Noxafil

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
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/04/2024		PL	
IA/0083	A.7 - Administrative change - Deletion of manufacturing sites	11/08/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

IA/0082/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	18/07/2023	n/a		
IG/1623	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	16/06/2023	18/10/2023	Annex II and PL	
IA/0080	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	23/05/2023	n/a		
PSUSA/2480/ 202210	Periodic Safety Update EU Single assessment - posaconazole	12/05/2023	n/a		PRAC Recommendation - maintenance
II/0077	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/02/2023	18/10/2023	SmPC, Labelling and PL	The SmPC section 5.2 of for the 300 mg gastro-resistant powder and solvent for oral suspension formulation has been updated as follows: "An in vitro dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40 %) on the dissolution of Noxafil gastro-resistant powder and solvent for oral suspension. Posaconazole was found to release faster from Noxafil gastro-resistant powder and solvent for oral

					suspension in the presence of alcohol in vitro, which may interfere with its delayed release characteristics." The PL has been updated accordingly.
IAIN/0079	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	13/01/2023	18/10/2023	Annex II and PL	
IA/0076	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)	05/12/2022	n/a		
IAIN/0075	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	28/11/2022	18/10/2023	Annex II and PL	
IB/0073	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	03/11/2022	n/a		
IA/0074/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	24/10/2022	18/10/2023	Annex II and PL	
IB/0072	B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	28/09/2022	n/a		

IG/1525/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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)	21/06/2022	n/a		
PSUSA/2480/ 202110	Periodic Safety Update EU Single assessment - posaconazole	10/06/2022	n/a		PRAC Recommendation - maintenance
WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/06/2022	n/a		
II/0067	Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to add drug-drug interaction information between posaconazole and venetoclax. The Package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/11/2021	04/02/2022	SmPC and PL	Clinical data from two publications (a clinical study and a PBPK modelling approach paper) and post-marketing safety data support this update of the product Information for Noxafil (posaconazole). Data from the clinical study show that concomitant use of posaconazole 300 mg, a strong CYP3A4 inhibitor, with repeated doses of venetoclax 50 mg and 100 mg (an antineoplastic agent), which is also mainly metabolised by

					CYP3A4, resulted in much higher venetoclax maximum concentrations and exposures compared with venetoclax 400 mg administered alone. Safety data from post-marketing experience identified seven serious cases of drug-drug interactions between posaconazole and venetoclax. All cases were considered serious and described a potential drug-drug interaction between posaconazole and venetoclax since the drugs were used concomitantly and the serious adverse events (TLS and neutropenia) reported were those that could be expected with venetoclax. The posaconazole - venetoclax contraindication during initiation and dose-titration phase in patients with chronic lymphocytic leukemia (CLL) was added to section 4.3 of the posaconazole SmPC.
X/0063/G	This was an application for a group of variations. Extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension), grouped with a type II variation (C.I.6.a) to extend the approved indications to the paediatric population for Noxafil gastro-resistant tablets and Noxafil concentrate for solution for infusion. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC, as well as Annex II and the package leaflet, are updated. The RMP (version 18.0) is approved with this procedure.	11/11/2021	06/01/2022	SmPC, Annex II, Labelling and PL	

	Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0062	Extension of indication to include primary treatment of invasive aspergillosis in adults for Noxafil gastroresistant tablet and concentrate for solution for infusion as result of conclusion of Study P069 (a Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 6.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP was approved with this procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/09/2021	19/10/2021	SmPC and PL	Please refer to Scientific Discussion 'Noxafil-H-C-000610-II-0062'.
PSUSA/2480/ 202010	Periodic Safety Update EU Single assessment - posaconazole	24/06/2021	18/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2480/202010.
IB/0068/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/08/2021	n/a		

	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
IA/0066/G	This was an application for a group of variations. 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) 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)	15/02/2021	n/a		
IAIN/0064	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	11/12/2020	18/08/2021	Annex II and PL	
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/09/2020	18/08/2021	SmPC, Labelling and PL	
IB/0060/G	This was an application for a group of variations. 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 B.II.g.5.b - Implementation of changes foreseen in	21/04/2020	n/a		

	an approved change management protocol - Requires further supporting data				
II/0059	Introduction of a post approval change management protocol (PACMP) related to the finished product. The PACMP addresses the planned introduction of Laboratoires Merck Sharp & Dohme Chibret in Route de Marsat, Riom, Clermont Ferrand Cedex 9, 63963, France as a manufacturing and testing site for posaconazole 300 mg concentrate for solution for infusion. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	21/11/2019	n/a		
II/0057	Submission of an updated RMP (version 15.1) in order to bring it in line with the guidance included in Good Phamacovigilance Practices (GVP) Module V (Rev. 2), with the consequent applicable re-evaluation of some safety concerns. In addition to the above updates, the MAH took the opportunity to include data from the completed clinical trial in paediatric subjects PN097 (the CSR for which was submitted to the Agency in February 2019: P46 029), and update the due date for submission of the final report for the ongoing post-marketing efficacy trial PN069 (changed from December 2019 to 4th quarter of 2020). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	03/10/2019	n/a		

	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				
II/0058	Update of section 4.8 of the SmPC in order to include 'pseudoaldosteronism' as an adverse event in post-marketing experience, following a review of six case reports in the scientific literature of concurrent hypertension and hypokalemia in patients treated with posaconazole. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest version of the QRD template (version 10.1) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/09/2019	15/10/2020	SmPC, Annex II and PL	The MAH evaluated post-marketing reports in the scientific literature of concurrent hypertension and hypokalemia that had the clinical features of pseudoaldosteronism or mineralocorticoid excess. The analysis of posaconazole-induced hypertension and hypokalaemia due to inhibition of the 11β-hydroxylase enzyme supports the causal association between posaconazole and pseudoaldosteronism. Inclusion of 'pseudoaldosteronism' as an adverse event to the SmPC and PL was accepted.
IA/0056	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	25/04/2019	n/a		
IA/0055	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	11/03/2019	n/a		

T/0054	Transfer of Marketing Authorisation	13/06/2018	06/07/2018	SmPC, Labelling and PL	
PSUSA/2480/201710	Periodic Safety Update EU Single assessment - posaconazole	17/05/2018	n/a		PRAC Recommendation - maintenance
IB/0052	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/12/2017	n/a		
PSUSA/2480/201610	Periodic Safety Update EU Single assessment - posaconazole	05/05/2017	n/a		PRAC Recommendation - maintenance
IA/0051	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)	04/05/2017	n/a		
II/0048	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	26/06/2017	SmPC, Labelling and PL	Section 4.4 was updated to reflect that concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. The corresponding information on vincristine toxicity in section 4.5 was also updated to reinforce the warning

					message. Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.
IAIN/0050	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	14/02/2017	26/06/2017	Annex II and PL	
IB/0047	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/01/2017	n/a		
II/0040	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	13/10/2016	n/a		
IB/0046	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/08/2016	26/06/2017	SmPC	
II/0044	Update of section 4.2 of the SmPC in order to strengthen the information about non-	23/06/2016	22/07/2016	SmPC, Annex II, Labelling	The tablet and oral suspension are not to be used interchangeably due to the differences between these two

	interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Labelling, Package Leaflet and the RMP (final version 13.1) are updated accordingly. Changes in the blister labelling packaging for the tablets have been introduced to further address the reduction of potential medication errors with the product. In addition the MAH took the occasion to update the Product Information in line with QRD template version 9.1 and to include some minor editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			and PL	formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.
II/0041	Update of sections 5.1 and 5.2 of the SmPC for Noxafil 40 mg/mL Oral Suspension in order to update pharmacological properties information after finalisation of paediatric study P03579 / PN032 from the paediatric investigation plan (PIP) EMEA-000468-PIP02-12-MO2 submitted under article 46 of the paediatric regulation (EC) No 1901/2006. In addition, the MAH took the opportunity to introduce an editorial correction in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	26/06/2017	SmPC and PL	In a study of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the prespecified target (Day 7 Cav between 500 ng/mL-2,500 ng/mL). In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years).

PSUSA/2480/ 201510	Periodic Safety Update EU Single assessment - posaconazole	13/05/2016	n/a		PRAC Recommendation - maintenance
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/05/2016	15/07/2016	PL	
IA/0043	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	28/01/2016	n/a		
IB/0039/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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 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 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	12/01/2016	n/a		

	batch control/testing takes place 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 originally approved batch size B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				

	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				

IA/0038/G	This was an application for a group of variations. 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 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 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	10/12/2015	n/a		
II/0036	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/07/2015	15/07/2016	SmPC and PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2015	15/07/2016	PL	
X/0033	Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration	24/07/2014	18/09/2014	SmPC, Annex II, Labelling and PL	
IA/0035	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-	20/08/2014	n/a		

	sterile medicinal products				
X/0028	Annex I_2.(d) Change or addition of a new pharmaceutical form	20/02/2014	23/04/2014	SmPC, Annex II, Labelling and PL	
IG/0366	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	08/11/2013	n/a		
II/0032	Update of section 5.1 with the addition of Epidemiologocal Cut-Off Values for Aspergillus spp., as recommended by the CHMP in the PAM REC 0026 outcome. In addition, the MAH proposed to correct minor linguistic errors from the Annexes of various languages. 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	19/09/2013	23/04/2014	SmPC, Labelling and PL	In 2012, the SmPC section 5.1 of Noxafil was updated with the newly published Candida spp clinical breakpoint. In the context of this variation, the MAH was asked to include posaconazole breakpoints for Aspergillus fumigatus and Aspergillus terreus as proposed by EUCAST. The MAH however raised several methodological and technical concerns regarding the appropriateness of those breakpoints. Following the meeting and discussion between the MAH and the EUCAST, the MAH provided the CHMP with responses to the outstanding issue of Aspergillus breakpoints explaining why it does not consider that it is able as yet to include these in the product information for Noxafil and requesting a further extension of the deadline for this. Considering the MAH's concerns and since the breakpoint information does not constitute part of the safety specification, the CHMP agreed to delay the inclusion of the breakpoints for A. fumigatus and A. terreus in the SmPC until further clinical data is available. Meanwhile, as recommended in situations where there is insufficient data to support breakpoints, the Noxafil SmPC section 5.1 was updated with inclusion of the Aspergillus epidemiological

					cut off values. This update does not affect the benefit/risk balance of Noxafil.
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	23/04/2014	PL	
IA/0030	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/05/2013	n/a		
IA/0029	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	17/04/2013	n/a		
IA/0027/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	25/03/2013	n/a		
II/0025	Update of section 5.1 of the SmPC with the addition of clinical breakpoints for posaconazole against Candida spp, as determined by the EUCAST. In addition, the MAH took the opportunity to remove the MAH address details from the bottle label text following request from the EMA. Minor updates have	19/07/2012	23/08/2012	SmPC, Labelling and PL	Following the publication of the clinical breakpoints for posaconazole against Candida spp as determined by the EUCAST, the MAH is proposing to update the Noxafil SmPC with these new breakpoints. The CHMP agreed with the Product Information updates to reflect this new information. These new clinical breakpoints information do

	also been made to the "What is in this leaflet" and list of local representatives sections in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				not change the benefit/risk assessment of Noxafil.
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
II/0023	Update of section 4.5 of the SmPC in order to add the drug-drug interaction between posaconazole and fosamprenavir, following the publication of an interaction study. The PL was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the PL and to remove the country-specific MA number extensions from the NO and IS SmPC, Labelling and PL. The Product Information was also brought in line with the latest QRD template and linguistic corrections in several languages implemented. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	19/12/2011	SmPC, Annex II, Labelling and PL	The publication Brüggemann et al, 2010 describes a well-conducted, single-centre, cross-over clinical study that evaluated the potential pharmacokinetic drug interaction when fosamprenavir and posaconazole are taken concurrently. The clinical need for patients to take both drugs concurrently may occur when a patient with underlying HIV infection experiences an episode of oropharyngeal candidiasis that may be refractory to other antifungal therapy. The results of the study indicate that the drug combination of fosamprenavir and posaconazole has the potential to reduce posaconazole exposure and therefore close monitoring for breakthrough fungal infections is recommended. The CHMP agreed with the Product Information updates to reflect this interaction.
IG/0117/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the	18/11/2011	23/08/2012	Annex II	

	back-up procedure of the QPPV C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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				
T/0022	Transfer of Marketing Authorisation	05/08/2011	06/10/2011	SmPC, Labelling and PL	
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/06/2011	n/a	Annex II and PL	
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2011	n/a	PL	
R/0018	Renewal of the marketing authorisation.	22/07/2010	30/09/2010	SmPC, Annex II, Labelling and PL	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 Noxafil continues to be favourable. Considering outstanding issues noted in the last PSUR, the CHMP agreed that the PSUR cycle should remain a yearly cycle until further notice.

IB/0019	To extend the shelf life of the packaged finished product from 24 months to 36 months. 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)	28/05/2010	n/a	SmPC	
II/0017	Update of section 4.8 of the SPC and section 4 of the PL with the ADR "confusional state". An introductory warning on possible serious ADRs is included in section 4 of the PL. Both these changes are further to the evaluation of PSUR 5 (covering the period from 26.10.07 to 25.10.08). The MAH took this opportunity to update information on local representatives in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	As part of PSUR 5, the MAH presented a cumulative review on cases of "confusional state". Further to the evaluation of the cases reported, the CHMP concluded that a casual relation with posaconazol could not be excluded and therefore requested to include the ADR "confusional state" in the product information. During the assessment of this type II variation II/17, it was noticed that introductory statements and a list of symptoms for which immediate consultation of a physician was needed in the PL. Some amendments were requested by the CHMP on the basis that patients are not always aware which symptoms may be a sign of a serious adverse reaction which needs immediate medical advice. Additionally, the patient should be made aware that also some of the other adverse reactions/symptoms may get severe and requires consultation of a doctor or pharmacist. Consequently the PL has been updated to clarify the different types of adverse reactions that the patient knows how to react.
II/0012	Update of sections 4.2, 4.4, 4.5 and 5.2 of the Summary of Product Characteristics regarding the use of posaconazole oral suspension in hepatically impaired subjects, regarding the influence of various gastric conditions on pharmacokinetics and	24/09/2009	28/10/2009	SmPC and PL	In response to the clinical Follow-Up Measures 004 and 008, the Marketing Authorisation Holder conducted studies on the effect of hepatic inpairment and different gastrointestinal conditions on posaconazole blood levels. The findings and consequent recommendations for use of

	absorption of posaconazole. Section 2 and 3 of the Package Leaflet are updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				posaconale were added to the Product Information as follows. Information regarding careful dosing in patients with hepatic impairment was introduced to sections 4.2, 4.4 and 5.2 of the Summary of Product Characteristics (SPC). Information on concomitant use of H2 receptor antagonists and PPIs, which should be avoided, was introduced to section 4.5 of the SPC. The positive effect on bioavailability of a split dose of 4 single doses instead of 2 when taken in a fasted state was reflected in section 5.2, and a consequent recommendation of this dosing scheme for patients with invasive fungal infections was added to section 4.2 of the SPC in order to assure optimal efficacy. Section 3 of the Package Leaflet (PL) was updated accordingly. The positive effect on bioavailability of intake together with a meal, especially when administering posaconazole with or directly afterwards the meal, was reflected in section 5.2 of the SPC, and a consequent recommendation to take the drug together or directly after food was included in section 4.2 of the SPC and sections 2 and 3 of the PL.
II/0016	Change(s) to the test method(s) and/or specifications for the finished product	22/01/2009	26/01/2009		
II/0011	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,	23/10/2008	04/12/2008	SmPC and 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

	Bulgaria, Finland and Poland in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet				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.
IA/0015	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	06/10/2008	n/a		
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	17/09/2008	n/a		
IA/0013	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	02/09/2008	n/a		
II/0007	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. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	03/03/2008	SmPC and 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 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.
IB/0009	IB_10_Minor change in the manufacturing process of the active substance	08/02/2008	n/a		
IA/0008	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/12/2007	n/a		
II/0004	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. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	30/10/2007	SmPC and 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.
IB/0006	IB_07_c_Replacement/add. of manufacturing site:	12/09/2007	n/a		

	All other manufacturing operations ex. batch release				
IB/0005	IB_10_Minor change in the manufacturing process of the active substance	04/06/2007	n/a		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/01/2007	n/a	PL	
II/0002	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. 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. Extension of Indication	21/09/2006	30/10/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific discussion: Noxafil-H-610-II-02-AR
II/0001	Update of the section 4.1 of the SPC to extend the 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. Extension of Indication	21/09/2006	30/10/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Noxafil-H-610-II-01-AR
