ECALTA

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/0053/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	27/06/2023		Annex II	

[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).

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.z - Change in control of the AS - Other variation A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
II/0052/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of	08/06/2023	n/a		

	the AS and/or the FP B.I.b.z - Change in control of the AS - Other variation B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP				
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2022		PL	
IA/0050/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	31/10/2022	n/a		
PSUSA/215/202201	Periodic Safety Update EU Single assessment - anidulafungin	29/09/2022	n/a		PRAC Recommendation - maintenance
IA/0049	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/08/2022	n/a		

N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/07/2021	19/10/2021	Labelling and PL	
IAIN/0046/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	30/10/2020	n/a		
IB/0045	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/10/2020	19/10/2021	SmPC and PL	
II/0040	Extension of the approved indication "treatment of invasive candidiasis (ICC)" to include paediatric patients aged from 1 month to less than 18 years of age; consequently, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated in order to add paediatric dosing instructions, warnings and precautions, clinical, and non-clinical information. The Package Leaflet is updated accordingly consequent to the revisions to the SmPC. In addition, the Marketing Authorisation Holder (MAH) has taken the opportunity to update the	30/04/2020	03/06/2020	SmPC and PL	Please refer to Scientific Discussion 'Ecalta-H-C-0788-II-0040

	information in the SmPC and Package Leaflet in line with the current excipient's guideline for fructose. The RMP Version number 13.1 was approved. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0044	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	10/04/2020	n/a		
IB/0043	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	28/02/2020	03/06/2020	SmPC and PL	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019	03/06/2020	PL	
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019	03/06/2020	PL	
IA/0038/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	31/10/2018	n/a		

	changes to an approved test procedure				
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	03/06/2020	PL	
T/0037	Transfer of Marketing Authorisation	11/07/2018	27/09/2018	SmPC, Labelling and PL	
II/0036	Submission of an updated RMP (version 12.1) in order to include new safety information, an update of incidence and prevalence of hepatotoxicity categorised as important identified risk and re-categorisation of convulsions from important potential risk to important identified risk based on ongoing study A8851008, PASS A8851030 study, the Global Antifungal Surveillance Program and the MAH's review and analysis of cumulative exposure data up to the data lock point of 31 August 2017. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/03/2018	n/a		
PSUSA/215/201701	Periodic Safety Update EU Single assessment - anidulafungin	28/09/2017	n/a		PRAC Recommendation - maintenance
R/0033	Renewal of the marketing authorisation.	22/06/2017	28/08/2017		Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of ECALTA in the approved indication remains favourable and therefore recommended the renewal of the marketing

					authorisation with unlimited validity.
IA/0035/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	22/08/2017	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	24/05/2017	PL	
II/0031/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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms	12/05/2016	24/05/2017	SmPC	

	manufactured by complex manufacturing processes B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products				
II/0030	Submission of final study results of study A8851030; a retrospective cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	24/05/2017	PL	
PSUV/0027	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/09/2014	24/05/2017	PL	
II/0026	Following the CHMP assessment of efficacy and safety data of Ecalta in neutropenic patients with invasive candidiasis and non-neutropenic patients with Cancida spp. deep tissue infection (MEA 014.3), extension of Indication to include neutropenic patient for Ecalta. As a consequence, update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to add a warning,	24/07/2014	26/08/2014	SmPC, Annex II, Labelling and PL	For further information, please refer to the Assesment Report: ECALTA-H-788-II-26-AR-en.

	update the safety information and reflect additional data in neutropenic patients. The Package Leaflet is updated in accordance. Furthermore, the SmPC is being brought in line with the latest QRD template version 9. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/08/2013	26/08/2014	PL	
IG/0235/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.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
R/0020	Renewal of the marketing authorisation.	21/06/2012	23/08/2012	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 by consensus that the risk-benefit balance of Ecalta in the treatment of invasive candidiasis remains favourable and therefore recommends the renewal of the marketing authorisation. The CHMP agrees that the identified hepatobiliary effects remain a serious concern for Ecalta. Hepatobiliary effects have been observed in preclinical as well as clinical studies before marketing authorisation.

					During post-marketing surveillance cases of various forms of hepatic injuries have been reported. Based on these pharmacovigilance grounds with the remaining concerns over identified serious hepatobiliary adverse effects, the CHMP agreed that the renewal for the Ecalta, powder for concentrate for solution for infusion, can be granted for a period of five years and that one additional five-year renewal is required.
II/0021	Update of sections 4.4 and 4.8 of the SmPC in order to include statements on anaphylactic reactions including shock. A warning regarding infusion-related adverse events was also introduced in section 4.4 and sections 4.2 and 6.6 were updated regarding infusion rate. The PL was updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	28/06/2012	SmPC and PL	Twenty-two cases of potential infusion-associated reactions were identified in the last PSUR (covering the period from 01.02.2011 to 31.01.2012), compared with 19 in the previous 1-year PSUR. In addition, an increased number of reports of anaphylactic reactions and anaphylactic shock were reported (2 cases versus 1 and 4 cases versus 1 respectively). Consequently, the CHMP agreed with the MAH's proposal to update the Ecalta Product Information in order to add a warning regarding anaphylactic reactions and infusion-related reactions as well as to add anaphylactic reaction and anaphylactic shock among the undesirable effects. Given the uncommon frequency of the adverse events anaphylactic shock and anaphylactic reaction and considering the established efficacy of Ecalta, the benefit risk balance of this medicinal product remains positive.
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	27/06/2012	n/a		
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance	08/06/2012	n/a		

	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				
A20/0019	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/788/A-20/0019
II/0017	Update of section 5.3 of the SmPC with new non-clinical data in juvenile rats. In addition, as requested by the CHMP, the MAH took the opportunity to propose an alternative wording to the hepatic effects warning in section 4.4. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC	The CHMP reviewed and assessed the new non-clinical data submitted by the MAH. In the pharmacokinetic study, it was noted that the anidulafungin brain concentration is increasing after repeated concentration. However, there was no discussion on the blood brain barrier and no interpretation for the human situation could be performed. The CHMP noted that, when the MAH will request an extension of the indication for a paediatric population, further discussion about the predictivity of animal data for the human situation will be needed. In one of the

					toxicological studies, the liver weight increased by approximately 15%. Though no microscopic changes were correlated to this increase. Some small and transient blood parameters changes were also noted. These findings were confirmed in the second toxicological study. Overall these pharmacokinetic and toxicological observations and the conclusions of the studies are in line with those observed in the previously submitted studies and did not affect the risk/benefit balance of Ecalta. The proposed changes to update sections 4.4 and 5.3 of the SmPC are acceptable.
IG/0044/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.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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	02/03/2011	n/a	Annex II	
IB/0016	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	28/02/2011	n/a	SmPC and PL	

IB/0015	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	26/11/2010	n/a		
IB/0014	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/10/2010	n/a	SmPC, Labelling and PL	
II/0013	Following the assessement of PSUR 4, to update section 4.8 of the SmPC to add the infusion-associated undesirable reactions and section 5.1 to update the microbiology data (activity in-vitro). In addition, section 4.4 was amended to clarify the description of hepatic failure. The MAH took the opportunity to update the internet address of the Agency in the Product Information and to update the RMP version number in Annex IIB. The Package Leaflet was updated accordingly. 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, Annex II and PL	The cumulative review of infusion-associated reactions provided by the MAH showed a total of 19 cases. Of these, 10 cases were considered to be possible or probable infusion associated reactions based on the timing of the events, response to actions taken, and possible alternative causes for the events. Consequently, the CHMP agreed to add the terms 'Dyspnoea', 'Hypotension' and 'Bronchospasm' to section 4.8 of the SmPC since they were reported in more than one case or represented a potentially more severe reaction than that ones already included in the SmPC. The CHMP also noted that the MAH will continue to monitor infusion-associated adverse events (inclusive anaesthetic exacerbations) and that the information in the SmPC may be further reviewed following the availability of on-going trials and on the basis of spontaneous reports. The CHMP agreed with the MAH proposal to replace the term 'Worsening hepatic failure' in section 4.4 of the SmPC with the corresponding Preferred Term 'Hepatic failure'. Three cases of 'hepatic failure' were reported in the MAH safety database. The MAH was also requested to follow-on and supplement the reported hepatic cases, as well as to perform a cumulative review and thoroughly discuss whether liver events will have to be included in the product

					information within the next PSUR. In view of the most recent available data on susceptibility, the information on reports of Candida isolates with reduced susceptibility to echinocandins was updated in section 5.1. Considering that susceptibility breakpoints for echinocandins are being revised and/or established, it was agreed that it was premature to include interpretive criteria for in-vitro susceptibility.
IA/0012	IA_13_a_Change in test proc. for active substance - minor change	24/09/2009	n/a		
X/0007	X-3-iv_Change or addition of a new pharmaceutical form	29/05/2009	23/07/2009	SmPC, Annex II, Labelling and PL	
II/0010	Update of the Detailed Description of Pharmacovigilance Systems (DDPS) to version 2.0, in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated with the new version number of the agreed DDPS. Update of DDPS (Pharmacovigilance)	25/06/2009	16/07/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
IB/0011	IB_37_a_Change in the specification of the finished product - tightening of specification limits	14/05/2009	n/a		
IB/0009	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	28/04/2009	n/a		
N/0008	Minor change in labelling or package leaflet not	24/02/2009	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0005	The MAH has applied for an additional manufacturer for the drug product with minor site specific changes to the manufacturing process. Change(s) to the manufacturing process for the active substance	20/11/2008	26/01/2009		
II/0006	Update of the Detailed Description of the Pharmacovigilance system. The contact details for the German representative are also updated in the package leaflet. Update of DDPS (Pharmacovigilance)	20/11/2008	06/01/2009	Annex II and PL	The Detailed Description of the Pharmacovigilance system has been updated in accordance with the Notice to Applicants Volume 9A - Pharmacovigilance for Medicinal Products for Human Use.
II/0004	The MAH has applied for a replacement site for the manufacture of drug substance intermediate and an additional site for the manufacture of the drug substance. Quality changes	23/10/2008	28/10/2008		
IA/0003	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	03/07/2008	n/a		
II/0002	Update of or change(s) to the pharmaceutical doc Update of or change(s) to the pharmaceutical documentation	30/05/2008	11/06/2008		