24 July 2014
EMA/605066/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ECALTA

International non-proprietary name: anidulafungin

Procedure No. EMEA/H/C/000788/II/0026

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 26 November 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
ECALTA	anidulafungin	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Following the CHMP assessment of efficacy and safety data of Ecalta in neutropenic patients with invasive candidiasis and non-neutropenic patients with Candida spp. deep tissue infection (MEA 014.3), the MAH applied for a an extension of indication with update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC . The Package Leaflet is updated accordingly.
In addition the MAH has taken the opportunity of this variation to bring the Product Information in line with the latest QRD template (version 9).

The variation proposed amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet.

Rapporteur: Pieter de Graeff

Co-Rapporteur: Jens Ersbøll

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/297/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/297/2011 is not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

Submission date:	26 November 2013
Start of procedure:	20 December 2013
Rapporteur's preliminary assessment report circulated on:	7 February 2014
PRAC Rapporteur assessment report circulated on:	17 February 2014
PRAC RMP advice and assessment overview adopted by PRAC on :	6 March 2014
Joint Rapporteur's assessment report circulated on:	17 March 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 March 2014
MAH's responses submitted to the CHMP on:	25 April 2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	12 June 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 June 2014
Second Request for supplementary information and extension of timetable adopted by the CHMP on:	26 June 2014
MAH's responses submitted to the CHMP on:	1 July 2014
PRAC RMP advice and assessment overview adopted by PRAC on :	10 July 2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 July 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	21 July 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

2.1. Introduction

Ecalta contains anidulafungin as active substance. Anidulafungin, a semi-synthetic lipopeptide of the echinocandin class, is a non-competitive inhibitor of 1,3-β-D-glucan synthase. The latter enzyme is required by many pathogenic fungi for synthesis of β-linked glucan, a component of the cell wall. Suppression of glucan production results in osmotically fragile cells that are easily lysed. Anidulafungin shows activity *in vitro* against a number of important pathogenic organisms, including *Candida* and *Aspergillus* species.

The currently approved therapeutic indication for Ecalta is:

Treatment of invasive candidiasis in adult non-neutropenic patients.

Ecalta has been studied primarily in patients with candidaemia and only in a limited number of patients with deep tissue Cancida infections or with abscess-forming disease (see section 4.4 and 5.1).

The recommended dose of Ecalta is a single 200 mg loading dose on Day 1, followed by 100 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

In September 2013, following the submission of data in neutropenic subjects and in subjects with deep tissue candidiasis (MEA 014.3. see attachment 13), the CHMP concluded that

- At that time, the data presented in neutropenic patients were considered too limited to support the extension of the indication to neutropenic patients, but - given the relevance to prescribers and patients - should be described in section 5.1 of the SmPC.
- The available data in non-neutropenic patients with DTI patients may be adequate to support adjustment of the SmPC, including the indication.

In the initial Ecalta marketing application, as the comparator arm contained fluconazole with no activity against *C.krusei, C.krusei* infections were not evaluated. Therefore, in the data provided for this variation application, patients with *C.krusei* included and the data collected assessed.

In this variation application, providing additional analyses of the initial MEA 014.3 data, the MAH proposes to extend of the Ecalta indication and include neutropenic patients and patients with deep tissue infections. In addition, sections 4.4, 4.8 and 5.1 of the SmPC are updated to include information on efficacy and safety of anidulafungin in neutropenic patients, patients with DTIs and patients with infections caused by *C. krusei*. The Package Leaflet is updated accordingly.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical efficacy aspects

The following studies have been submitted in support of this variation:

Study	**Title**
A8851021	Efficacy and safety of Eraxis™/Ecalta® (anidulafungin) compared to Cancidas® (caspofungin) in neutropenic patients with invasive *Candida* infection
A8851022	Efficacy and safety of Eraxis™/Ecalta® (anidulafungin) compared to Cancidas® (caspofungin) in patients with *Candida* deep tissue infection (DTI)
Regional candidiasis studies	
A8851011	Phase IV open-label non-comparative trial of IV anidulafungin followed by oral azole therapy for the treatment of candidemia and invasive candidiasis
A8851015	Open-label, non-comparative, study of intravenous anidulafungin, followed optionally by oral voriconazole, for treatment of documented candidemia/invasive candidiasis in hospitalized patients
A8851016	A phase IIIb pilot study of efficacy and safety of anidulafungin in the treatment of candidemia in Asian patients
A8851019	Open-label, non-comparative, study of intravenous anidulafungin, followed optionally by oral voriconazole or fluconazole therapy, for treatment of documented candidemia/invasive candidiasis in intensive care unit patient populations

The CHMP assessment of the individual studies is outlined in the Rapporteur's assessment report for MEA 014.3 adopted by the CHMP on 19 September 2013 (Attachment 13).

For the purpose of this extension of indication application, the MAH has pooled all available data into single datasets and the pooled data are discussed in this assessment report.

2.3.1. Methods – analysis of data submitted

An overview of the study designs, demographics and baseline characteristics for the comparator controlled Studies A8851021 and A8851022, and the 4 open-label regional studies is presented in table 1.

It is noted that the study designs and methods were previously discussed and approved by the CHMP.

Study Participants

1. Neutropenic subjects: Study A8851021 + subjects from the regional studies (A8851011, A8851015, A8851016 and A8851019) with neutropenia at baseline identified based on the absolute neutrophil count at baseline being ≤500 cells/mm^3 or if the investigator indicated neutropenia as a risk factor on the Case Report Form (CRF) page at baseline (or screening)
2. Subjects with DTI: Study A8851022 + subjects from the regional studies (A8851011, A8851015, A8851016 and A8851019) with confirmed deep tissue candidiasis (identified based on a qualifying non-blood culture site from which Candida spp. was isolated), or
3. Subjects with *C. krusei*: These data were pooled from subjects across all studies (A8851021, A8851022, A8851011, A8851015, A8851016 and A8851019).

Table 1. Comparison of Study Designs Across the Comparative Studies A8851021, A8851022 and Open-Label Non-Comparative Regional Anidulafungin Candidiasis Studies (A8851011, A8851015, A8851016 and A8851019)

			----------Regional Studies----------			
	A8851021	**A8851022**	**A8851011**	**A8851015**	**A8851016**	**A8851019**
Region	Europe, USA, Canada	Europe, USA, Canada	USA and Korea	Latin America	Asia	Europe and Canada
Target population	Neutropenic subjects	Subjects with deep tissue *Candida* infection	Infection with *Candida albicans* and non-*Candida albicans* species	Infection with candidemia/ invasive candidiasis in hospitalised/critically ill subjects	Asian subjects with invasive candidiasis and an APACHE II score ≤20	Infection with candidemia/ invasive candidiasis in ICU subjects
Target age	≥16 years	≥16 years	≥18 years	≥18 years	≥18 years	≥18 years
Study design	Randomised, comparative, double-blind, double-dummy	Randomised, comparative, double-blind, double-dummy	Open-label, non-comparative	Open-label, non-comparative	Open-label, non-comparative	Open-label, non-comparative
Study phase	3b	3b	4	4	3b	3b
Anidulafungin dosing	Anidulafungin: 200 mg IV LD x1 on Day 1, 100 mg IV daily MD OR Caspofungin: 70 mg IV LD x1 on Day 1, 35/50/70 mg IV daily MD	Anidulafungin: 200 mg IV LD x1 on Day 1, 100 mg IV daily MD OR Caspofungin: 70 mg IV LD x1 on Day 1, 35/50/70 mg IV daily MD	Anidulafungin Loading Dose: 200 mg IV x1 on Day 1 Maintenance Dose: 100 mg IV daily	Anidulafungin Loading Dose: 200 mg IV x1 on Day 1 Maintenance Dose: 100 mg IV daily	Anidulafungin Loading Dose: 200 mg IV x1 on Day 1 Maintenance Dose: 100 mg IV daily	Anidulafungin Loading Dose: 200 mg IV x1 on Day 1 Maintenance Dose: 100 mg IV daily
Duration of treatment	14 days after last positive blood/tissue culture and resolution of signs/symptoms	14 days after last positive blood/tissue culture and resolution of signs/symptoms	14 days after last positive blood/tissue culture and resolution of signs/symptoms	14 days after last positive blood/tissue culture and resolution of signs/symptoms	14 days after last positive blood/tissue culture and resolution of signs/symptoms	14 days after last positive blood/tissue culture and resolution of signs/symptoms
Minimum duration of IV treatment	10 days	10 days	5 days	5 days	5 days	10 days
Maximum duration of treatment	42 days	42 days	28 days	42 days	42 days	42 days

			----------Regional Studies----------			
	A8851021	**A8851022**	**A8851011**	**A8851015**	**A8851016**	**A8851019**
Switch to oral therapy permitted	Yes (fluconazole or voriconazole) after at least 10 days of IV treatment with anidulafungin	No	Yes (fluconazole or voriconazole) after at least 5 days of IV treatment with anidulafungin	Yes (voriconazole only) after at least 5 days of IV treatment with anidulafungin	Yes (voriconazole only) after at least 5 days of IV treatment with anidulafungin	Yes (fluconazole or voriconazole) after at least 10 days of IV treatment with anidulafungin
Primary efficacy endpoint	Global response at EOIVT in the MITT population	Global response at EOT in the MITT population	Global response at EOT	Global response at EOT	Global response at EOT	Global response at EOT
Secondary efficacy endpoint	Global response at EOT and 2 and 6 weeks after EOT in the MITT population	Global response 2 and 6 weeks after EOT in the MITT population	Global response at EOIVT and 2 and 6 weeks after EOT	Global response at EOIVT and 2 weeks after EOT	Global response at EOIVT, 2 and 6 weeks after EOT, and 12 weeks after baseline	Global response at EOIVT and 2 and 6 weeks after EOT

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; EOIVT = end of intravenous treatment; EOT = end of treatment; ICU = intensive care unit; IV = intravenous; LD = loading dose; MD = maintenance dose; MITT = modified intent-to-treat; USA = United States of America

Module 2.7.4 Summary of Clinical Safety Table 1

Endpoints and analyses

Efficacy endpoints included global, clinical and microbiological responses and were recorded at each visit in the MITT population. The global response was a combination of the overall clinical and microbiological responses and was derived programmatically for all subjects in the pooled regional studies as follows:

Overall Clinical Response	**Overall Microbiological Response**	**Global Response**
Success	Any Response but Failure	Success
Any response	Failure	Failure
Failure	Any Response	Failure
Missing	Any Response but Failure	Missing
Unknown	Any Response but Failure	Unknown

For subjects in studies A8851021 and A8851022, the global response was calculated programmatically from the overall clinical and microbiological responses as follows:

Overall Clinical Response	**Overall Microbiological Response**	**Global Response**
Success	Success	Success
Any response	Failure	Failure
Failure	Any Response	Failure
Missing	Any Response but Failure	Missing
Indeterminate	Any Response but Failure	Indeterminate
Any Response but Failure	Indeterminate	Indeterminate

For the purpose of this pooled analysis, a response of "Unknown" was considered the same as a response of "Indeterminate".[1] A global response of failure at any visit was carried forward as failure at all subsequent visits, regardless of whether the response was missing or observed.

In studies A8851021 and A8851022, responses at the follow-up visit were required only for subjects who did not discontinue study drug for any reason.

Primary Endpoint

The primary endpoint was the proportion of subjects in the MITT population with a successful global response at their EOIVT visit in each of the pooled data sets. This was reported along with the 95% confidence interval. Global response values that were missing or unknown/indeterminate were

[1] Note: "Indeterminate" was used in studies A8851021 and A8851022; "missing" (microbiological response was missing or clinical response was missing) or "unknown" (microbiological response was present and clinical response was unknown) were the categories used in the regional studies.

considered as failures in this analysis. Sensitivity analyses which excluded subjects with global response values that were missing or unknown/indeterminate was also performed.

Secondary Endpoints

Secondary endpoints included:

- The proportion of subjects in the MITT population with successful global responses at their EOT visit in each of the subgroups.
- The proportion of subjects in the MITT population with successful clinical and microbiological responses at their EOIVT and EOT visits (reported separately for each visit) in each of the subgroups.
- The proportion of subjects in the MITT population with successful global responses at their EOIVT and EOT visits (reported separately for each visit) by baseline pathogen in each of the subgroups.
- The overall proportion of subjects in the MITT population who died as well as the proportions of subjects in the MITT population who died by Day 14 and Day 28, respectively.
- The proportion of subjects in the neutropenic MITT subgroup with successful global responses at their EOIVT and EOT visits (reported separately for each visit) for subjects with persistent neutropenia and those with resolved neutropenia.
- The proportion of subjects in the deep tissue infection MITT subgroup with successful global responses at their EOIVT and EOT visits (reported separately for each visit) by baseline site of infection.

The analyses of the secondary endpoints involving the clinical, microbiological and global response were similar to the analysis of the primary endpoint. Clinical, microbiological and global responses from the follow-up visits were summarized separately for the pooled regional studies and individually for studies A8851021 and A8851022. Since studies A8851021 and A8851022 required these responses only for subjects who had not discontinued study drug as versus the regional studies which did not have such a restriction, these responses were not pooled across the regional studies and studies A8851021 or A8851022. The proportions of subjects who died (overall, by Day 14 and by Day 28) were calculated out of the total number of MITT subjects.

Due to the differences in design (controlled vs. open-label) and differences in populations (neutropenia based on absolute neutrophil count in study A8851021 vs. neutropenia based on the absolute neutrophil count or on investigator report in the open-label studies), the CHMP recognised the limitations of pooling data from the comparative and non-comparative studies.

2.3.2. Results

Table 2 summarises the number of subjects enrolled by study and population type. Overall 53 neutropenic subjects, 131 subjects with DTI and 19 subjects with *C. krusei* were included in the pooled safety analyses for ITT population (i.e. subjects who received at least 1 dose of anidulafungin). Of these, 46 neutropenic subjects, 129 subjects with DTI and 19 subjects with *C. krusei* were included in the pooled efficacy analyses for the MITT populations (i.e., subjects treated with at least 1 dose of anidulafungin and who had microbiologically confirmed Candida infection).

Table 2. Comparison of Subject Numbers Across Studies

Study	Study Design	Overall Safety Population[a]		Anidulafungin Only- Subjects with					
		Anidulafungin	Caspofungin	Neutropenia		DTI		*C. krusei*	
				ITT[a]	MITT[b]	ITT[a]	MITT[b]	ITT[a]	MITT[b]
Study in Neutropenic Subjects									
A8851021*	Phase 3b, comparative, double-blind study of anidulafungin vs caspofungin for the treatment of culture confirmed invasive candidiasis due to *Candida* species in neutropenic subjects	15	6	15	11	N/A	N/A	2	2
Study in Subjects With Deep Tissue Infection									
A8851022*	Phase 3b, comparative, double-blind study of anidulafungin versus (vs) caspofungin for the treatment of culture confirmed deep tissue infection due to *Candida* species	26	13	N/A	N/A	26	24	1	1
Regional Studies That Included Subjects With Neutropenia and/or Deep Tissue Infection									
A8851011 (USA and Korea[c])	Phase 4 open-label, non-comparative trial of IV anidulafungin followed by oral azole therapy for the treatment of candidemia and invasive candidiasis (with *Candida albicans* and non-*Candida albicans* species)	282	N/A	15	14	39	39	11	11
A8851015 (Latin America[d])	Phase 4 open-label, non-comparative, study of intravenous anidulafungin, followed optionally by oral voriconazole, for treatment of documented candidemia/ invasive candidiasis in hospitalized patients	54	N/A	7	7	10	10	3	3
A8851016 (Asia[e])	Phase 3b open-label, non-comparative, pilot study of efficacy and safety of anidulafungin in the treatment of candidemia in Asian patients	43	N/A	1	1	0	0	0	0
A8851019 (Europe and Canada[f])	Phase 3b open-label, non-comparative study of intravenous anidulafungin, followed optionally by oral voriconazole or fluconazole therapy, for treatment of documented candidemia/invasive candidiasis in intensive care unit patient populations	216	N/A	15	13	56	56	2	2

Total Number of Subjects in Regional Studies	*595*	*0*	*38*	*35*	*105*	*105*	*16*	*16*
Total Number of Subjects in All Studies	**636**	**19**	**53**	**46**	**131**	**129**	**19**	**19**

Abbreviations: N/A = not applicable; USA = United States of America
a. Number of subjects who received at least 1 dose of study drug (safety population).
b. Number of subjects who receieved at least 1 dose of study drug and has microbiologically confirmed *Candida* infection (efficacy population).
c. Regions: United States and Republic of Korea
d. Regions: Brazil, Chile, Columbia, Mexico, Panama
e. Regions: India, Philippines, Taiwan, and Thailand
f. Regions: Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Russian Federation, Slovakia, Turkey, Ukraine and United Kingdom.
* Bosnia And Herzegovina, Bulgaria, Canada, Croatia, France, Italy and United States
** Belgium, Bulgaria, Canada, Croatia, Netherlands, Portugal and United States

The mean duration of neutropenia in the 28 subjects who had both baseline and post-baseline measurements for neutropenia was 15.4 days (range 1-43 days [Module 2.7.4 Summary of Clinical Safety Section 2.7.4.1.3.1]) with 42.9% (12 subjects) having duration from 15 to 28 days.

Populations

A total of 46 neutropenic subjects, 129 subjects with DTI and 19 subjects with *C. krusei* are included in the overall MITT population pools for the efficacy analyses. Baseline characteristics are provided in Table 3 hereafter.

Table 3. Demography and Baseline Characteristics (Modified-Intent-to-Treat Population)

	Neutropenic Subjects[a] N=46	Subjects with Deep Tissue Infection[b] N=129	Subjects with *Candida krusei*[c] N=19
Gender, n (%)			
Male	28 (60.9)	73 (56.6)	8 (42.1)
Female	18 (39.1)	56 (43.4)	11 (57.9)
Age			
Mean	56.0	60.2	58.3
Range	18-86	20-89	28-89
Race, n (%)			
White	33 (71.7)	104 (80.6)	14 (73.7)
Black	0	10 (7.8)	2 (10.5)
Asian	5 (10.9)	1 (0.8)	1 (5.3)
Other	8 (17.4)	7 (5.4)	2 (10.5)
Unspecified	0	7 (5.4)	0
APACHE II score by category[d], n (%)			
≤20	32 (69.6)	108 (83.7)	14 (73.7)
>20	12 (26.1)	21 (16.3)	4 (21.1)
Mean	16.9	14.9	15.6
Range	4-30	2-44	5-24
Baseline Absolute Neutrophil Count, n (%)[e]			
≤500 cells/mm^3	27 (58.7)	4 (3.1)	8 (42.1)
>500 cells/mm^3	0	67 (51.9)	7 (36.8)
Site of infection, n (%)[f]			
Abdomen	-	19 (14.7)	-
Blood only	39 (84.8)	0	11 (57.9)
Blood and other sterile site	2 (4.3)	21 (16.3)[g]	2 (10.5)
Eye	-	2 (1.6)	-
Gallbladder	-	2 (1.6)	-
Hepatobiliary	-	9 (7.0)	-
Kidney	-	4 (3.1)	-
Lung	-	4 (3.1)	-

Table 3. Demography and Baseline Characteristics (Modified-Intent-to-Treat Population)

	Neutropenic Subjects[a] N=46	Subjects with Deep Tissue Infection[b] N=129	Subjects with *Candida krusei*[c] N=19
Other	-	19 (14.7)	-
Other sterile site	5 (10.9)	-	6 (31.6)
Peritoneal cavity	-	70 (54.3)	-
Pleural cavity	-	7 (5.4)	-
Baseline *Candida* pathogen, n (%)[h]			
Candida albicans	7 (15.2)	83 (64.3)	2 (10.5)
Candida ciferrii	2 (4.3)	0	0
Candida dubliniensis	1 (2.2)	0	0
Candida famata	2 (4.3)	0	0
Candida glabrata	7 (15.2)	40 (31.0)	1 (5.3)
Candida guilliermondii	1 (2.2)	0	0
Candida kefyr	4 (8.7)	1 (0.8)	1 (5.3)
Candida krusei	9 (19.6)	7 (5.4)	19 (100.0)
Candida norvegensis	1 (2.2)	0	0
Candida parapsilosis	8 (17.4)	2 (1.6)	0
Candida sake	0	1 (0.8)	0
Candida species	0	2 (1.6)	0
Candida tropicalis	16 (34.8)	15 (11.6)	2 (10.5)

The causative pathogens are listed in the table above.

The mean duration of neutropenia in the 28 subjects who had both baseline and post-baseline measurements for neutropenia was 15.4 days (range 1-43 days) with 42.9% (12 subjects) having duration from 15 to 28 days. Duration of treatment was at most 42 days (see Table 4).

Table 4. Duration of Intravenous Anidulafungin Therapy (Intent-to-Treat Population)

	All Pooled Neutropenic Subjects[a] N=53	All Pooled Subjects with DTI[b] N=131	All Pooled Subjects with *Candida krusei*[c] N=19
Median (days)	10.0	14.0	13.0
Range	1-42	1-42	4-27

Response rates

Results of the pooled analysis in neutropenic subjects demonstrated an overall global response success rate at the EOIVT (primary endpoint) of 56.5%.

Table 5. Global Response Rates at End of Intravenous Treatment with Anidulafungin (Primary Efficacy Endpoint) and at End of Treatment (Secondary Efficacy Endpoint): Neutropenic Subjects (Modified-Intent-to-Treat Population)

	Neutropenic Subjects[a] N=46
End of intravenous treatment (EOIVT)	
Subjects in analysis, n	46
Success, n (%)	26 (56.5%)
[95% Confidence Interval[b]]	[42.2%, 70.8%]
End of treatment (EOT)	
Subjects in analysis, n	46
Success, n (%)	24 (52.2%)
[95% Confidence Interval[b]]	[37.7%, 66.6%]

Because of the low number of evaluable subjects in the comparative treatment group, it is difficult to draw meaningful conclusions about the comparative efficacy of the 2 studied echinocandins caspofungin (n=3 in the mITT population in study A8851021) and anidulafungin (n=11) in neutropenic subjects. The response rates in the anidulafungin arms are provided in Table 6.

Table 6. Success Rates in Neutropenic Subjects from All Anidulafungin Studies: (Modified Intent-to-Treat)[a]

	Number of Successful responses/Number Subjects in Study Drug n/N (%)	Number of Successful responses/Number Subjects in Study Drug n/N (%) [Comparator]
Anidulafungin Pooled Regional Studies (EOIVT)[b]	18/35 (51.4)	NA
Anidulafungin Study A8851021 (EOIVT)[c]	8/11 (72.7)	3/3 (100) [Caspofungin]
Anidulafungin Total Pooled Neutropenic Subjects (EOIVT)[d]	**26/46 (56.5)**	**NA**
Neutropenic subjects from the registrational ICC study[e]	2/3 (66.7)	2/4 (50.0) [Fluconazole]
Total neutropenic subjects from all anidulafungin studies	**28/49 (57.1)**	**NA**

Comparison of the response rates generated by the comparative study A8851021 (72.7%) and the pooled data generated by the regional studies (51.4%): is also difficult to interpret due to the small sample size.

Due to the differences in design (controlled vs. open-label) and differences in populations (neutropenia based on absolute neutrophil count in study A8851021 vs. neutropenia based on the absolute neutrophil count or on investigator-report in the open-label studies), the CHMP noted the limitations of pooling data from the comparative and non-comparative studies is considered questionable.

The influence of persistent neutropenia on the response rates is presented in comparison with the response rates in patients with resolved neutropenia: see Table 7. Neutropenia was considered resolved if absolute neutrophil count was >500 cells/mm3 before the end of treatment, and persistent if absolute neutrophil count $\leq$500 cells/mm3 for the entire treatment duration.

Table 7. Global Response Success Rates for Anidulafungin-Treated Subjects with Persistent Neutropenia or Resolved Neutropenia (Pooled Neutropenic Data[a]) – Modified Intent-to-Treat Population

	Subjects with Neutropenia Resolved[b]		Subjects with Neutropenia Persistent[b]	
	n (%)	95% Confidence Interval[c]	n (%)	95% Confidence Interval[c]
Number of Subjects in this analysis[d]	28		28	
End of intravenous treatment (EOIVT)				
Subjects in analysis	15		13	
Success	12 (80.0%)	(59.8%, 100.0%)	7 (53.8%)	(26.7%, 80.9%)
End of treatment (EOT)				
Subjects in analysis	15		13	
Success	10 (66.7%)	(42.8%, 90.5%)	7 (53.8%)	(26.7%, 80.9%)

The CHMP agreed that the generated data have shown the contribution of granulocytes in the clearance of Candida infections. The reason why this data is provided only from 28 patients and not for all subjects is unclear, since this is a routine laboratory measurement with implications for therapy. The MAH explained that only for these subjects both baseline and post-baseline measurements for absolute neutrophil count were available. The CHMP acknowledged this explanation but, considering the severity of disease, the reasons why the measurements were not performed in the other 18 patients remains unclear.

Deep tissue infection

Anidulafungin provided an overall global response success rate at the EOIVT (primary endpoint) of 79.1% (Table 8). Treatment response was higher in subjects with infection at a deep tissue site alone (n=108) compared to subjects with concomitant blood stream infection (n=21) : 81.5% vs. 66.7%.

Table 8. Global Response Rates at End of Intravenous Treatment (Primary Efficacy Endpoint) and at End of Treatment (Secondary Efficacy Endpoint) (Modified-Intent-to-Treat Population)

	Subjects with Deep Tissue Infection[a] N=129
End of intravenous treatment (EOIVT)	
Subjects in analysis, n	129
Success, n (%)	102 (79.1%)
[95% Confidence Interval[b]]	[72.0%, 86.1%]
End of treatment (EOT)	
Subjects in analysis, n	129
Success, n (%)	94 (72.9%)
[95% Confidence Interval[b]]	[65.2%, 80.5%]

The most common sites of infection included

- peritoneal cavity (70 subjects), global response rate: 51/70 (72.9%; 95% CI 62.4%, 83.3%)
- hepatobiliary (9 subjects), global response rate: 7/9 (77.8%; 95% CI 50.6%, 100.0%)
- pleural cavity (7 subjects), global response rate: 6/7 (85.7%; 95% CI 59.8%, 100.0%)
- kidney infections (4 subjects), global response rate: 3/4 (75.0%; 95% CI 32.6%, 100.0%)

The pooled data provides evidence of activity of anidulafungin, but since only 4 patients with neutropenia were included in the regional studies (none in the comparative study in the anidulafungin arm vs caspofungin that included 26 vs. 13 patients, respectively) the additional contribution of granulocytes in resolution of infection cannot be established.

Candida krusei

Studies A8851021, A8851022 and the 4 regional studies added 19 subjects with infection due to *C. krusei* to the overall database. In the pooled analyses, the global response success rate at EOIVT (primary endpoint) was 14/19 = 73.7%. Nearly half of subjects identified (8/19, 42.1%) were considered neutropenic at baseline. The global response success rate in these 8 subjects at the EOIVT (primary endpoint) was 50.0%, suggesting that immune dysfunction is a significant factor in treatment outcome.

C.krusei susceptibility was comparable to other non-albicans Candida (except *C.parapsilosis*) based on the breakpoints established by EUCAST. In total 9 from 46 neutropenic patients had invasive candidiasis due to *C.krusei* (19.6%), demonstrating its relevance as pathogen in this patient group (Table 5). Anidulafungin demonstrates efficacy in this patient group. Again, the contribution of granulocytes to resolution of infection was clear: 73.7% for the total group, 50% for those with neutropenia.

2.3.3. Discussion on clinical efficacy

A total of 46 neutropenic subjects (global response rate EOIVT 56.5%[42.2%, 70.8%]), 129 subjects with DTI (global response rate EOIVT 79.1%[72.0%, 86.1%]) and 19 subjects with *C. krusei* (global response rate EOIVT 73.7% [53.9%, 93.5%]) were included in the overall MITT population pools for the efficacy analyses. These results are relatively similar to those in 245 non-neutropenic patients with invasive candidiasis (VER002-9) that resulted in registration of anidulafungin: EOIVT 75.6% in the anidulafungin group and 60.2% in the fluconazole group.

The results of the individual studies have been discussed during the post-authorisation procedure MEA 014.3 (see attachment 13). The presented pooled data in neutropenic patients from all comparative and single arm studies show that anidulafungin has high anti-candida activity regardless of immune status of the human host.

Neutropenia

From the comparative studies, providing the most relevant data, only 21 patients (15 anidulafungin vs. 6 caspofungin) provided data on treatment response in neutropenia. Ultimately, only 11 patients in the anidulafungin arm contributed to overall analysis (being the MITT population). Therefore, the majority (n=35) of the 46 patients with invasive candidiasis and neutropenia were from regional single arm studies. Although Candida infection was confirmed in these patients, lack of insight in selection of these patients is hampering interpretation of study results from this group. The data generated in this group is at most supportive. This is further complicated by the fact that from 18 of these 35 subjects no quantitative neutrophil count was presented, but only that the investigator labelled the patient as neutropenic. Considering this lack of information in 18/35 patients and the fact that single arm studies are not to be pooled with comparative studies, the data should be interpreted with caution.

EOIVT global response rates in the mITT population in A8851021 were 8/11 (72.7%) and 3/3 (100%) for anidulafungin vs. caspofungin. The interpretation of these results is limited by the small number due to enrolment issues, which was accepted by the CMHP. These patient numbers are even lower

than those in comparative studies with micafungin (n=24) and caspofungin (n=14) in neutropenic patients, who did however show similar response rates: 75% and 50% respectively.

The influence of neutropenia was demonstrated in the pooled analysis for 28 from 46 subjects that contributed to an analysis to differentiate the influence of persistent vs. resolved neutropenia: global response rates 53.8% vs. 80% respectively.

The methodological concern about pooling data from studies with different study designs is illustrated by the differences in response: A8851021 success rate at EOIVT 72.7% and the pooled open-label non-comparative studies in 504 candidiasis cases EOIVT 51.4%, which may have been caused by higher APACHE II scores in the subjects from regional studies. At most it can be concluded that pooling data from the small comparative study and the non-comparative studies did not result in inflated response rates due to selection of relatively severe cases in the latter studies. Thus, possible erroneous inclusion of 18/35 non-neutropenic patients due to non-recorded neutrophil counts did not result in inflated high response rates considering the known deleterious effect of persistent neutropenia on outcome.

The provided data in neutropenic patients from the comparative study is limited but the total number of subjects and treatment response appear relatively similar to other patient groups treated with anidulafungin or with other echinocandins.

Following the CHMP discussions, additional information was made available on those patients enrolled in comparative studies with no details on the quantification of neutropenia were initially provided. Although based on the provided clinical information one could expect that the 11 patients listed are neutropenic to some extent, one may not conclude they fulfil the predefined criterion WBC count of $\leq$ 500 cells/mm3 at baseline. The subanalysis for those patients with quantification and those without suggest a possible numerical better response at EOT and 2 weeks post treatment, but numbers are too small to come to any conclusion. The CHMP agreed that the limitations of these data should be adequately addressed in the SmPC.

Different Candida species

Whereas *in vitro* data and determination of susceptibility of Candida species mostly did not show differences between the echinocandins in their anti-fungal efficacy (studies by Pfaller et al.), the CHMP noted that some studies and animal models did find differences, especially in *C.glabrata*. Arendrup et al. (2012) recently evaluated the *in vivo* efficacy of the three echinocandins in an immunocompetent mouse model (AAC, 2012). Three clinical *C. glabrata* isolates with or without *fks* hot spot mutations and low, medium, and high echinocandin MICs, respectively were evaluated using three doses of each echinocandin. In this study - and in remarkable contrast to caspofungin and micafungin - anidulafungin failed to induce a>1-log reduction for any of the isolates. In general, anidulafungin was clearly the less active echinocandin against the *C.glabrata* isolates with a rank order of activity of micafungin>caspofungin> anidulafungin.

In support of these observations, a similar rank order was observed by Andes et al, who investigated the *in vivo* activities of all three echinocandins against *Candida* spp., including *C .glabrata*, in a neutropenic murine model of disseminated candidiasis (AAC, 2008). Further support comes from a study by Spreghini et al, AAC, 2012, who observed that while all three drugs were often fungicidal *in vitro*, they were not able to completely eradicate the infection in this murine neutropenic model of Candidiasis and that the efficacy of anidulafungin in a model of *C.glabrata* infection appeared significantly reduced compared to the other echinocandins.

The extent these *in vivo* murine observations may have implications for the clinical use of anidulafungin is unclear. Overall, the efficacy observed for patients without neutropenia and invasive

infection with *C.glabrata* observed in the regional observational trial seems comparable to other species and appears is in line with response rates reported for the other echinocandins, but the numbers are small.

In this context, the observed response rate for patients with *C.glabrata* in the pivotal Reboli trial is of particular interest (NEJM, 2007); In contrast *to C.albicans* in which the response rate and time to culture negativity was high and significantly better for anidulafungin compared to fluconazole (81% vs 62%), the lowest global response rates were observed for *C.glabrata* with response rates of 56% for anidulafungin and 50% for fluconazole.

Since *C.glabrata* is a major pathogen in neutropenic patients the implications of decreased susceptibility to anidulafungin may impact treatment outcomes and as such may have direct consequences for the proposed indication of use of Ecalta in neutropenic patients.

Therefore, in order to address this concern, MAH re-analysed data from 4 regional studies (A8851011, A8851015, A8851016, A8851019), the anidulafungin registrational study (VER002-9), and Studies A8851021 and A8851022. The latter 2 were excluded from the neutropenia analysis. In these studies 149 patients were infected with *C. glabrata* compared to 388 infections with *C. albicans*. Baseline characteristics were comparable. Global response rates the end of IV therapy (EOIVT), end of all therapy (EOT), 2 and 6 Week Follow-Up visit and the rate of all-cause mortality was more or less similar for *C. glabrata* compared to *C. albicans*, although response rates were numerically slightly lower and mortality rates slightly higher. Due to the absence of confidence intervals one cannot conclude non-difference between the 2 pathogens. Furthermore data need to be interpreted with care as they are derived from different studies and patients with different underlying conditions may have contributed unevenly the response to therapy.

Interestingly, the results from the neutropenic subpopulation suggests a slightly better response to treatment for *C. glabrata* strains, although numbers are too small for final conclusions.

Based on the expected susceptibility (EUCAST) it is to be expected that *C. glabrata* infections should respond to anidulafungin treatment. Patients with candidemia usually have complex underlying conditions that may contribute to their overall response to treatment and survival and pathogenicity of *C. albicans* and *C. glabrata* may differ these patients. Candidemia was diagnosed in more than 80% of the patients.

Despite these uncertainties, the CHMP concluded that the number of patients infected with *C. glabrata* in the different studies and the EUCAST epidemiological distribution on more than 300 observations provide a sufficient level of evidence to suggest that anidulafungin may have an acceptable response in these patients.

Deep tissue infection

Study A8851022 was a descriptive randomized, double-blind comparative study to evaluate efficacy and safety of anidulafungin (n=26) compared to caspofungin (n=13) in the treatment of patients with DTI. Despite efforts to improve enrolment, the planned number of patients was not attained in this study. On approval of the study design, it was already noted that the study was not powered to provide conclusive evidence of comparative efficacy and safety in this population. Despite this limitation, an acceptable treatment effect was observed: EOT were 20 (83.3%) of 24 subjects and 8 (61.5%) of 13 subjects for anidulafungin vs caspofungin, respectively. This was, furthermore, confirmed by pooled results in a relatively large number of patients (n=105) from open-label non-comparative studies that did include only 4 neutropenic patients.

The overall success rate at EOIVT in the pooled analysis (79.1%) was numerically higher than the success rate reported in a study of micafungin versus caspofungin (Pappas et al, 2007) in non-candaemic patients with deep tissue candidiasis (53.4% [31/58] and 57.7% [15/26], respectively).

In total, data on 129 patients with DTI were submitted. The available data are considered supportive and consistent across studies and across sites of infection. This may be reflected in the SmPC. No misclassification of neutropenia can influence results in these cohorts, since only 4 from 129 were neutropenic, with little influence on final outcome.

C. krusei

The CHMP agrees that, compared to other Candida spp. and other patient groups, overall treatment response was similar for *C.krusei* infections. This supports the inclusion of this pathogen in the indication of anidulafungin.

2.3.4. Conclusions on the clinical efficacy

The evaluation of efficacy in neutropenic patients is based on a limited number of patients and very limited comparative data. However, based on the available data, the efficacy data from non-neutropenic patients and the absence of any clear efficacy concerns in neutropenic patients, the extension of indication by not excluding neutropenic patients is acceptable.

2.4. Clinical safety

2.4.1. Methods – analysis of data submitted

The safety profile of anidulafungin in the currently approved SmPC was originally determined based on 204 subjects from the registrational Phase 3 study (ICC dataset). For this submission the two comparative studies (A8851021, A8851022) and four open-label (A8851011, A8851015, A8851016, A8851019) studies were pooled into single datasets: neutropenic subjects (n=53, 15 subjects in Study A8851021 and 38 subjects in the regional studies), subjects with deep tissue candidiasis (n=131, 26 subjects in Study A8851022 and 105 subjects in the regional studies), and subjects with infection due to *C. krusei* (n=19) who all received at least 1 dose of anidulafungin. Baseline characteristics were relatively similar between studies, except for higher APACHE II scores in the regional studies (more severely ill).

2.4.2. Results

Exposure

Exposure was median 2 weeks, but could be extended to at most 42 days depending on the last positive blood or tissue culture and resolution of symptoms.

Table 9. Duration of Intravenous Anidulafungin Therapy (Intent-to-Treat Population)

	All Pooled Neutropenic Subjects[a] N=53	All Pooled Subjects with DTI N=131[b]	All Pooled Subjects with *C. krusei*[c] N=19	ICC Dataset N=204[d]
Median (days)	10.0	14.0	13.0	14.0
Range	1-42	1-42	4-27	1-38

Due to the low sample sizes in Studies A8851021 and A8851022, differences with the regional studies as well as any potential differences in frequencies with caspofungin are not likely to be informative and should be interpreted with caution. No new safety data was identified.

Adverse Events

Most common AEs were compared between the different study populations, without major differences from the original data (ICC data set) from registration.

Table 10. Incidence of Treatment-Emergent All-Causality System Organ Class Events: Anidulafungin-Treated Subjects (Intent-to-Treat Population)

System Organ Class	Overall Neutropenic Subjects[a] N=53	Overall Subjects with DTI[b] N=131	Overall Subjects with *Candida krusei*[c] N=19	ICC Dataset N=204
Blood and Lymphatic System Disorders	8 (15.1)	21 (16.0)	4 (21.1)	50 (24.5)
Cardiac Disorders	13 (24.5)	26 (19.8)	6 (31.6)	54 (26.5)
Congenital, familial and genetic disorders	0	0	0	1 (0.5)
Ear and Labyrinth Disorders	1 (1.9)	0	0	1 (0.5)
Endocrine Disorders	1 (1.9)	1 (0.8)	1 (5.3)	3 (1.5)
Eye Disorders	5 (9.4)	0	2 (10.5)	16 (7.8)
Gastrointestinal Disorders	23 (43.4)	64 (48.9)	10 (52.6)	128 (62.7)
General Disorders and Administration Site Conditions	23 (43.4)	42 (32.1)	7 (36.8)	106 (52.0)
Hepatobiliary Disorders	3 (5.7)	11 (8.4)	1 (5.3)	12 (5.9)
Immune System Disorders	2 (3.8)	0	1 (5.3)	1 (0.5)
Infections and Infestations	28 (52.8)	58 (44.3)	10 (52.6)	113 (55.4)
Injury, Poisoning and Procedural Complications	4 (7.5)	19 (14.5)	3 (15.8)	39 (19.1)
Investigations	14 (26.4)	31 (23.7)	4 (21.1)	101 (49.5)
Metabolism and Nutrition Disorders	10 (18.9)	34 (26.0)	6 (31.6)	89 (43.6)
Musculoskeletal and Connective Tissue Disorders	6 (11.3)	12 (9.2)	2 (10.5)	37 (18.1)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	6 (11.3)	4 (3.1)	2 (10.5)	6 (2.9)
Nervous System Disorders	8 (15.1)	17 (13.0)	6 (31.6)	43 (21.1)
Psychiatric Disorders	7 (13.2)	29 (22.1)	3 (15.8)	60 (29.4)
Renal and Urinary Disorders	11 (20.8)	10 (7.6)	4 (21.1)	40 (19.6)
Reproductive System and Breast Disorders	2 (3.8)	1 (0.8)	1 (5.3)	5 (2.5)
Respiratory, Thoracic, and Mediastinal Disorders	19 (35.8)	40 (30.5)	8 (42.1)	98 (48.0)
Skin and Subcutaneous Tissue Disorders	11 (20.8)	18 (13.7)	5 (26.3)	53 (26.0)
Surgical and Medical Procedures	0	3 (2.3)	0	3 (1.5)
Vascular Disorders	8 (15.1)	38 (29.0)	4 (21.1)	63 (30.9)

SAE

SAEs were reported in 56.6% of neutropenic subjects, 58.8% of subjects with DTI, 57.9% of subjects with *C. krusei,* and 50.0% of subjects in the ICC dataset, without showing new safety data.

Death

Anidulafungin treated subjects had an AE with an outcome of death in 47.2% of neutropenic subjects, 32.1% of subjects with DTI, 42.1% of subjects with C. krusei and 23.5% of subjects in the ICC dataset. Although higher than in the ICC dataset, the individual cases resulting in death in the 3 populations were carefully reviewed and the AEs associated with the fatal outcome in the 3 populations were due to the patient's underlying disease or its complications or co-morbidities.

Discontinuation

AEs resulted in permanent discontinuation of anidulafungin in 18.9% of neutropenic subjects, 6.9% of subjects with DTI, and 15.8% of subjects with *C. krusei*, and 10.3% of subjects in the ICC dataset. The main causes of the discontinuations were the underlying diseases or concurrent diseases with the exception of 2 neutropenic subjects: hypotension and tachycardia in 1 subject and convulsion in the other. The convulsion continued despite discontinuing anidulafungin.

Comparison comparative studies vs regional studies

There was a higher rate of AEs in the regional studies than in Studies A8851021 or A8851022. This may be reflective of the fact that subjects in the regional studies appeared to be more severely ill as evidenced by the slightly higher mean APACHE II score and higher frequency of subjects with APACHE II scores >20. Due to the low sample sizes in Studies A8851021 and A8851022, differences with the regional studies as well as any potential differences in frequencies with the comparator (caspofungin) are not likely to be informative and should be interpreted with caution.

Comparison anidulafungin vs caspofungin

The review of anidulafungin safety data from comparative studies (A8851021 and A8851022) compared to the caspofungin data within the study and compared to the safety data from the appropriate regional subject pools did not identify any new safety information.

Anaphylaxis and Infusion-Associated Reactions

These reactions are important identified risks in the RMP. A total of 24 neutropenic subjects, 48 subjects with DTI and 11 subjects with *C. krusei*, reported 43, 65 and 16 potential anaphylactic reactions respectively. A review of the details of each case returned by the search, confirmed that none of these cases actually showed events of anaphylaxis.

A total of 12 neutropenic subjects, 23 subjects with DTI and 6 subjects with *C. krusei*, reported 15, 29 and 6 potential IARs respectively. A review of the events potentially representing symptoms of IARs suggests that majority of these AEs were associated with the underlying diseases or their complications rather than reflecting true IARs. The remaining AEs that were likely due to administration of anidulafungin were mild to moderate and resolved. A head to head comparison of the frequency of these events to the ICC dataset is not possible as the timing of AE occurrence was not captured for the ICC dataset. For comparison, in the literature the rate of infusion related reactions for caspofungin was reported as 20.2%.

Hepatobiliary events

Heptobiliary disorders represent an important identified risk with administration of anidulafungin per the RMP. The MAH is closely monitoring hepatobiliary events and as part of a post approval commitment is planning on conducting a post authorisation safety study (PASS) as an additional pharmacovigilance activity for this risk (Study A8851030: A Retrospective Cohort Study of the Risk of

Severe Hepatic Injury in Hospitalised Patients Treated with Echinocandins for Candida Infections).The rate of AEs reporting Hepatobiliary disorders for the 3 populations was lower than that for the ICC dataset (20.8% of neutropenic subjects, 19.8% of subjects with DTI, and 15.8% of subjects with C. krusei, and 25.9% of subjects in the ICC dataset). No true cases of Hy's law were reported in any of the 3 populations.

Other risks

A review of cases of convulsion and potential events of QTc prolongation/Torsades de Pointes identified no new safety information.

Laboratory measurements

A head to head comparison of haematology parameters between the ICC dataset and the pooled dataset was not possible due to the differences in the abnormality criteria applied at the time of the analysis.

2.4.3. Discussion on clinical safety

No new safety information was derived from analyses in the 3 treatment groups. All AE rates are lower or similar to those reported in the ICC dataset. There are currently no known drug-drug interactions with anidulafungin, and dosage adjustment in patients with renal and/or hepatic impairment is not required. Given the increased clinical experience of anidulafungin use (from 204 patients in the original submission to 840 patients evaluated in the clinical studies up to date) section 4.8 of the SmPC is proposed to be updated. Infusion related reactions require mentioning in the SmPC, because potentially infusion related AEs occurred in 17.6%-31.6% although no true cases of anaphylaxis were reported. Hepatobiliary disorders – present in 15.8-20.8%, predominantly increase of alkaline phosphatase are subject to post-approval commitments.

Although no new safety information was obtained from subjects in different treatment groups, compared to the anidulafungin-treated subjects in Study A8851021, the subjects in the regional studies reported more SAEs (63.2% vs. 40%) and more severe AEs (60.5% vs. 46.7%) but there were less discontinuations due to AEs (15.8% vs. 26.7%) or temporary discontinuations due to AEs (2.6% vs. 6.7%). The higher rate of SAEs in the regional studies may be reflective of the higher mean APACHE II score in those studies which suggests that the patient population within the regional studies was more severely ill.

2.4.4. Conclusions on clinical safety

Based on the review of the available safety data, the CHMP agreed that no new safety concerns were noticed in the evaluated patients.

2.4.5. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. Risk management plan

No changes were made to the risk minimisation measures. Routine risk minimisation measures remain sufficient to minimise the risks of anidulafungin in the authorised indication.

No additional risk minimisation activities are considered necessary.

The elements for the public summary have updated to reflect the changes to the RMP. This is accepted.

2.6. Update of the Product information

Following the assessment of the available data, the CHMP agreed to extend the indication of Ecalta and update the section 4.1 of the Ecalta SmPC to:

Treatment of invasive candidiasis in adult patients (see sections 4.4 and 5.1).

As a consequence of this new indication, section 4.4 was updated to warn that the efficacy of Ecalta has only been evaluated in a limited number of neutropenic patients and delete the mention that patient with known *C.krusei* infection have not been studied. Sections 4.8 and 5.1 of the SmPC have been also been updated to reflect the updated efficacy and safety data in the neutropenic and non-neutropenic with deep tissue infections patients .

The Package Leaflet has been updated accordingly.

Changes were also made to the Product Information to bring it in line with the current Agency/QRD template which were reviewed and accepted by the CHMP.

3. Benefit-Risk Balance

Initially, in order to overcome possible limitations in interpretation of results due to small sample size in the comparative studies and subsequently provide justification of the extension of indication in neutropenic patients (n=46), deep tissue infections (n=108) and *C.krusei* infections (n=19), that partly overlap, the MAH pooled and submitted all available data on efficacy and safety of anidulafungin both from the two comparative studies and from four other single arm studies. The data were obtained from 2 comparative studies with caspofungin as comparator (neutropenia: 11 and 3 subjects in the anidulafungin and caspofungin arm; and deep tissue infection 26 and 13 subjects, respectively) and from 4 single arm open-label studies with 504 subjects with microbiologically confirmed invasive candidiasis, from whom 35 subjects with neutropenia. The data from the latter 4 studies had been pooled and submitted as such during the post-authorisation measure procedure (MEA 014.3), which was accepted since these studies were relatively similar in design.

Following the list of questions, the MAH discussed data from 4 regional studies (A8851011, A8851015, A8851016, A8851019), the anidulafungin registrational study (VER002-9), and Follow-Up Measure Studies A8851021 and A8851022 (excluded from the neutropenia analysis). These studies included 748 patients in the MITT population for whom 55 patients with neutropenia, subdivided as follows for the different species: *C. albicans* (N=388), *C. glabrata* (N=149), *C. parapsilosis* (N=97), *C. tropicalis* (N=95) and *C. krusei* (N=19).

Benefits

Beneficial effects

- The response rate in neutropenic patients 8/11 (72.7%) in the comparative study was similar to that in non-neutropenic patients (75.6%).
- For invasive candidiasis similar global response rates were shown as have been reported in neutropenic patients for the other two compounds of the class of echinocandins: caspofungin (50%) and micafungin (75%), which underlines the similarities in their class-specific shared mechanism of anti-fungal activity.
- The total number of included neutropenic patients in the comparative trial (n=11 in the anidulafungin arm) was similar to those in studies with other echinocandins (n=14 in caspofungin study, n=24 in micafungin study) allowing a tentative comparison demonstrating similar response rates.
- In the other non-comparative single arm studies that included 35 neutropenic patients with invasive candidiasis who received anidulafungin, the global response rate at end of intravenous treatment was 18/35 (51.4%), which supports the findings from the comparative study and is in line with results with other echinocandins.
- Overall response rate in neutropenic patients based in the updated analysis following the first round of questions was 31/55 (56%), which is numerically slightly lower but includes data from studies and with low numbers can not exclude similar responsiveness.
- Results in the neutropenic patients suggested a slightly better response for *C. glabrata*. *C. glabrata* is a frequent cause of infection in neutropenic patients, at this stage, and acknowledging the limitations of numbers of patients, these data are sufficient to recommend empiric use of anidulafungin in these patients at this stage.
- The global response rate in deep tissue infections was relative similar to that in candidemia as has been achieved with anidulafungin, which reflects adequate tissue penetration. In comparison with the other echinocandins efficacy in this type of infection was at least similar (79.1% vs. 53.4% in micafungin and 57.7% in caspofungin).
- In *C.krusei* infection, a fungal pathogen not susceptible to fluconazole, anidulafungin demonstrated similar global response rates as the overall response rate.

Uncertainty in the knowledge about the beneficial effects

- The submitted overall efficacy results by pooling data from studies with different study designs: both comparative and non-comparative studies, is not methodologically validated. Data from pooled single-arm studies is only considered supportive at most.
- Included numbers of neutropenic patients were low, therefore comparisons of efficacy in neutropenic patients between comparative studies and non-comparative single arm studies and between the other echinocandins and anidulafungin are of limited value.
- The interpretation of data was additionally compromised by the inclusion of patients without quantitative neutrophil count at baseline (18/35 neutropenic patients in the regional studies) for unknown reasons, was explained by the MAH in the response to questions. However, for 11 patients there is still no quantification of neutropenia. This should be reflected in the SmPC (see SmPC assessment, Annex I).
- Overall 149 patients infected with *C. glabrata*, a pathogen frequently unsusceptible to fluconazole, showed more or less similar response rates to *C. albicans* at different follow up times although

numerically response rate was slightly lower and mortality rate was slightly higher. Due to the absence of confidence intervals one can not conclude non-difference.

Risks

- Patients were exposed during about 14 days of anidulafungin i.v. followed by oral azoles. No new safety data from the 3 treatment groups was obtained.

Unfavourable effects

- Hepatobiliary disorders were frequent (20%). A PASS study to further investigate hepatotoxicity in echinocandins is agreed (to be submitted).
- Potential anaphylactic reaction appear frequently (~20%), although true cases of anaphylaxis did not occur.
- Treatment discontinuations occurred more frequently in neutropenic patients (18.9%) than in the ICC data base (10.3%), although most were related to underlying illness.

Uncertainty in the knowledge about the unfavourable effects

- Due to the small numbers in the comparative studies a safety benefit of anidulafungin over caspofungin could not be determined.
- Due to different study designs (comparative vs. non-comparative studies) the data from the comparative studies that only included 50 patients in the safety population, cannot be compared with data obtained in 595 subjects from open-label single arm studies.

Discussion on the Benefit-Risk Balance

The proposed extension of indication to treatment of invasive candidiasis also in neutropenic patients is supported by data from a limited number of neutropenic patients. The premature termination of the comparative study due to slow enrolment has been accepted by the CHMP (see MEA 014.3 assessment report). Furthermore, efficacy data in neutropenic patients was supported by earlier results from single arm studies. The submitted study data from this limited number of patients show similar outcomes as have been shown in non-neutropenic patients receiving anidulafungin, and as have been recorded in neutropenic patients receiving other antifungal agents within the same class. Despite the limitations, it appears that this holds for all Candida species and for neutropenic patients who are especially prone to infection with *C.glabrata*. Based on the MAH's responses of the questions raised, the currently proposed broad indication of candida treatment in all types of patients, in particular neutropenic patients, can be accepted.

The evaluation of efficacy in neutropenic patients is based on a limited number of patients and very limited comparative data. However, based on the available data, the efficacy data from non-neutropenic patients and the absence of any clear efficacy concerns in neutropenic patients, the extension of indication by not excluding neutropenic patients is acceptable.

No new safety concerns were noticed in the evaluated patients.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

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, update the safety information and reflect additional data in neutropenic patients. The Package Leaflet is updated in accordance.

Furthermore, the Product Information is being brought in line with the latest QRD template version 9.