minor change in the manufacturing process of the active substance		04/06/2007
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	03/01/2007

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