EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2010
EMA/186797/2010
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ' Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease' (CHMP/EWP/1343/01 Rev.1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EFPIA welcomes the revision of the existing guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease. EFPIA wishes to raise the following key comments, regarding some of the concepts presented in the draft guideline. These key points are followed by other important comments presented according to the different sections of the draft guideline. In order to streamline the document, no editorial or typographical comments are provided.	
	1. The guidance states that data from one RCT (with a double blind design) is the minimum required for adequate proof of efficacy. The size and type of study obviously may vary based on the disease under evaluation (invasive aspergillosis [IA] and invasive candidiasis [IC] vs. esophageal or oropharyngeal candidiasis [EC/OPC]). Inclusion of the power and delta required for each of these diseases should be considered. Based on the relative infrequency of invasive fungal infections, a delta of 10% is too strict for most diseases. For invasive infections, a delta of 15 to 20% should be acceptable.	It is not possible to prescribe the acceptable non-inferiority margins in this guideline. These may be justifiably different between studies depending on the primary objective. A sentence has been added to direct readers to the separate CHMP guideline on this topic.
	2. The reference to rapid diagnostic tests should be clarified. The guidelines should clearly differentiate the tests and diseases to which they are referring. Clearly, PCR (or other rapid Ag tests) are not yet standardized and therefore not be acceptable. In contrast, the sandwich galactomannan ELISA for *Aspergillus* and beta glucan for *Candida* is accepted, and, is, in fact, part of the EORTC/MSG criteria for fungal infections (as long as other clinical and host criteria are also present).	The use of rapid diagnostic tests is suggested as a possibility in the guideline for the purposes of patient selection if sponsors wish to use them. It is clearly stated that the final classification of patients according to certainty of diagnosis should be based on the most recent version of the EORTC/MSG criteria. During the lifetime of this revision of the CHMP guideline the criteria may be updated further to incorporate more rapid diagnostic tests. Therefore it is

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		considered appropriate that the current version is not more specific.
	3. Much emphasis is placed on using EUCAST methodology to assess breakpoints. Although applicable for polyenes and azoles, the EUCAST breakpoints for echinocandins are not yet established, and it may take some time before such breakpoints are established for echinocandins or other new class of agents. Industry proposes that breakpoints from other institutions (e.g., CLSI) be accepted for inclusion within the SPC if the criteria are not yet established by EUCAST. There is a substantial number of laboratories in Europe that follow CLSI guidelines when performing susceptibility testing and the bulk of published in vitro susceptibility data for antifungal agents was generated using CLSI methods and interpretive criteria. We would also propose that both CLSI and EUCAST breakpoints could be included if these differ significantly?	Currently there are no breakpoints included in SmPCs for antifungal agents. The issue of potentially adding EUCAST breakpoints as currently specified resulted from a discussion at a CHMP SAG meeting. In line with the antibacterials guideline revision only EUCAST breakpoints will be included. Those laboratories in the EU that are using CLSI methods also have access to the CLSI breakpoints and therefore there is no strong justification for adding these to SmPCs.
	4. We applaud CHMP for incorporating EORTC/MSG criteria for diagnostic certainty in the Guideline. However, the inclusion of the efficacy outcome criteria from the EORTC/MSG may be somewhat premature. Although endorsed by the EORTC/MSG, many of the components and the time points outlined in this recently published document have not been validated in clinical trials. Furthermore, some of these components may result in significantly larger sample sizes or in an inability to distinguish outcome between treatment groups. For example, the inclusion of mortality in the criteria for IC outcome may not be prudent, recognizing that most patients with IC are critically ill, ICU patients in whom the risk of death due to other conditions predisposing them to being admitted to the ICU cannot be adequately treated by antifungal therapy.	Agreed. Wording has been added to indicate that alternatives may be used if these are adequately justified.

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	Some flexibility is warranted.	
	5. We also applaud the CHMP for including some mention of preemptive therapy studies using diagnostic measures within the Guidance (in lieu of or as an adjunct to empirical therapy studies). Some further details, such as outcome measurements for these studies, should be outlined. A huge de-emphasis of the empirical therapy indication is included in this Guidance. As there is no approved alternative for these patients and empirical therapy remains the standard of care, it would seem premature to downplay the value of empirical therapy at this point, until further data on other early treatment paradigms are available.	It has been clarified that the aim in pre-emptive treatment studies should be the same as that in empirical treatment studies. There has not been a huge de-emphasis of empirical therapy. What has been proposed is an indication that accurately reflects what such studies really demonstrate, which is clearly not treatment of febrile neutropenia, which is and has always been an inappropriately worded indication. Therefore no change is made. It should be noted that the position stated is comparable with that in the revision of the antibacterials guideline.
	6. Lines 328 -331: The guidance suggests that if “superiority over … a well established comparator has been shown based on one or more alternative efficacy variables provided that non-inferiority has been demonstrated based on clinical and mycological outcomes.” The guidance should really describe / clarify what the “alternative efficacy variables” could be.	A modification of the text has been made. However, it is not possible to overly specific here and it is already recommended that the matter should be discussed with EU Regulators.
	7. Lines 499 – 505: The guidance states that the primary analysis for a prophylaxis study should be the comparison of breakthrough infections. However, a secondary analysis looking at patients who are able to tolerate prophylaxis for a specified duration is allowed. If a comparator is used in a prophylaxis design that has activity against aspergillus, it may not be possible to demonstrate a significant reduction in breakthrough IFIs (unless we enroll a prohibitively large number of patients) however it may that better tolerability could be demonstrated. Therefore, could tolerability of the new agent be considered a primary variable to study in this case?	An indication for prophylactic use must be based on a demonstration of efficacy based on breakthrough infection rates.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 4.2.2 (lines 194-197):	1	Comments: Recommending an expert panel for all studies is not practical and unnecessary. An expert panel is not really required for EC/OPC trials if a favorable response requires symptom resolution and reduction in grade of visual endoscopic lesions. Well-defined grading systems for EC exist and photographic evidence of extent of disease can be obtained routinely. A similar argument against use of an expert panel for IC can be made; a favorable response requires resolution of symptoms and eradication of the infecting *Candida* pathogen. However, an expert panel is useful for diseases such as IA or other mild infections where the diagnosis and evaluation of patients are somewhat complex (allowing probable and definite disease and complete and partial response) and where consistency across all sites is essential. An expert panel may also be useful in empirical or prophylactic studies where the objective of the study is to determine the presence of breakthrough infections where complex criteria are used to confirm or deny the presence of an infection.	The current wording strongly recommends the use of such a panel. It is not an absolute demand. If the sponsor considers that use of such a panel is not needed then it should be justified in the dossier.
Section 4.2.4 (lines 366-374):	1	Comments: Three months of follow-up is recommended for all infections. Although this makes sense for IA or other mold infections, one can debate its utility in IC. Two months of follow-up is likely to be sufficient; a longer follow-up period is associated with greater risk of including patients with new infections as opposed to true relapses. For IA and other molds, longer-term	In fact the wording already allows flexibility and mentions that shorter follow-up may anyway be appropriate when treatment is commonly followed by prophylaxis. However, it is agreed that the text might mention two or three months and this change has been implemented.

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		follow-up is important because favorable responses include partial responses, and it is important to determine if relapse is more common in these patients. As for EC/OPC, it isn't clear that there is any utility for follow-up after the primary endpoint (which should be assigned as a timepoint after the drug levels reach zero). Most of the EC/OPC patients receive (or should receive) antifungal prophylaxis, since disease in chronically immunosuppressed patients is likely to recur. The utility of relapse assessments in patients who are expected to develop recurrences with time is questionable.	
Section 4.3 (lines 417-525):	1	Comments: The CHMP suggests that only proven cases of infection should be included in salvage studies. Again, this is dependent on the disease under study. The inclusion of proven cases in an IC salvage study makes sense; however, it is appropriate to include both proven and probable cases in an IA study, as the diagnosis of IA is complex and a proven diagnosis is difficult to obtain in many high-risk patients.	Accepted. An appropriate change has been made.
Section 4.5 (lines 475-510):	1	Comments: The document makes no mention for comparators in prophylaxis studies. Are placebo-controlled trials for prophylaxis possible? For instance, high-risk patients in an ICU represent a potential population in whom a prophylaxis-based study may be reasonable. A definitive benefit of prophylaxis in this setting has not been shown and, therefore, depending on the design, a placebo-controlled prophylaxis study may be appropriate.	It is agreed that there are some patient populations in which prophylactic therapy is not yet of proven benefit and is not yet in routine use. A modification of the wording has been made.