Vfend

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
IB/0153/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging	03/04/2024		SmPC and PL	

[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).

	components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking				
IB/0152	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/02/2024	n/a		
WS/2270	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Annex II and RMP to include the results from final clinical study report (CSR) following the completion of a non-interventional (NI) post-authorisation safety study (PASS): A1501103 "An Active Safety Surveillance Program to Monitor Selected Events in Patients with Long-term Voriconazole Use". MEA091 is fulfilled with this procedure. In addition, the MAH took this opportunity to introduce editorial changes to the RMP and transition from the EMA GVP 1 template to the new template GVP 2.1. The frequency categories for the ADRs 'periostitis', 'phototoxicity' and 'squamous cell carcinoma (SCC)' of the skin in the ADR table in section 4.8 of the Vfend SmPC and section 4 of the Vfend Package Leaflet were amended.	28/09/2023		SmPC, Annex II and PL	The additional Risk Minimisation Measures (consisting of an HCP Checklist, HCP Question & Answer Brochure for phototoxicity, SCC and Hepatic toxicity) were removed from Annex IID of the Vfend Product Information. As a result of the assessment of the submitted data, the SmPC was updated with newly calculated frequencies for the following ADRs (already included) in section 4.8: - SCC (including cutaneous SCC in situ or Bowen's disease): "not known" to "common" - Phototoxicity: "uncommon" to "common" - Periostitis: "not known" to "uncommon" The PL was updated accordingly. For more information, please refer to the Summary of Product Characteristics.

	Version 6.3 of the RMP is approved with this procedure. 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				
WS/2415	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC to include increased risk of skin toxicity with concomitant use of voriconazole and methotrexate and potentially other drugs associated with ultraviolet (UV) reactivation to the current warning on photosensitivity skin reactions, based on post-marketing data and literature. The Package Leaflet is updated accordingly. In addition, the WSA took the opportunity to implement editorial changes to section 4.4 and 4.5 of the SmPC C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/08/2023		SmPC and PL	The following warning was added to SmPC section 4.4 under the sub-header "Serious dermatological adverse reactions" and bullet point "Phototoxicity": "There is a potential increased risk of skin reactions/toxicity with concomitant use of photosensitising agents (e.g. methotrexate, etc)". For more information, please refer to the Summary of Product Characteristics.
WS/2482/G	This was an application for a group of variations following a worksharing procedure according to	20/07/2023	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. B.III.1.a.5 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate of a non-sterile AS that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IAIN/0151	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2023		SmPC and PL	
IB/0146/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) C.I.7.a - Deletion of - a pharmaceutical form	04/05/2022	05/05/2023	SmPC, Labelling and PL	To delete the HDPE bottles 50mg film-coated tablets presentations, the HDPE bottles 200mg film-coated tablets presentations and the pharmaceutical form 200mg Powder and solvent for solution for infusion ('needle-free kit').
PSUSA/3127/ 202102	Periodic Safety Update EU Single assessment - voriconazole	11/11/2021	06/01/2022		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3127/202102.
II/0142/G	This was an application for a group of variations. Update of sections 4.3, 4.4, and 4.5 of the SmPC in	16/09/2021	19/10/2021	SmPC, Labelling and	Sections 4.3, 4.4, and 4.5 of the SmPC were updated, as follows: - Section 4.3 Contraindications:

	order to add new contraindications to naloxegol and tolvaptan and add a Drug-Drug Interaction with lurasidone, include clarification text regarding adrenal insufficiency and Cushing's syndrome to the warnings and precautions for use, and re-order some of the drug-drug interaction information, respectively. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to correct an oversight from a previous procedure in the labelling (addition of the excipient sodium benzoate in Section 3 of the outer and inner label for the Powder for oral suspension in line with SmPC Section 2 and PL Sections 2 and 6). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			PL	- Addition of naloxegol, tolvaptan and lurasidone; - Change in position of existing information on coadministration with St John's Wort. - Section 4.4 Special warnings and precautions for use: - Addition of clarifying text regarding adrenal insufficiency and Cushing's syndrome; - Deletion of text on coadministration of naloxegol from Section 4.4 (consequential to its addition to Section 4.3). - Section 4.5 Interaction with other medicinal products and other forms of interaction: - Addition of the DDI with lurasidone - Change in position of information on naloxegol, tolvaptan and everolimus (interactions table) - Addition of clarification text to the recommendations for statins and addition of midazolam PK DDI data. For more information, please refer to the Summary of Product Characteristics. The Package Leaflet (PL) was updated accordingly.
N/0145	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2021	06/01/2022	PL	
II/0143	Update of sections 4.4 and 4.5 of the SmPC in order to add a new warning on co-administration with glasdegib and add drug-drug interaction information with eszopiclone, glasdegib, tretinoin and tyrosine	02/09/2021	19/10/2021	SmPC and PL	Section 4.4. is updated to include a warning that coadministration of voriconazole is expected to increase glasdegib plasma concentration increasing the risk of QTc prolongation and increase tyrosine kinase inhibitor plasma

	kinase inhibitors metabolised by CYP3A4; 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				concentration and the risk of adverse reactions. Section 4.5. is updated to inform about drug-drug interactions and provide recommendations concerning coadministration with glasdegib, tyrosine kinase inhibitors and tretinoin. For more information, please refer to the Summary of Product Characteristics.
WS/1939	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to add new contraindications (concomitant use with ivabradine and venetoclax), and add drug-drug interaction information between voriconazole and ivabradine and venetoclax to the Interactions section. The Package Leaflet is updated accordingly. In addition, the WSA took the opportunity to align with the current Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), 22 November 2019, EMA/CHMP/302620/2017 Rev. 1*, for lactose, and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2021	26/03/2021	SmPC and PL	Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4 and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzym. Venetoclax is predominantly metabolised by CYP3A and ivabradine is metabolized by CYP3A4 solely. Increased plasma concentrations of ivabradine can lead to bradycardia and conduction disturbances, including QTc prolongation and rare cases of torsades de pointes. Coadministration of voriconazole and venetoclax at initiation and during venetoclax dose titration phase was also contraindicated since voriconazole is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome. Sections 4.3 of the SmPC was therefore updated to add two contraindications (concomitant use with ivabradine and venetoclax). Additionally, drug-drug interaction information between voriconazole and ivabradine and venetoclax was added to the Interactions in section 4.5. The Package Leaflet was updated accordingly. For more information, please refer to the Summary of Product Characteristics.

IAIN/0141/G	This was an application for a group of variations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	10/12/2020	n/a		
IAIN/0140/G	This was an application for a group of variations. 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 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.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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	12/11/2020	n/a		

	manufacturing sites				
II/0137/G	This was an application for a group of variations. Grouping of two type II variations: -to update of section 4.4 of the SmPC in order to add a new warning on adrenal events, along with editorial changes to the paragraph and the abbreviation of severe cutaneous adverse reactions (SCARs), -to update section 4.5. of the SmPC in order to add drug-drug interaction information with naloxegol, ivacaftor and corticosteroids following PRAC request during the assessment of PSUR 18 (for corticosteroids) and the French National Agency for the Safety of Medicines and Health Products (ANSM) update of the French "Medical Interaction Thesaurus" (May 2018), where voriconazole is classified as a strong CYP3A4 inhibitor. In addition, the MAH has taken the opportunity to update the information in the SmPC in line with the EU excipient guidance from October 2017 (SANTE-2017-11668) for sodium and cyclodextrin, to introduce a correction to the amount of sodium per vial for the IV presentations in Sections 2. QUALITATIVE AND QUANTITATIVE COMPOSITION and 4.4 Special warnings and precautions for use of the SmPC. The Package Leaflet is updated accordingly. Following a recent discussion with EMA/EDQM; the	10/09/2020	26/03/2021	SmPC, Annex II, Labelling and PL	The SmPC for Vfend was revised to add text on adrenal events in section 4.4 and the interactions between voriconazole and naloxegol, ivacaftor and corticosteroids in the interaction table in SmPC section 4.5. A statement explaining that voriconazole is a strong CYP3A4 inhibitor was also added to section 4.5. For more information, please refer to the Summary of Product Characteristics.

	MAH is also updating Annex IIIA Outer carton text for both iv presentations 16. INFORMATION IN BRAILLE to include: "Justification for not including Braille accepted." In addition, the MAH took the opportunity to bring the PI in line with the latest 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1846	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Section 4.5 of the SmPC in order to include additional text regarding interactions between voriconazole and letermovir & tolvaptan in the interaction table. 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	09/07/2020	26/03/2021	SmPC and PL	The CHMP considered that there is sufficient evidence to support updating the prescribing information for voriconazole to add letermovir and tolvaptan to the interactions section of the SmPC. The reduction in voriconazole exposure with letermovir coadministration was considered potentially clinically significant by the Committee. As tolvaptan is metabolised by CYP3A4 and voriconazole is a strong inhibitor of CYP3A4, the interaction is mechanistically substantiated and can be extrapolated from interactions of tolvaptan with other strong CYP3A4 inhibitors. For more information, please refer to the Summary of Product Characteristics.
N/0136	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019	26/03/2021	PL	

IA/0135	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	18/11/2019	n/a		
IB/0134/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	11/09/2019	n/a		

	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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation				
N/0133	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019	26/03/2021	PL	
PSUSA/3127/ 201802	Periodic Safety Update EU Single assessment - voriconazole	18/10/2018	12/12/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3127/201802.
IA/0132	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)	06/12/2018	n/a		

N/0131	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	26/03/2021	PL	
T/0130	Transfer of Marketing Authorisation	24/08/2018	28/09/2018	SmPC, Labelling and PL	
IAIN/0129/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	06/06/2018	28/09/2018	SmPC and Labelling	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.				

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IAIN/0127/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	06/04/2018	28/09/2018	SmPC, Annex II, Labelling and PL	
IB/0126	B.IV.z - Quality change - Change in Medical Devices -	05/10/2017	n/a		

	Other variation				
PSUSA/3127/ 201702	Periodic Safety Update EU Single assessment - voriconazole	28/09/2017	n/a		PRAC Recommendation - maintenance
N/0125	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/09/2017	19/02/2018	Labelling	
IA/0124	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	20/09/2017	n/a		
II/0121	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	19/02/2018	SmPC and PL	
PSUSA/3127/ 201602	Periodic Safety Update EU Single assessment - voriconazole	29/09/2016	n/a		PRAC Recommendation - maintenance
WS/0898/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	22/09/2016	n/a		

	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.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.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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement				

	or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other				

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
N/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	19/02/2018	PL	
II/0115	Submission of the final study report for a Non-Interventional Post Authorisation Safety Study (PASS) A1501097 "Evaluation of the potential association between voriconazole use and squamous cell carcinoma (SCC) of the skin among patients with lung or lung/heart transplants" (MEA/071.11); consequently, the RMP v.4.0 is agreed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/05/2016	n/a		
IA/0118/G	This was an application for a group of variations.	16/05/2016	n/a		

	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IB/0117/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	04/04/2016	n/a		
IA/0116	B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number	17/02/2016	n/a		
PSUSA/3127/ 201502	Periodic Safety Update EU Single assessment - voriconazole	22/10/2015	16/12/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3127/201502.
IAIN/0114/G	This was an application for a group of variations.	09/12/2015	n/a		

	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible 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)				
II/0110/G	This was an application for a group of variations. Update of the SmPC sections 4.4, 4.8 and 5.1 to reflect the safety and efficacy data from studies in paediatric population. The Package leaflet and RMP have been revised accordingly. Furthermore, the PI is brought in line with the latest QRD template version 9.1. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/10/2015	16/12/2015	SmPC and PL	In this variation the MAH included data from two prospective, open-label, non-comparative, multi-centre clinical trials enrolling fifty-three paediatric patients aged 2 to <18 years with possible, proven or probable invasive aspergillosis (IA) or invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy. For patients with IA the overall rates of global response at 6 weeks were 64.3% (9/14), the global response rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age. For patients with ICC the global response rate at EOT was 85.7% (6/7) and for patients with EC the global response rate at EOT was 70% (7/10). The overall rate of response (ICC and EC combined) was 88.9% (8/9) for 2 to <12 years old and 62.5% (5/8) for 12 to <18 years old. Overall, the safety profile of voriconazole was similar to that in adults; however a trend towards a higher frequency of liver enzyme elevations, reported as adverse events in clinical trials was observed in paediatric patients as compared to adults (14.2% transaminases increased in paediatrics compared to 5.3% in adults).
IB/0113	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/08/2015	19/11/2015	SmPC	

II/0108	Update of the section 6.6 of the SmPC 'Special precautions for disposal and other handling' in order to clarify the instructions for preparation of the oral suspension as recommended by the CHMP. 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	30/07/2015	19/11/2015	SmPC and PL	In this variation the MAH updated the instructions for the preparation of the oral suspension by clarifying the amount of water needed for reconstitution and the final volume of the suspension in the product information.
IA/0111	A.7 - Administrative change - Deletion of manufacturing sites	20/05/2015	n/a		
N/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/04/2015	19/11/2015	PL	
IA/0107	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)	23/01/2015	n/a		
IAIN/0106	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	11/11/2014	19/11/2015	Annex II and PL	
IAIN/0105	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	11/11/2014	19/11/2015	Annex II and PL	
PSUSA/3127/	Periodic Safety Update EU Single assessment -	09/10/2014	n/a		PRAC Recommendation - maintenance

201402	voriconazole				
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2014	19/11/2015	PL	
II/0097	Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Vfend SmPC to include information pertaining to the proposed new indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity of this variation to update the SmPC, Annex II and PL in line with the latest QRD template. The contact details of the Greek and Cyprus local representatives were updated in the PL. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/05/2014	23/06/2014	SmPC, Annex II and PL	Please refer to the scientific discussion of the Assessment Report Vfend-H-387-II-97-AR.
II/0100	Following the review with the MAH's voriconazole Core Data Sheet and the Vfend SmPC, update of section 4.8 of SmPC to harmonise the safety information including addition of adverse drug reactions 'fixed drug eruption', 'eczema' and 'atrial arrhythmia' with the frequency 'uncommon' and update of estimated frequencies. The PL was updated accordingly. In addition, the MAH took the opportunity of this variation to implement editorial changes throughout the SmPC and PL.	23/01/2014	23/04/2014	SmPC and PL	The changes proposed by the MAH are to align the Vfend PI with the most up-to-date reference safety information available for this product. In particular, the adverse drug reactions 'fixed drug eruption', 'eczema' and 'atrial arrhythmia' with the frequency 'uncommon' were added and the estimated frequencies of ‘dysgeusia’ and ‘hypertonia’ were updated from rare to uncommon. The CHMP agreed that the proposed changes are relevant and should be included in the Vfend PI. These changes do not alter the overall benefit-risk profile of Vfend, which remains

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				favourable when used in accordance with the updated PI.
IB/0101/G	This was an application for a group of variations. 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	21/01/2014	n/a		

	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
IB/0102/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	19/12/2013	n/a		
N/0099	Inclusion of additional local representative of the marketing authorisation holder for the new member state Croatia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2013	23/04/2014	PL	
II/0098	Following the MAH's review on post-marketing data for hyponatremia, update of section 4.8 of the SmPC with addition of the ADR 'Hyponatremia'. The Package Leaflet is updated accordingly. In addition, the MAH is taking the opportunity of this variation to update the SmPC sections 4.3 and 4.5 to clarify the wording regarding the contraindication of	24/10/2013	23/04/2014	SmPC and PL	Following the review of the post-marketing data for hyponatremia and update of MAH's Core Data Sheet , the MAH proposes in this variation application to update the Vfend SmPC section 4.8 with addition of the adverse drug reaction Hyponatremia. Considering the temporal relation consistent with the voriconazole treatment in the 3 reported cases, the

	voriconazole with efavirenz. Also, as requested by the CHMP, the MAH takes the opportunity to clarify the paediatric dosing text in SmPC Section 4.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				absence of confounding medications, the positive dechallenge in 2 cases and also considering that adrenal insufficiency, a listed Vfend ADR, may induce hyponatremia, the CHMP acknowledges that there is a reasonable possibility that this event is caused by voriconazole and agrees to add hyponatremia in the SmPC section 4.8, with the frequency uncommon. The Package leaflet was updated accordingly. In addition, the wording of SmPC sections 4.3 and 4.5 regarding the contraindication of voriconazole with efavirenz was clarified, as well as the paediatric dosing text in Section 4.2. The addition of the adverse event hyponatremia to the list of undesirable effects does not affect the benefit/risk of Vfend.
II/0095	As requested by the CHMP following the assessment of the PSUR 11 and subsequent follow-up information regarding the risk of squamous cell carcinoma, update of sections 4.4 and 4.8 of the SmPC regarding the risk of SCC, with reinforcement of the warnings and precautions for use. The PL is updated accordingly. In addition, the MAH took the opportunity of this variation to correct the German translation of the PL instructions for use of the Vfend powder and solvent kit. 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	27/06/2013	23/04/2014	SmPC and PL	The mechanism and factors involved in the relation between the use of voriconazole and squamous cell carcinoma remain unclear. Squamous cell carcinoma following the use of voriconazole is atypical in behaviour, possibly due to the immunological response in the presence of immune suppression. Photosensitivity reactions, whether drug-induced or purely the result of environmental factors, can contribute to the cumulative effects of photo-ageing and possibly skin cancers especially in the presence of immunosuppressed conditions. However, review of currently available information reported to MAH's safety database does not provide sufficient evidence of a direct causal association between photo-ageing and SCC to treatment with voriconazole. As discussed, only 30 children and younger adults developed photo-ageing, only 6 of which reported

	MAH				SCC. All the patients reporting these events were either immunosuppressed or had conditions suggesting an immune-compromised status. The MAH will monitor these events closely and will re-evaluate its position as new information becomes available. It is known that voriconazole can cause phototoxicity and, in the view of these cumulative review data, a higher reporting rate of phototoxicity reported in children compared to adults was reported. It was agreed that this should be reflected in the Vfend Product Information. The CHMP noted the on-going non-clinical investigational studies lead by an independent research team and review the preliminary in vitro data. It recognised that the MAH does not own the control of these studies and the resulting data, and noted the willingness of the MAH to provide the results to the CHMP once available. Following the review of the current and available body of evidence (signals, spontaneous reports, non-clinical and clinical study data) regarding the phototoxicity and voriconazole, including the risk of squamous cell carcinoma, the CHMP agreed that a causal relationship between voriconazole and SCC is possible to exist and therefore that this adverse reaction should be listed in the section 4.8 of the Vfend SmPC. The CHMP also agreed that the special warnings and precautions for use of Vfend should be updated with reinforcement of the recommendations for sunscreen (high sun protection factor) protection, especially in children, as well as a systematic and regular dermatologic evaluation whenever phototoxicity-related lesions occur and discontinuation of Vfend if premalignant skin lesions or SCC are identified.

					The CHMP agreed in principle with the RMP measures relating to the SCC safety concern, including Patient Alert Card, HCP check list and Q&A. Readjustment of the messages could be dealt with at national level. Considering the Risk Management Measures put in place and the updated Product Information, the CHMP was of the opinion that the risk benefit balance of Vfend remains positive.
IAIN/0096	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	12/06/2013	n/a		
II/0094	Update of sections 4.2 and 4.4 of the SmPC in order to inform prescribers of the limited safety data in patients with abnormal liver function tests and redefine the monitoring of hepatic function, as requested by the CHMP following the assessment of the PSUR 11 and subsequent follow-up information. In addition, minor corrections were made in section 4.8. 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	25/04/2013	23/04/2014	SmPC	Following the CHMP request to propose additional pharmacovigilance and risk minimisation measures relating to the hepatotoxicity concern of Vfend, the CHMP agreed with the MAH's proposal to update sections 4.2 and 4.4 of the SmPC in order to inform prescribers of the limited safety data in patients with abnormal liver function tests and re-define the monitoring of hepatic function. The update describes in more details the liver function tests monitoring to be performed for patients receiving Vfend and indicates that the period of treatment should be as short as possible. The CHMP agreed that these updates are an improvement and adequately address the safety concerns on hepatotoxicity. The benefit/risk balance of Vfend is not affected by these updates.
IG/0236/G	This was an application for a group of variations.	03/12/2012	n/a		

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV				
II/0091	Update of sections 4.4 and 4.8 of the SmPC with a warning regarding periostitis following the CHMP assessment of the PSUR 11 and subsequent follow-up information. The PL is updated accordingly. In addition, the MAH took the opportunity to update the PL regarding the agreed contra-indication with high dose efavirenz. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/09/2012	29/10/2012	SmPC and PL	Following a signal regarding long-term use of voriconazole and periostitis, the cumulative review of the cases and the literature led to the conclusion that there seems to be evidence that long-term use of voriconazole is associated with periostitis. Causality is expected on the basis of a positive time-relationship and condition improvement upon discontinuation in most patients, as well as a plausible mechanism. Consequently, the CHMP is of the opinion that the relationship between long-term voriconazole use and periostitis should be adequately reflected in the SmPC, both in section 4.4 Special warnings and precautions for use and in the section 4.8 Undesirable effects. The PL was updated accordingly. The new identified risk of periostitis does not affect adversely the benefit/risk balance of Vfend. Periositis, together with all bone disorders, will be closely monitored by the MAH and reported to the CHMP through the PSURs.
II/0088/G	This was an application for a group of variations. This was an application for a group of variations to add Vfend powder and solvent for solution for infusion as new presentation, which will be provided as a complete injection kit, to register a new manufacturing, primary packaging and QC testing	20/09/2012	29/10/2012	SmPC, Labelling and PL	

	site for the new presentation and to register yet another site as secondary packaging and QC testing site for the new presentation. B.II.a.z - Change in description and composition of the Finished Product - Other variation B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
II/0090	Update of sections 4.6 and 5.3 of the SmPC to include the results of the fertility study following the renewal assessment of Vfend. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	23/08/2012	SmPC	The rat fertility study showed that at doses up to 50 mg/kg/day, no impairment of fertility was seen in male or female rats. The observed foetal development toxicity is an expected effect as developmental toxicity was seen in previous studies. Likewise, for the single malformed foetus, a treatment-related effect cannot be completely ruled out, as voriconazole has been shown to be teratogenic in rats. Based on these results, the Vfend SmPC sections 4.6 and 5.3 were updated to reflect that, in an animal study, no impairment of fertility was demonstrated in male and female rats.

II/0089	In line with the current efavirenz interaction mentioned in section 4.5, update of SmPC section 4.3 to add contraindication of coadministration with high dose efavirenz. Section 4.4 was updated accordingly and section 4.5 clarified. In addition, the MAH took the opportunity to clarify section 4.2. Furthermore, following discussions with the Agency and considering that Vfend IV is only administered by healthcare professionals, the MAH proposes to delete the Braille statement from Labelling. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/07/2012	23/08/2012	SmPC and Labelling	The CHMP agreed with the MAH's proposal to clarify the section 4.2 – dosing recommendations for adults and adolescents by adding a statement that the cut-off for patients less than 40 kg is applicable to patients aged 15 years and older. The CHMP, consistently with the current cross-reference in section 4.5 to section 4.3, agreed with the addition of the contra-indication of voriconazole with high dose efavirenz in section 4.3. In addition, considering the Vfend IV is only administered by healthcare professionals, the Braille statement in the labelling was deleted.
IB/0087/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	19/07/2012	n/a		
II/0086	Submission of the first Vfend RMP and update of Annex IIC condition to submit a RMP properly reflecting the safety profile of Vfend to replace it with the standard QRD statement.	24/05/2012	28/06/2012	Annex II	The CHMP endorsed the RMP version 1.2 and considered the Vfend condition set in Annex II to submit a RMP properly reflecting the safety profile of Vfend appropriately fulfilled.

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	08/06/2012	n/a		
II/0084	Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to increase the clarity regarding the exposure equivalence between intravenous (IV) and oral dosing and regarding the appropriate duration of IV and oral therapy. In addition, the MAH took the opportunity to correct the erroneous number of vials to be used for dilution in the SmPC and PL of the powder for solution for infusion formulation. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC and PL	Based on study data already submitted and assessed by the CHMP for the initial Vfend Marketing Authorisation (pivotal aspergillosis study 150-307/602), in order to ensure that prescribers maintain patients appropriately on iv voriconazole or the oral dose, the need to clarify the exposure equivalence between intravenous and oral dosing and reflect the duration of IV and oral therapy in the clinical study was discussed. Considering that no new data were submitted and that the current dosing recommendations have been appropriately supported by efficacy and safety data in the approved indications for Vfend, the CHMP agreed that the dose recommendations should remain unchanged. However, in order to provide further clarity on the exposure equivalence and treatment durations, the

					CHMP agreed that further clinical data on the treatment durations in the Aspergillos study should be included in section 5.1 and that exposure equivalence between iv and oral dosing should be included in section 5.2. This additional updates do not impact on the benefit/risk balance of Vfend.
IB/0085/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	02/03/2012	n/a		
R/0082	Renewal of the marketing authorisation.	15/12/2011	21/02/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers that the risk-benefit balance of Vfend in the treatment of invasive aspergillosis, of candidemia in non-neutropenic patients, of fluconazole-resistant serious invasive Candida infections (including C. krusei) and treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp. remains favourable and therefore recommends the renewal of the marketing authorisation.
II/0079	Update of section 4.2 of the SmPC in order to clarify in the dose adjustment that the concomitant use of	15/12/2011	21/02/2012	SmPC and PL	The interaction between voriconazole and rifabutin, a potent CYP450 inducer, is complex. Although a

	voriconazole with rifabutin should be avoided except if strictly needed. Section 4.4 was updated to rearrange the order of the text. In addition, as requested by the CHMP, the MAH has revised the presentation of the information on drug-drug interactions in section 4.5 in a table view. As requested by the CHMP, the MAH also took the opportunity to reformat the section 5.1 according to the Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease. This reformatting also affected section 5.2. 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				contraindication could be considered, the CHMP was of the opinion that it would hamper physicians in the management of some critical clinical situations, when the concomitant use of voriconazole and rifabutin could be managed with dosage adjustments of both drugs and careful therapeutic drug monitoring. It was agreed to maintain but clarify the current dose adjustments in the Vfend SmPC when voriconazole is co-administered with rifabutin, as well as the recommendations for careful monitoring of adverse events. As requested by the CHMP, the drug-drug interactions part in section 4.5 was reformatted with a more user-friendly table view and the section 5.2 reworded in compliance with the Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease (CHMP/EWP/1343/01 Rev. I, 22 April 2010). The updates do not change the benefit/risk assessment of Vfend.
II/0083	Update of sections 4.2, 4.8, 5.2 and 6.6 of the SmPC in order to reflect the updated information on paediatric dosing, following the submission of paediatric studies under Article 46 (P46-069 and P46-070 and follow-up FU2 069.1 and FU2 069.2). The PL is updated in accordance. In addition, the MAH took the opportunity to clarify the section 1 of the PL. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a	17/11/2011	14/12/2011	SmPC and PL	In accordance with Article 46 of Regulation 1901/2006, the MAH submitted information about paediatric studies, including two pharmacokinetic studies (one children aged 2 to <12 years and one in children aged 12 to < 17 years). These data were then completed by an integrated population pharmacokinetic analysis based on data from 5 studies. The assessment of these pharmacokinetic paediatric data suggested that the current SmPC paediatric dosing information could be optimised to achieve a better exposure comparable to that in adults. Based on these results and conclusions, it appeared that – in children

	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				between 2 and <12 years and in young adolescents (12 to 14 years and < 50kg) - a dose of 9 mg/kg q12h at day 1, followed by an i.v. maintenance dose of 8 mg/kg i.v. q12h or a maintenance oral dose 9 mg/kg q12h would result in a comparable exposure to that in adults receiving a loading dose of 6 mg/kg, an iv maintenance dose of 4 mg/kg i.v. q12h or a maintenance oral dose 200 mg/kg q12h. In addition, analyses show that Vfend use in all adolescents between 12 to 14 years and ≥50 kg and 15 to 16 years regardless of body weight of age should be dosed as adults. The Vfend Product Information was updated to reflect these optimised paediatric dosing information and the studies results. The CHMP endorsed these updates.
II/0080	to add 0.9% sodium chloride (NaCl) as an alternate reconstitution agent for voriconazole powder for solution for infusion. B.II.a.z - Change in description and composition of the Finished Product - Other variation	22/09/2011	10/11/2011	SmPC and PL	
II/0078	Following the signal detection interaction with everolimus (FUM 079), update of sections 4.4 and 4.5 of the SmPC. The PL is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/07/2011	24/08/2011	SmPC and PL	The co-administration of everolimus, a CYP3A4 substrate, with potent CYP3A4 inhibitors such as voriconazole, is currently not recommended in the everolimus SmPCs due to expected large increases in everolimus plasma concentrations which could potentially lead to exacerbation of toxicity or over-immunosuppression. A signal detection from the Eudravigilance database shows that 5 cases of suspected interaction between voriconazole and everolimus were retrieved. In addition, a further case was retrieved in the literature. This interaction does not affect the benefit/risk of Vfend.

					The CHMP agreed that sections 4.4 and 4.5 of the SmPC should be updated with a warning that the coadministration of everolimus and voriconazole is not recommended. The Package Leaflet was updated accordingly.
IA/0081	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	19/08/2011	n/a		
II/0075	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.5 of the SmPC to include the potential for drug interactions with concomitant use of voriconazole with fentanyl, oxycodone or fluconazole. The Package Leaflet was amended accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC and PL	Voriconazole is metabolized by and is also an inhibitor of the CYP P450 isozymes, CYP3A4, CYP2C19, and CYP2C9. Considering that fentanyl and oxycodone are substrate for CYP3A4 and that fluconazole is an inhibitor of CYP2C19 and 2C9, the results of these pharmacokinetic interactions studies in healthy volunteers are expected. Voriconazole decreased fentanyl clearance by 25%, resulting in increased exposure by 34%. Moreover, the AUC of the metabolite norfentanyl decreased by about 60%. Administered with voriconazole, AUC of oxycodone increased by about 2.6 fold, Cmax by about 1.7-fold and t1/2 by about 2-fold. As a results of the decreased metabolism to noroxycodone, AUC levels of oxycodone decreased by 67%. Furthermore, oxymorphone metabolism into noroxymorphone is decreased resulting in about 6.3-fold higher AUC levels for oxymorphone and -53% decreased AUC levels for noroxymorphone. With fluconazole, voriconazole AUCtau and Cmax levels in extensive metabolisers increased statistically significant

					with 1.8-fold and 1.6-fold respectively. The sections 4.4 and 4.5 of the SmPC have been updated with this new information and the PL was amended accordingly.
II/0074	Update of Summary of Product Characteristics Following the assessment of follow-up measures 24.2 and 24.3, update of section 5.1 of the SmPC to include the finalized EUCAST MIC breakpoints for voriconazole for Candida species. 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	21/10/2010	29/11/2010	SmPC	The results of the comparative study for testing triazoles (including voriconazole) MICs for Candida spp using both the CLSI method (24h and 48h endpoints) and the EUCAST method were provided and showed agreement between both methods. The section 5.1 of the SmPC was updated with the final EUCAST data for the sensitivity of Candida species for voriconazole, including breakpoints for C. albicans, C. parapsilosis and C. tropicalis.
IB/0077	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	22/09/2010	n/a		
IA/0076/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a	17/09/2010	n/a	SmPC and PL	

	non-significant specification parameter (e.g. deletion of an obsolete parameter B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
II/0073	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	22/07/2010	01/09/2010	SmPC	
IB/0072	IB_10_Minor change in the manufacturing process of the active substance	05/02/2010	n/a		
IB/0071	IB_10_Minor change in the manufacturing process of the active substance	05/02/2010	n/a		
II/0063	Update of section 4.8 of the SPC following the assessment of a pharmacovigilance follow-up measure on the higher incidence of skin reactions in children compared to those in adults. Update of Summary of Product Characteristics	23/07/2009	27/08/2009	SmPC	As part of the fulfilment of the pharmacovigilance follow-up measure, the MAH provided a cumulative review including all case narratives of cases under SOC "skin and subcutaneous disorders" in children. Further to the assessment, a substantial higher rate of ADR reports of skin reactions, especially erythema, in the paediatric population compared to adults became obvious. It should be noted that frequencies of skin reactions in children and in adults remain within the range already described in the frequency groups in the Product Information.

II/0064	To add an alternate aseptic manufacturing facility within an existing site. As a result, a new batch size has been introduced for Voriconazole Powder for Solution for Infusion and other minor changes to the manufacturing process in relation to updated and improved equipment. Quality changes	23/07/2009	18/08/2009		
IB/0065	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	13/08/2009	n/a		
IA/0070	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	12/08/2009	n/a		
IA/0069	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/08/2009	n/a		
IA/0068	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/08/2009	n/a		
IB/0067	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	24/07/2009	n/a		
IB/0066	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	21/07/2009	n/a		
IB/0062	IB_33_Minor change in the manufacture of the finished product	20/05/2009	n/a		
II/0061	Update of section 4.5 of the SPC to add information	18/12/2008	02/02/2009	SmPC and PL	Following the assessment of PSUR 8 covering the period

	on interaction between Voriconazole and non-steroidal anti-inflammatory drugs (NSAIDs). Section 2 of the PL was updated accordingly. The MAH took the opportunity to update the contact details and to introduce corrections in the PL for Germany. Update of Summary of Product Characteristics and Package Leaflet				from 1 March 2007 to 29 February 2008, the CHMP requested to update the section 4.5 of the SPC to include the interaction between voriconazole and diclofenac based on the results of the study of Hynninen et al. (2006) showing that the AUC (Area under the Curve) and Cmax (Concentration maximum) of diclofenac increased by 78 and 114% respectively, due to concomitant administration with voriconazole. The MAH submitted a variation with information on interaction of voriconazole with diclofenac and also ibuprofen. The data from Hynninen et al. (2007) explained that Voriconazole increased the AUC and Cmax of S-(+) ibuprofen by about 100 and 20%, respectively, due to concomitant administration with voriconazole. Therefore, the monitoring of adverse events and toxicity related to non steroidal anti-inflammatory drugs (NSAIDs) when administered with Voriconazole is recommended together with dosage adjustments. The product Information of Vfend has been modified to include this recommendation.
IA/0060	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/10/2008	n/a	Annex II and PL	
II/0056	Update of section 4.4 and 4.8 of the SPC to add information on serious visual adverse events following the assessment of a clinical follow-up measure. Update of Summary of Product Characteristics	24/04/2008	20/06/2008	SmPC	Further to the assessment of PSUR 6 covering the period from 1 March 2005 to 28 February 2006, an consequential clinical follow-up measures, the SPC of Vfend has been amended to add prolonged visual adverse events including blurred vision, optic neuritis and papilloedema in section 4.4 and section 4.8. The CHMP concluded that the PL did not need to be amended at this stage.

IA/0059	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/03/2008	n/a		
IA/0058	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/02/2008	n/a		
II/0054	Update of sections 4.4 and 4.5 of the SPC with information pertaining to the co-administration of voriconazole and alfentanil based on relevant literature data. The MAH also took the opportunity of this variation to update sections 4.2, 4.3, 4.4 and 4.5 of the SPC with information regarding dose adjustment for efavirenz and voriconazole when co-administration is deemed necessary in line with recommendations agreed by the CHMP in May 2007 for the efavirenz product information. Section 2 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	28/01/2008	SmPC and PL	Alfentanil is a short-acting synthetic opioid analgesic, which is extensively metabolised, mainly by hepatic cytochrome (CYP) P450 3A enzymes. Voriconazole is metabolized by and is also an inhibitor of the CYP P450 isozymes, CYP3A4, CYP2C19, and CYP2C9. Therefore, there is a theoretical concern that concomitantly administered alfentanil and CYP3A inhibitors may exhibit clinically important drug interactions. Within the dossier submitted to support this Type II variation II/54, the MAH submitted data on the pharmacokinetics of oral voriconazole and alfentanil from a randomised, controlled, open-label, 3-way crossover clinical study of 12 healthy subjects published in the literature (Saari et al. 2006). The data from Saari et al. show that co-administration of voriconazole markedly inhibits the metabolism of alfentanil. Although the study only investigated alfentanil, other data show that clinically relevant pharmacokinetic interaction between voriconazole and fentanyl can occur. Therefore physicians are now warned in section 4.4 of Vfend SPC of the co-administration of voriconazole with other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4, such as fentanil and sufentanil.
IB/0055	IB_10_Minor change in the manufacturing process of the active substance	13/11/2007	n/a		

N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/08/2007	n/a	Labelling	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/07/2007	n/a	Labelling and PL	
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/07/2007	n/a	PL	
II/0046	Update of Summary of Product Characteristics	24/05/2007	09/07/2007	SmPC	
II/0045	Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	09/07/2007	SmPC and PL	
II/0047	Quality changes	24/05/2007	06/06/2007		
IB/0048	IB_17_a_Change in re-test period of the active substance	08/05/2007	n/a		
R/0042	Renewal of the marketing authorisation.	26/02/2008	02/05/2007		
IA/0050	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	16/04/2007	n/a		
IA/0049	IA_13_a_Change in test proc. for active substance - minor change	16/04/2007	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/01/2007	n/a	PL	
IA/0043	IA_09_Deletion of manufacturing site	30/11/2006	n/a		

II/0039	Update of Section 4.3, 4.4 and 4.5, to support adjusted dose of voriconazole when administered in conjunction with efavirenz. Section 2 of the Package Leaflet has been updated accordingly. In addition, the Swedish telephone number in Section 6 of the PL has been updated. The MAH took also opportunity to amend Part 1A to include updated contact details under 2.4.3 for the person authorised for communication; amend 2.4.4 to add a Deputy Qualified Person and update contact numbers for the QP. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	26/10/2006	SmPC and PL	
II/0038	Update of Section 4.8 of the SPC according to MedDRA System Organ Class following the CHMP assessment of PSUR5 (covering the period 01/03/04-28/02/05). The MAH took the opportunity of this variation to update the contact details of Sweden in the section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	During the assessment of the PSUR covering the period from 1 March 2004 to 28 February 2005, the CHMP highlighted that the tables and line listings were listed by MedDRA System Organ Class while the SPC was listed according to WHO-ART. Therefore, the MAH was requested to update the section 4.8 "Undesirable effects" of the SPC according to MedDRA System Organ Class. This Type II variation was submitted in May 2006 in order to answer to this request.
II/0041	Update of or change(s) to the pharmaceutical documentation	27/07/2006	03/08/2006		
II/0036	Update of Section 4.5 of the SPC to include	27/04/2006	31/05/2006	SmPC and PL	This variation relates to an open-label, 3 periods, fixed

	information from the results from an Open Label, Fixed Sequence Oral Multiple Dose Study to assess the Pharmacokinetics, Tolerability and Safety of Voriconazole and an Oral Contraceptive Co-Administered at Steady State in healthy Female Subjects. Section 2 of the Package Leaflet has been updated accordingly. In addition, minor corrections have been made to Section 4.5 (ciclosporin instead of cyclosporin+ order of interactions have been revised) of the SPC. The MAH took the opportunity to delete somnolence during infusion from section 4.8 of the SPC and feeling sleepy during infusion from the PL for the tablets and the powder for oral suspension as it does only apply for the IV formulation. Update of Summary of Product Characteristics and Package Leaflet				sequence clinical study, in which each treatment period was separated by a minimum of 7 days. Sixteen healthy pre-menopausal females between 18 and 40 years of age, who were naïve to oral contraceptive usage or who had stopped using oral contraceptives at least three months prior to the study, participated in this study conducted between April and December 2004. The results of this clinical study showed that both voriconazole and oral contraceptives (made of estrogen and progestagen) levels increased significantly at co-administration of both products. Considering the possible concomitant use and need for adequate contraception during voriconazole treatment (e.g. with an oral contraceptives), it is important that this interaction is included in section 4.5 "Interaction with other medicinal products and other forms of interaction" of the SPC and in the Package Leaflet of Vfend. Prescribers should also be warned in the SPC that voriconazole levels will be more variable when co-administered with cyclic oral contraceptives due to the pill-free week. Furthermore, despite no increase of the incidence of hormonal related adverse events was observed in this study, it can not be excluded that, due to the concomitant use, higher estrogen and progestagen levels may cause notably nausea and menstrual disorders.
II/0035	Update of sections 4.2 and 4.4 of the SPC, to avoid the use of voriconazole in children less than 2 year-old as requested by the CHMP following the assessment of post-marketing data. Addition of convulsion in section 4.8 as requested by the CHMP following the assessment of variation II-	14/12/2005	31/01/2006	SmPC	Although, in the clinical programme children under 2 years of age were excluded, 22 patients less than 2 year-old with life-threatening fungal infections were treated in compassionate use programmes. Furthermore post-marketing data reported that 3 children under 2 year-old received voriconazole. The CHMP requested the MAH to

	26. Update of Summary of Product Characteristics				propose measures to avoid the use of voriconazole in children less than 2 years of age. Sections 4.2 and 4.4 of the SPC were updated accordingly and references to section 4.8 were added. The CHMP agreed to add convulsion to section 4.8 as a rare event and the Package Leaflet has been updated accordingly.
II/0034	Update of sections 4.4 and 4.5 of the SPC, following an interaction study with low dose ritonavir. Update of Summary of Product Characteristics and Package Leaflet	14/12/2005	31/01/2006	SmPC and PL	Low dose ritonavir (100 mg q 12 hr) when co-administered with therapeutic dose of voriconazole (200 mg q 12 hr) reduced voriconazole AUC0-Tau by approximately 40% and Cmax by approximately 25%, under steady-state conditions. The N-oxide metabolite (UK-121,265) mean steady-state AUC0-Tau and Cmax values increased by 23% and 28%, respectively, indicating that enzyme induction had occurred after the introduction of ritonavir. Low dose ritonavir had a less marked effect on voriconazole pharmacokinetics than previously seen with higher doses of ritonavir (400 mg q 12 hr). Therefore the current strict contraindication for concomitant use of voriconazole and high doses of ritonavir is not warranted for low "booster" doses of ritonavir and the section 4.4 "Special warnings and special precautions for use" of Vfend SPC was updated with the relative contraindication for the use of low doses ritonavir in voriconazole treatment ("Coadministration of voriconazole and low dose ritonavir (100mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of voriconazole."). The section 4.5 "Interaction with other medicinal product and other forms of interaction" was also updated to includ the results of the new interaction study.

					The Package Leaflet was updated accordingly in section 2.
IB/0033	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	10/11/2005	n/a		
II/0026	Update of the section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SPC, to include dosing recommendations for children aged 2 to <12 years, following the results of previously reported pharmacokinetic studies, compassionate use programmes and a clinical pharmacokinetic study recently conducted to investigate the pharmacokinetics, tolerability and safety of higher doses of voriconazole in hospitalised children (2 to <12 years of age) requiring treatment for the prevention of systemic fungal infection. The Package Leaflet has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	27/10/2005	SmPC and PL	Following the results of pharmacokinetic studies, compassionate use programmes and a clinical pk study conducted to investigate the pharmacokinetics, tolerability and safety of higher doses of voriconazole in hospitalised children (2 to <12 years of age) requiring treatment for the prevention of systemic fungal infection, the SPC was updated to include dosing recommendations for children aged 2 to <12 years. The updated sections are: - 4.2 "Posology and method of administration", to adjust the pediatric voriconazole doses to 7 mg/kg intravenously and 200 mg orally, - 4.4 "Special warnings and special precautions for use", to include that liver function tests should be closely monitored in pediatric patients (as in adults) and that clinicians should consider the likely impact of malabsorption and body weight on oral voriconazole exposure. - 4.8 "Undesirable effects", to mention that safety of voriconazole was investigated in 245 paediatric patients aged 2 to <12 years who presented similar safety profile that in adults. - 5.1 "Pharmacodynamic properties", to delete that there was no data in children below the age of 12 years treated for the indication Candidaemia in non-neutropenic patients. - and 5.2 "Pharmacokinetic properties", to add more information on the findings of the above-mentioned studies.

					Furthermore, for the dosage form 200 mg Powder for Solution for Infusion, the section 6.6 of the SPC "Instructions for use and handling" was updated.
IB/0032	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	01/09/2005	n/a	SmPC	
IB/0031	IB_37_b_Change in the specification of the finished product - add. of new test parameter IB_38_c_Change in test procedure of finished product - other changes	07/06/2005	n/a		
IA/0029	IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	20/04/2005	n/a		
IA/0028	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	20/04/2005	n/a		
II/0025	Further to findings on methadone co-administration with voriconazole from a placebo-controlled clinical study. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC, Annex II and PL	The SPC has been updated in its sections 4.4 "Special warnings and special precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" further to results from a clinical study conducted to assess the effects of voriconazole on the pharmacokinetics, tolerability and safety of methadone co-administered at a steady state in methadone patients. The results showed that in subjects receiving a methadone maintenance dose (32-100mg once daily), coadministration of oral voriconazole (400mg twice daily for 1 day, then 200mg twice daily for four days) increased the Cmax and AUCt of pharmacologically active R-methadone by 31% and

					47%, respectively, whereas the Cmax and AUCt of the S-enantiomer increased by approximately 65% and 103%, respectively. Comparison with historical data showed that voriconazole plasma concentrations during coadministration of methadone were comparable to voriconazole levels in healthy subjects without any comedication. The mean QTc interval was similar in both the Methadone + Placebo and Methadone + Voriconazole groups. It might therefore be concluded that administration of the standard therapeutic voriconazole doses did not lead to serious QTc prolongation in patients treated with methadone dosages of 32-100 mg. Furthermore, relevant QTc prolongation is not expected at regular voriconazole dosages of 200 mg. However, it should be noticed that the power of this study is very low and sensitivity can be doubted, hence frequent monitoring for adverse events and toxicity related to increased plasma concentrations of methadone, including QT prolongation, is recommended during coadministration. Dose reduction of methadone may be needed.
IA/0027	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/01/2005	n/a		
II/0020	to include "treatment of serious Candida infection". Extension of Indication	18/11/2004	10/01/2005	SmPC and PL	Please refer to the Scientific discussion: Vfend-H-387-II-20-AR
II/0024	Further to post-marketing surveillance. Update of Summary of Product Characteristics and	16/09/2004	09/11/2004	SmPC and PL	The SPC has been updated in its sections: - 4.8 "Undesirable effects" to include "Ventricular tachicardia" as rare adverse event as requested further to

	Package Leaflet				the assessment of PSUR4 covering the period 01.09.2003 - 29.02.2004, - and 6.1 "the powder for solution for injection " of the powder for solution for injection SPC by deleting "Water for injections", which is not part of the finished product.
II/0021	Further to the results of a Phase I Clinical study. Update of Summary of Product Characteristics and Package Leaflet	23/06/2004	11/08/2004	SmPC and PL	The SPC has been updated in its sections 4.3 "Contraindications" and 4.5 "Interaction with other medicinal products and other forms of interaction" to include the contraindication with efavirenz following results of a Phase I, single blind, randomised, placebo-controlled, parallel group, oral multiple-dose study to assess the pharmacokinetics, tolerability and safety of voriconazole and efavirenz co-administered at steady state in healthy subjects.
II/0019	Further to the results of a Phase I clinical study. Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	09/06/2004	SmPC, Annex II and PL	The SPC has been updated in its sections 4.3 "Contraindications" and 4.5 "Interaction with other medicinal products and others forms of interactions" to include a contraindication with ritonavir 400mg following results of a a phase I, single blind, randomised, placebo-controlled, parallel group, oral multiple dose study to assess the pharmacokinetics, tolerability and safety of voriconazole and ritanovir co-administered at steady state in healthy subjects..
II/0018	Further to the results of a clinical study. Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	08/06/2004	SmPC and PL	The SPC has been updated in its section 4.8 "Undesirable effects" information on long term visual effects following results of a multicentre, pilot, efficacy trial of voriconazole for the long term treatment of acute and chronic paracoccidioidomycosis with itraconazole as a control group. In addition, the MAH has completed the list of local

					representatives in the section 6 of the Package Leaflet in accordance with EMEA/QRD templates, to include the 10 accession countries.
IA/0023	IA_37_a_Change in the specification of the finished product - tightening of specification limits	03/06/2004	n/a		
IA/0022	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	25/03/2004	n/a		
X/0009	To add a new pharmaceutical form, powder for oral solution (POS) 40mg/ml. X-3-iv_Change or addition of a new pharmaceutical form	25/09/2003	23/02/2004	SmPC, Labelling and PL	Please refer to the Scientific discussion: Vfend-H-387-X-09-AR
II/0013	Further to post-marketing experience. Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	24/10/2003	SmPC and PL	The SPC of Vfend 200mg powder for solution for infusion has been updated in its section 6.6 "Use and handling" in order to give clearer and more detailed guidance on the administration of the product.
II/0012	Further to post-marketing surveillance. Update of Summary of Product Characteristics	26/06/2003	24/10/2003	SmPC	The SPC has been updated in its section 4.8 "undesirable effects" to change the frequency of occurence of "visual disturbances effects" from "common" to "very common".
II/0011	Further to the results of a pharmacodynamic study and to postmarketing surveillance. Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	24/10/2003	SmPC and PL	The SPC of VFEND 50 mg and 200 mg film-coated tablets and 200 mg powder for solution for infusion has been updated in its sections: - 4.2 "Posology and method of administration" recommending to correct electrolyte disturbances before therapy. - 4.4 "Special warnings and special precautions for use" by

					warning patients with cardiovascular high risks , or with potentially proarrhythmic conditions. - 4.8 "Indesirable effects" by adding "Torsade de pointes" and "QT prolongation" as rare cardiovascular effects. - 5.1 "Pharmacodynamic properties" by adding results on a placebo-controlled, randomised, single-dose, crossover study evaluating the effect on the QT interval of healthy volunteers. To provide clearer information to clinicians, the SPC of VFEND 200 mg powder for solution for infusion has been as well updated in its section 6.2 "Incompatibilities".
I/0017	15_Minor changes in manufacture of the medicinal product	07/10/2003	17/10/2003		
IB/0016	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/10/2003	n/a	SmPC	
I/0014	20_Extension of shelf-life as foreseen at time of authorisation	31/07/2003	16/09/2003	SmPC	
I/0015	25_Change in test procedures of the medicinal product	31/07/2003	13/08/2003		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2003	09/07/2003	PL	
I/0006	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/01/2003	24/02/2003	Annex II and PL	

I/0008	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/01/2003	31/01/2003		
I/0007	15a_Change in IPCs applied during the manufacture of the product	22/01/2003	31/01/2003		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/08/2002	03/10/2002	PL	
I/0004	17_Change in specification of the medicinal product	30/07/2002	02/08/2002		
I/0003	15a_Change in IPCs applied during the manufacture of the product	30/07/2002	02/08/2002		
I/0002	14_Change in specifications of active substance	30/07/2002	n/a		
I/0001	15_Minor changes in manufacture of the medicinal product 16_Change in the batch size of finished product 01_Change following modification(s) of the manufacturing authorisation(s)	30/07/2002	n/a		