Mycamine

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
IAIN/0053/G	This was an application for a group of variations. 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.b.2.a - Change to importer, batch release	19/11/2024		Annex II 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).

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
T/0052	Transfer of Marketing Authorisation	12/09/2024	09/10/2024	SmPC, Labelling and PL	
PSUSA/2051/ 202210	Periodic Safety Update EU Single assessment - micafungin	12/05/2023	n/a		PRAC Recommendation - maintenance
II/0047	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	09/02/2023	01/02/2024	Annex II	Annex IID of the Product Information was amended to delete the text on additional risk minimisation measures (aRMM - a prescriber´s checklist). The RMP safety concerns addressed with the prescriber´s checklist were also removed from the RMP (with the exception Hemolytic Adverse Events). However, the safety concerns will continue to be part of PSUR reporting in order to monitor the development of the known Mycamine-associated important risks after removal of the above aRMM. For more information, please refer to the Product Information.
IAIN/0051/G	This was an application for a group of variations. 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.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	08/02/2023	01/02/2024	Annex II and PL	

	site				
IB/0049/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/02/2023	01/02/2024	SmPC	
IAIN/0048/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.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/06/2022	n/a		
IA/0046/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.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	17/06/2022	n/a		

	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				
II/0044/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.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.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	07/04/2022	n/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 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 B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the				

	finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2021	01/02/2024	PL	
PSUSA/2051/ 202010	Periodic Safety Update EU Single assessment - micafungin	10/06/2021	n/a		PRAC Recommendation - maintenance
IA/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/02/2020	04/02/2021	SmPC, Labelling and PL	
IB/0041/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	10/02/2020	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/2051/ 201810	Periodic Safety Update EU Single assessment - micafungin	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0039	Update of section 4.4 of the SmPC in order to update the safety information, based on the Final Mortality Report and the 30-day Reanalysis Report from the MYCOS Study. The MYCOS Study is a post-authorisation commitment (MEA 013.7) to investigate the short and long-term safety of micafungin and other parenteral antifungal agents. In addition, the MAH took the opportunity to implement a statement on a sodium excipient in the Package Leaflet, in accordance with the Annex of the updated Guideline on Excipient Labelling (EMA/CHMP/302620/2017). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/01/2019	18/12/2019	SmPC and PL	The outcomes of the final study report from the MYCOS study (an Observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma - HCC) including the Final Mortality Report and the 30-day Reanalysis Report were reassuring with regards to the frequency of occurrence of renal or hepatic injuries. The risk of re-hospitalisation for treatment of fungal infection was similar between all patient groups. The provided final mortality report is in line with the previous reports. Nevertheless, due to the limited duration of follow-up (because of high mortality in the cohorts) and the low event rate, no definite conclusions regarding the potential risk of HCC mortality in clinical practice could be drawn. This supported a change to a statement on the potential relevance of preclinical hepatic findings. The SmPC section 4.4 has been updated to read as follows: "Hepatic effects: The development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were observed in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The clinical relevance of this finding is not known".
II/0038	Submission of an updated Annex IID (conditions)	17/01/2019	18/12/2019	Annex II	As part of the additional risk minimisation measures listed

	and RMP version 22.1 in order to streamline and improve the educational programme and communication to physicians prescribing Mycamine as requested in variation II/0035. 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				in Annex II of the marketing authorisation the prescriber's checklist has been updated to focus on the specific important risks. The prescriber's checklist is streamlined to contain information on hepatic events, haemolytic events, renal events and potential risk of liver tumour formation. The "Administration and Monitoring Guide", designed as an educational tool to inform nurses is deleted asno additional benefit of this material is expected. The safety information is already covered in the Prescriber's Checklist and displayed in the SmPC section 4.2; 4.4 and 6.6. The RMP was also updated according to GVP V Rev. 2.
PSUSA/2051/ 201710	Periodic Safety Update EU Single assessment - micafungin	31/05/2018	26/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2051/201710.
II/0035	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	14/06/2018	n/a		
IB/0037/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.b.1.z - Change in the specification parameters and/or limits of an AS, starting	04/05/2018	n/a		

	material/intermediate/reagent - Other variation				
R/0034	Renewal of the marketing authorisation.	14/12/2017	19/02/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Mycamine in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/2051/ 201610	Periodic Safety Update EU Single assessment - micafungin	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0031	Update of sections 4.2, 4.9 and 5.2 of the SmPC with further information related to posology in newborns and children less than 4 months of age. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/05/2016	29/06/2016	SmPC and PL	A PK/PD bridging study demonstrated dose-dependent penetration of micafungin into CNS with the minimum AUC of 170 µg*hr/L required to achieve maximum eradication of fungal burden in the CNS tissues. Population PK modeling demonstrated that a dose of 10 mg/kg in children less than 4 month of age would be sufficient to achieve the target exposure for the treatment of CNS Candida infections. Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS. Mean weight-adjusted clearance in children less than 4 months of age is approximately 2.6-fold greater than older children (12-16 years) and 2.3-fold greater than in adults. The safety and efficacy in children (including neonates) less than 4 months of age of doses of 4 and 10 mg/kg for the treatment of invasive candidiasis with CNS involvement has not been adequately established in controlled clinical studies.

PSUSA/2051/ 201510	Periodic Safety Update EU Single assessment - micafungin	13/05/2016	n/a		PRAC Recommendation - maintenance
IB/0032	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	17/02/2016	n/a		
II/0029	Update of section 5.2 of the SmPC with the results of population PK analyses in paediatric patients 4 months and older. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	29/06/2016	SmPC	In paediatric patients AUC values were dose proportional over the dose range of 0.5 4 mg/kg. Clearance was influenced by weight, with mean values of weight-adjusted clearance 1.35 times higher in the younger children (4 months to 5 years) and 1.14 times higher in paediatric patients aged 6 to 11 years. Older children (12-16 years) had mean clearance values similar to those determined in adult patients. Mean clearance in premature infants (gestational age approximately 26 weeks) is approximately 5 fold greater than in adults.
PSUSA/2051/ 201410	Periodic Safety Update EU Single assessment - micafungin	21/05/2015	28/07/2015	Annex II	Please refer to Mycamine EMEA/H/C/000734 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0026	Submission of a revised RMP version 17 in order to: update the information related to the safety specification, pharmacovigilance plan and risk minimisation measures. 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	23/07/2015	n/a		

IB/0028/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 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.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	27/02/2015	n/a		
PSUV/0023	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IB/0024/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	05/05/2014	n/a		

IAIN/0025	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	05/03/2014	n/a		
II/0021	In compliance with the conclusion of the post-authorisation measure FUM 009, the MAH proposed the update of SmPC section 5.1 with published EUCAST breakpoints for micafungin. The MAH took the opportunity to update the PI with the latest QRD template and update the list of local representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	20/02/2014	SmPC, Annex II and PL	Following the EUCAST publication of clinical breakpoints for micafungin, the Mycamine Product Information was updated with addition of the micafungin clinical breakpoints for Candida. In addition, it was agreed to update the section PK/PD relationship of the SmPC with the new AUC/MIC data observed in animal models.
IAIN/0022/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - 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 PhV system	20/09/2013	n/a		
IAIN/0020/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance	14/05/2013	n/a		

	system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of 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				
IAIN/0019	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	18/03/2013	n/a		
IAIN/0018/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of 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	08/02/2013	n/a		
IAIN/0017	A.1 - Administrative change - Change in the name and/or address of the MAH	21/01/2013	20/02/2014	SmPC, Labelling and PL	
R/0015	Renewal of the marketing authorisation.	18/10/2012	20/12/2012		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 Mycamine in the treatment

					and prevention of Candida infections in children and adults if other antifungals are not appropriate remains favourable and therefore recommends the renewal of the marketing authorisation. Considering the safety profile of Mycamine and specially the potential risk of hepatocellular carcinoma, the CHMP agreed that one additional 5-year renewal is required.
IAIN/0016	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	23/10/2012	n/a		
IAIN/0014/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	03/02/2012	n/a		

IA/0013	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	08/11/2011	n/a		
IA/0012/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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)	10/10/2011	n/a		
II/0010	Update of section 4.3 of SmPC with hypersensitivity to other echinocandins and section 4.8 with disseminated intravascular coagulation, erythema multiforme, SJS and TEN. Section 4.4 was updated to include a warning regarding exfoliative cutaneous reactions. The Annex II and PL are updated accordingly. In addition, the MAH took the opportunity to update Annex II and 127a with the amphotericin B concomitant administration and to update the Prescriber Checklist and Administration and Monitoring Guide as committed following the variation II-06. In addition, the version of DDP was deleted in Annex II and the list of local representatives updated in the PL. C.I.z - Changes (Safety/Efficacy) of Human and	23/06/2011	24/08/2011	SmPC, Annex II and PL	Following the CHMP request following the assessment of the 4th PSUR, the MAH performed an analysis of the cumulative safety data of micafungin and concluded that the contraindication 'hypersensitivity to other echinocandins' should be added to the European SmPC of Mycamine. In addition, following signal evaluation analysis of the cumulative safety data of micafungin as mentioned in the latest 5th PSUR, the MAH concluded that the adverse reactions disseminated intravascular coagulation, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis should be added to the section 4.8 of SmPC. Based on the severity of the bullous skin reactions like TEN and SJS and in line with SmPC guideline and other EU SmPCs, an additional warning in section 4.4 is included.

	Veterinary Medicinal Products - Other variation				The Prescriber Checklist and Administration and Monitoring Guide, as well as the Annexes II and 127a, were updated in accordance. Although disseminated intravascular coagulation, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis are serious adverse reactions, their incidence is very low. Provided that all the safety measures are taken into account as requested, the benefit-risk ratio of Mycamine remains favourable.
IA/0011/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of 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	07/04/2011	n/a		
IA/0009	B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	31/01/2011	n/a		
II/0006	Update of Summary of Product Characteristics and	18/11/2010	20/12/2010	SmPC and PL	Section 4.5 of the SmPC already includes a statement in

	Package Leaflet As per CHMP request following the assessment of FU2 016.2, update of section 4.4 of the SmPC to include a statement relating to toxic adverse reactions due to the interaction with sirolimus, nifedipine or itraconazole. In addition, the term 'anaphylactic' was added to the anaphylactoid reactions warning in section 4.4 and a minor editorial change in section 4.5 in the statement concerning co-administration of micafungin and amphotericin was made. The Package Leaflet was updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				relation to concomitant use of micafungin with sirolimus, nifedipine and itraconazole and monitoring of toxicity. Following the CHMP request and in accordance with the Guideline on the SmPC, a warning statement to monitor the toxicity of sirolimus, nifedipine and itraconazole, and to reduced the dosage if necessary, when co-administrered with micafungin was added to the section 4.4 of the SmPC. The interaction section of the PL was updated accordingly.
IA/0007/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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 C.I.9.c - Changes to an existing pharmacovigilance	17/08/2010	n/a	Annex II	

	system as described in the DDPS - Change of the back-up procedure of the QPPV				
II/0005	Update of Summary of Product Characteristics, Annex II and Package Leaflet Following the CHMP request, update of section 4.4 "Special warning and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC to include the safety information for the interaction with amphotericin B, and of section 4.8 "Undesirable effects" to include toxic skin eruption. The Package Leaflet was updated accordingly. In addition the MAH took the opportunity to update the European Medicines Agency website address in the product information and the local representative contacts in Romania and Bulgaria in the Package Leaflet. The European Medicines Agency acronym was updated in the Annex II. Update of Summary of Product Characteristics and Package Leaflet	20/05/2010	06/08/2010	SmPC, Annex II and PL	Following a study investigating the PK interaction between intravenous micafungin and amphotericin B following repeated administration to healthy male subjects and the PK simulation results, it was suggested that concomitant treatment of amphotericin B and micafungin for 14 days would result in an increase of plasma amphotericin B concentrations of about 33%. This is to be expected as amphotericin B accumulates to steady state. Therefore, due to the clinical significance of the increase of nephrotoxic amphotericin B concentration, the CHMP agreed that information of the co-administration should be added in section 4.5 of the SmPC, together with an additional statement in section 4.4. Concerning the serious skin adverse events, a review of safety data from micafungin clinical trials was performed. 27.5% patients treated with micafungin had skin adverse events compared to 31.9% patients on the active control arm. Most of these adverse events were mild to moderate in severity and there were 9 serious adverse events in the skin SOC reported with micafungin (0.2% of all adverse events reported). No reports of toxic epidermal necrolysis, Stevens Johnson syndrome, Lyell syndrome, DRESS, toxicoderma, bullae and erythema multiforme were noted. The review of the MAH safety database showed 59 events of skin adverse events. 22 of the events were serious and 37 were non-serious. Of the 22 serious skin, 3 were Stevens Johnson syndrome, 5 were Toxic Epidermal Necrolysis, 4 were toxic skin eruption, 6 were drug

					eruption, and 4 were stomatitis. In all of these cases, there were other causative factors but the relationship between the events and micafungin could not be completely excluded. Consequently, the adverse reaction 'toxic skin eruption' was added to the SmPC with an "unknown frequency" and the bullous skin reactions will continue to be closely monitored and reported in the PSURs.
II/0004	Update of sections 4.2, 4.4 and 5.1 of the SPC following the assessment of a clinical Follow-up Measure on pharmacokinetic data in patients with severe hepatic impairment. The MAH took the opportunity to update the information on the local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	20/11/2009	SmPC and PL	In a pharmacokinetic study performed in patients with severe hepatic impairment (Child-Pugh score 10-12) (n=8), lower plasma concentrations of micafungin and higher plasma concentrations of the hydroxide metabolite (M-5) were seen compared to healthy subjects (n=8). These data are insufficient to support a dosing recommendation in patients with severe hepatic impairment.
II/0002	The manufacturing of an intermediate in the manufacture of micafungin sodium is being transferred to a new plant. Quality changes	23/07/2009	20/08/2009		
IB/0003	IB_33_Minor change in the manufacture of the finished product	16/04/2009	n/a		
T/0001	Transfer of Marketing Authorisation	13/08/2008	29/09/2008	SmPC, Labelling and PL	