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DRAFT

GUIDELINE ON THE CLINICAL EVALUATION OF ANTIFUNGAL AGENTS FOR THE TREATMENT AND PROPHYLAXIS OF INVASIVE FUNGAL DISEASE

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This guideline replaces Points to consider on the clinical evaluation of new agents for invasive fungal infections (CHMP/EWP/1343/01).

KEYWORDS	*Invasive fungal disease (IFD), rapid diagnostic tests, proven and probable IFD combination regimens, salvage therapy, patients with febrile neutropenia, fungaemia.*

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GUIDELINE ON THE CLINICAL EVALUATION OF ANTIFUNGAL AGENTS FOR THE TREATMENT AND PROPHYLAXIS OF INVASIVE FUNGAL DISEASE

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EXECUTIVE SUMMARY

This guideline replaces the *Points to consider on the clinical evaluation of new agents for invasive fungal infections* (CHMP/EWP/1343/01), which came into operation in November 2003. It is intended to address the clinical development of antifungal agents for the treatment and prophylaxis of invasive fungal disease (IFD).

The guidance includes:

- Consideration of the non-clinical data on antifungal activity that should be generated prior to and during the clinical development programme. In addition to characterising the spectrum of in-vitro antifungal activity and investigating the mode of action and potential mechanisms of resistance it is expected that the pharmacokinetic/pharmacodynamic relationship is explored.
- Recommendations for the design of studies that evaluate antifungal agents for treatment or prophylaxis of IFD. In particular, the guidance recommends that the categorisation of IFD by certainty of diagnosis and the assignment of outcomes should be reviewed in all studies by an independent panel of experts and should follow the recommendations published by the Invasive Fungal Infections co-operative Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) of the National Institute of Allergy and Infectious Diseases (NIAID) i.e. EORTC/MSG.
- Updated or expanded sections that address the assessment of combination therapy, salvage therapy, studies in neutropenic patients and the assessment of antifungal agents for prophylaxis.
- Consideration of the potential for using biomarker data to guide enrolment of patients who are likely to have the types of IFD under study (although at present the final categorisation of certainty of diagnosis cannot be based on these tests) and to follow responses to treatment.
- With the advent of regulations that require provision of a paediatric development plan the section on studies in children and adolescents makes reference to the need for paediatric investigation plans.
- A short section on the assessment of clinical safety. Reference is made to available CHMP guidance and the need for risk management plans.
- A new section that addresses the layout and content of Sections 4.1 and 5.1 of the SPC. This includes a detailed proposal for the presentation of the mycological data and recommendations for summarising the pertinent clinical data.

The guidance cannot cover all possible scenarios of clinical development programmes for antifungal agents. Sponsors are encouraged to discuss their plans with EU regulators at intervals as experience is gained from clinical studies.

1. INTRODUCTION (BACKGROUND)

This guideline addresses the clinical development of antifungal agents for the treatment and prophylaxis of invasive fungal disease (IFD).

IFD occurs in a heterogeneous group of patients, most of whom have evidence of debilitation and/or immunosuppression. The range of clinical presentations includes disseminated disease affecting several vital organs and deep tissues as well as more localised infections (e.g. endocarditis, meningitis and infections in the lungs or sinuses). IFD may occur with or without detection of fungi in blood cultures. In some cases fungi are detected in blood cultures but no primary source of infection is identifiable despite extensive investigations. A large number of fungal genera/species may be associated with IFD in humans but the commonest belong to the genera *Candida* or *Aspergillus*.

Factors such as infection site and fungal pathogen, complexity of the underlying illness, variable degree and duration of immunosuppression and its mode of management and incidence of concomitant infections with bacteria and viruses may affect the mycological response to therapy and the overall clinical outcome. Therefore the assessment of clinical efficacy of antifungal agents in the treatment and prophylaxis of IFD is complicated. Recognition of the difficulties surrounding the design and

interpretation of clinical studies to assess the efficacy of antifungal agents led to the development of the Points to consider on the clinical evaluation of new agents for invasive fungal infections (CHMP/EWP/1343/01). This document was developed during 2001-2003 and came into operation in November 2003.

- Since the development of CHMP/EWP/1343/01 several changes in clinical practise have occurred that have implications for clinical development programmes for antifungal agents. For example:
- The availability of an increased number of antifungal agents has stimulated new interest in the potential value of combination therapy.
- There has been an increase in the routine use of antifungal prophylaxis during periods of high risk, such as profound neutropenia, especially against yeasts.
- Rapid diagnostic tests (e.g. detection of fungal cell wall constituents or the use of PCR to identify fungal DNA) are increasingly being used to help guide decisions for implementation of specific antifungal therapy. There is also increasing interest in the potential for use of such biomarkers to monitor the response to therapy.
- The Invasive Fungal Infections co-operative Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) of the National Institute of Allergy and Infectious Diseases (NIAID) have published revised definitions of IFD and a revised categorisation of treatment outcomes.

In addition, progress has been made in standardising methods for antifungal susceptibility testing and the setting of interpretative criteria (i.e. susceptibility testing breakpoints). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has published susceptibility testing methodologies for *Candida* and *Aspergillus* and has an ongoing work programme for setting breakpoints.

Therefore this guideline, which replaces the previous Points to Consider document, updates the previous advice on many issues in the light of advances in the field and changes in clinical practise.

2. SCOPE

The guideline is primarily concerned with the content of clinical development programmes to assess the safety and efficacy of antifungal agents administered by oral or parenteral routes for the treatment and prophylaxis of IFD. Oropharyngeal and oesophageal candidiasis are problematic superficial fungal infections in debilitated and immunosuppressed patients and should be considered to be within the scope of this document although they do not constitute IFD. Superficial fungal infections affecting only the skin and subcutaneous tissue, hair or nails, and infections of the mucus membranes in immunocompetent patients are not covered.

The guidance includes:

- Consideration of the non-clinical data on antifungal activity that should be generated prior to and during the clinical development programme.
- Criteria for enrolment and criteria for assessing the certainty of diagnosis.
- The assessment of clinical efficacy including the design of studies that evaluate antifungal agents for treatment or prophylaxis of IFD.
- The assessment of clinical safety.
- Reflection of the mycological and clinical data in the SPC.

There are several CHMP and ICH guidelines that are particularly relevant to the clinical development of anti-fungal agents, which should be taken into account along with this document. Among others, reference should be made to ICH Topics E 9, E 10 and E 11, the Points to consider on applications with 1. meta-analyses 2. one pivotal study (CHMP/EWP/2230/99), the Note for guidance on the investigation of drug interactions (CHMP/EWP/560/95) and the Guideline on clinical trials in small populations (CHMP/EWP/83561/2005).

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and parts I and II of the Annex I to Directive 2001/83 as amended.
Pertinent elements outlined in current and future EU and ICH guidelines, should also be taken into account.

4. CLINICAL EVALUATION

4.1 Assessment of anti-fungal activity

Before and during the clinical development programme for an antifungal agent it is expected that efforts will be made to investigate the following:

- Spectrum of in-vitro antifungal activity.
- Mode of action.
- Mechanism(s) of resistance.
- Cross-resistance within and between anti-fungal drug classes.
- Synergy or antagonism with antifungal agents of different classes.
- Efficacy in animal models.
- Pharmacokinetic/pharmacodynamic (PK/PD) relationship.

Depending on the properties of the antifungal agent it is recognised that it may not always be possible to fully document all of the above.

During the conduct of clinical studies of efficacy it is expected that:

- All fungi that are isolated and considered to be causative of IFD should be forwarded to one or more designated reference laboratories for confirmation of identity and susceptibility testing.
- Clinical and mycological outcomes should be analysed in the light of in-vitro susceptibility and patient pharmacokinetic data to further assess the PK/PD relationship.
- See also Section 4.3 regarding the following issues:
- It is recommended that at least some of the in-vitro data should be generated using susceptibility testing methodologies published by EUCAST since this will facilitate the setting of EUCAST-recommended breakpoints.
- Any available EUCAST-recommended susceptibility testing breakpoints for common Candida species and Cryptococcus species should be included in the SPC (see Section 3.8.3). If validated methods to determine breakpoints become available for other yeasts or for filamentous fungi then any available EUCAST-recommended breakpoints may also be included in the SPC.
- Susceptibility and resistance should be further assessed in the post-approval period.

4.2 Primary treatment of invasive fungal disease

4.2.1 Patient selection criteria

Sponsors may choose to enrol patients who already have proven or probable IFD (see 3.2.2 below)**.**

Alternatively, studies may enrol patients who are considered likely to have the type of IFD under investigation. In general, the likelihood of patients eventually meeting the criteria for proven or probable IFD would be expected to increase with the number of inclusion criteria that are met. Therefore, the minimum diagnostic criteria to be met for enrolment should be stated in the protocol.

Patient selection criteria may include:

- Clinical history, signs and symptoms.

- Imaging studies.
- Microscopic findings in suitable specimens.
- Rapid antigen or nucleic acid detection tests.
- Culture results from suitable specimens.
- Histological findings.

Depending on the objectives of individual studies, other criteria that may be important for determining patient eligibility may include:

- The presence (degree and prior duration) or absence of neutropenia at baseline.
- Prior IFD within a defined timeframe and/or during a previous period of neutropenia.
- Specific pre-disposing factors for IFD (e.g. HIV infection, type of immunosuppressive therapy).

If patients are enrolled before the diagnosis of IFD is confirmed then the sample size calculation should take into account the predictive value of the enrolment criteria for IFD, including the positive and negative predictive values of any rapid diagnostic tests used.

4.2.2 Categorisation of patients according to laboratory confirmation of the diagnosis

In the analyses of outcomes, patients should be categorised according to the EORTC/MSG definitions for proven, probable and possible IFD that have been derived for the purposes of clinical and epidemiological research. The most recent recommendations should be followed, applying genus/species-specific definitions as appropriate. In brief, the categories can be summarised as:

Proven IFD: requires demonstration of fungal elements in diseased tissue (based on histology or culture) for most conditions.

Probable IFD: requires host factors, clinical features and mycological evidence.

Possible IFD: requires host factors and clinical evidence of IFD but not mycological evidence.

The category of proven IFD can apply to any patient (regardless of any degree of immunosuppression) whereas the probable and possible categories apply only to immunocompromised patients.

As pointed out by EORTC/MSG there are several unanswered questions regarding the sensitivity and specificity, appropriate cut-offs and standardisation of some of the rapid diagnostic tests in use. Full details of the tests used should be provided along with any available validation data, estimates of positive and negative predictive values and a justification of the interpretative criteria applied.

In all clinical efficacy studies of antifungal agents for IFD it is strongly recommended that an expert panel (preferably independent of study personnel) that is unaware of treatment assignments should assess the certainty of diagnosis in individual patients and that the decisions of the panel should be used to derive the population included in the primary analysis of outcomes.

4.2.3 Treatment regimens

<u>Monotherapy</u>

The selection of proposed regimen(s) to be studied in confirmatory studies of clinical efficacy should be based on all the available non-clinical data, human pharmacokinetic data and exploration of the PK/PD relationship. The need for and extent of formal dose-ranging studies in patients with IFD and the possibility of conducting confirmatory studies that employ an adaptive design may be considered on a case by case basis. For example, in some instances it may be appropriate that a higher than usual (or higher than was initially approved) dose of an antifungal agent is projected to be necessary to treat certain fungi and/or IFD involving certain body sites.

Whenever possible the active comparative therapy should be restricted to a single regimen. This may be a single agent throughout or a single initial parenteral agent followed by a single oral agent. The chosen regimen should be one of the optimal available therapies for the type of IFD to be treated in an individual study. Allowing the investigators a limited choice with regard to the comparative regimen (e.g. choice of liposomal or lipid complex amphotericin preparation) may be unavoidable in some

instances. If the comparative regimen selected for a study and/or the dose regimen is/are not approved in some EU countries the applicant should provide a careful justification for the final choice.

The protocol should pre-define a minimum duration of therapy for patient evaluability and a maximum duration beyond which patients who have not met the response criteria should be considered to have failed therapy.

Combination therapy

The use of combination antifungal therapy outside of specific types of IFD (e.g. in patients with cryptococcal meningitis and those with certain deep-seated candida infections) remains controversial, especially for initial treatment. Nevertheless, results from limited clinical studies have stimulated interest in regimens such as combining an echinocandin with an azole for the treatment of aspergillosis and amphotericin with an azole for treatment of invasive candidiasis.

The choice of antifungal agents to be co-administered should take into account the in-vitro activity of the combination against target genera/species. However, the results of in-vitro combination studies (that may be expressed in various terms including synergy, addition, indifference or antagonism) may differ according to the methodologies used and cannot be relied upon to predict the clinical effect that may be obtained. Therefore, if possible, the selection of combination regimens to treat specific types of IFD should also be supported by a demonstration of benefit for co-administration over each agent given alone in an animal model.

Consideration should also be given to the potential for significant drug-drug pharmacokinetic or pharmacodynamic interactions to occur, which may preclude co-administration or may indicate a need for dose adjustment of one or both agents. An extensive evaluation of pharmacokinetics in patients and population PK and PK/PD analyses may be indicated in these circumstances.

Parenteral and oral formulations and switching

- If parenteral and oral formulations of the antifungal agent under investigation are available studies may allow for one route of administration throughout or a switch from parenteral to oral therapy (which may or may not involve a “step-down” in terms of systemic exposure) provided that pre-defined protocol-specified criteria are met.
- If the antifungal agent is for parenteral use only but a switch to an oral therapy is desirable for routine patient management a minimum duration of initial parenteral therapy should be set. The choice of oral follow-on therapy, including the selection of an agent from the same or a different class, will require careful justification.
- If the antifungal agent is for oral administration only then confirmatory studies of efficacy to support specific indications should be confined to patients who are able to tolerate oral medication and are expected to achieve potentially clinically useful systemic concentrations.
- Studies that involve parenteral to oral switching (which may apply to one or both of the test and reference therapy groups) pose additional problems for maintaining a double-blind design. If it is considered that a double-blind study is not feasible then any alternative design will require careful justification and every effort should be made to ensure that patient outcomes are assessed by persons who are unaware of the treatment assignment.

4.2.4 Issues for study design

Patient recruitment and randomisation

Since accrual rates in the low single figures of patients per centre per year are common, large numbers of study sites are usually used to complete enrolment within a reasonable timeframe. It is not uncommon that many sites ultimately enrol less than 5-10 patients each so the randomisation scheme should employ an appropriate block size. Individual sites may employ different strategies for the treatment of concomitant infections and underlying disease processes and these may change during the duration of a study. Therefore recruiting a small number of patients per centre and/or performing a study over an extended time frame have implications for the analyses of the results.

Range of IFD to be studied

For antifungal agents with limited spectra of antifungal activity *in vitro* the studies of clinical efficacy will inevitably be limited to IFD associated with specific fungal pathogens. However, even if an antifungal agent possesses a broad spectrum of antifungal activity *in vitro* it is usual that each clinical study of efficacy is confined to the treatment of IFD caused by a single genus (e.g. *Aspergillus* or *Candida*) or caused by a range of fungi that is otherwise limited (e.g. by specified yeast genera). Within each genus there may be species that are inherently resistant to an antifungal agent. The detection of these species only after enrolment and the commencement of treatment should be taken into account in the study design.

In addition, studies may be restricted to patients with IFD caused by designated fungi at specific anatomical sites (e.g. broncho-pulmonary aspergillosis) or with specific baseline characteristics (e.g. presence or absence of neutropenia at baseline). This approach reduces the heterogeneity of the patient population and IFD within each study and facilitates interpretation of the results. As described in section 3.8 the indications that may result from such studies strictly reflect the types of IFD treated and may also be qualified according to the patient population.

On occasion sponsors have chosen to enrol patients with fungaemia, usually associated only with a single genus (e.g. *Candida*), regardless of the known or unknown primary focus of infection. It is critical that in such studies every effort is made to identify underlying foci of infection. Nevertheless, it is common that a very low proportion of the patients enrolled have, or are found to have, an underlying focus of infection and in some cases the fungaemia is ascribed to an indwelling catheter. While these studies reflect a common clinical situation the results are difficult to interpret due to the heterogeneity of the patient population. Also, the removal of the suspect catheter may or may not be the critical factor in management of the fungaemia, depending on whether colonisation of the catheter resulted from an established focus of fungal infection and/or has already resulted in a new focus of infection by the time of removal.

However, the majority of patients with fungaemia in association with identifiable predisposing factors for IFD likely have an underlying focus of infection even if this has not been identified. Therefore such a study may be used to support an indication for use in IFD (e.g. invasive candidiasis). It is critically important that the proportions of the patient population that do and do not have an identified focus of infection are clearly documented. Among those with an underlying focus identified, any suggestion from the data that the antifungal agent may not perform optimally at certain body sites should be discussed along with a detailed presentation of the data from all patients who fail to respond to therapy. .

If the antifungal agent is expected to be clinically efficacious against some rarely encountered fungal genera/species a possible alternative approach would be a study that allows enrolment of patients with any documented IFD provided that the causative fungi are known or expected to be susceptible to study therapy. Nevertheless, as in studies that are restricted to the treatment of IFD due to specified fungi the majority of causative organisms will likely belong to a small number of species. Section 3.8 gives consideration to how the results of such studies and limited experience in treatment of rarely encountered species might be reflected in the SPC.

Randomised controlled studies

Monotherapy

Data from at least one randomised and double blind study that compares test and reference antifungal regimens would normally be considered necessary to demonstrate a satisfactory risk-benefit relationship for use of an agent in a specific type of IFD. The use of a randomised control group has the particular advantage that the patients would be enrolled into both treatment groups across the same study sites and within the same timeframe. Thus, all patients could be expected to undergo similar concomitant therapeutic measures (drugs and other modes of management) that might markedly affect their responses to anti-fungal therapy.

These studies should be of adequate power to demonstrate at least non-inferiority for the test versus reference regimen using an appropriate value of delta. If there is no comparative agent approved for treating a specific type of IFD or there is no comparative regimen widely held to be adequately efficacious (e.g. if the study aims to treat very rare and/or difficult to treat species) then it may be

appropriate to seek to demonstrate superiority of the test regimen versus the "best available" reference regimen.

Combination antifungal therapy

Several possible scenarios need to be considered. In the following examples it is assumed that the sponsor of the study is interested in the clinical effect of adding the "test" antifungal agent to another antifungal agent that is already approved for use against a specific type of IFD. The "test" antifungal agent may or may not have already been shown to be efficacious alone in the type of IFD under study. Possible study designs include:

- Superiority of co-administration compared to each agent administered alone. This is the preferred study design since it not only allows for an assessment of any benefit of co-administration in terms of efficacy but also facilitates the interpretation of the safety data.
- Superiority of co-administration compared to an approved monotherapy. This would be an acceptable alternative study design if there is a well-established and widely-recommended monotherapy that could be used as a comparator for a specific type of IFD.

In both the examples above it may be difficult to demonstrate superiority for co-administration with respect to standard clinical or mycological outcomes if monotherapy with the test and/or reference therapy is highly efficacious. Consideration may be given to approval of a combination regimen for which superiority over each agent administered alone or 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. It is essential that the primary and secondary efficacy variables and overall study design should be discussed with EU Regulators before the study commences.

For example, it may be appropriate to investigate any superiority for co-administration for some or all of:

- Faster clearance of fungi from the bloodstream.
- Earlier switch to oral therapy based on pre-defined criteria that must be met.
- Shorter duration of co-administration compared with a standard duration of approved monotherapy.
- Improved efficacy against specific fungal species and/or in specific types of infection.
- Better tolerability for co-administration using a lower dose of one agent.

In all the possible scenarios the pre-defined criteria for a judgement of superiority and the pre-defined margin for non-inferiority must be carefully justified in accordance with the primary endpoint(s). CHMP guidance should be consulted.

<u>Other study designs</u>

Alternative study designs may be used only in exceptional circumstances and must be very carefully justified. If well-founded estimates of the numbers of patients that might be recruited in a reasonable timeframe across a sufficient number of centres support a conclusion that an adequately powered, randomised and controlled clinical study is not feasible then an alternative study design may be considered acceptable.

It is strongly recommended that any alternative study design should still include a randomisation step because the availability of an internal control group makes the interpretation of the outcomes considerably more reliable compared to studies that do not employ randomisation. Consideration may be given to employing unbalanced randomisation as a compromise between exposing a sufficient number of patients to an investigational antifungal agent while still including an appropriate internal control group.

There may be exceptional instances in which data from one or more prospective non-comparative studies, with or without a comparison with valid external (or as a last resort historical) controls, might be considered sufficient to support an initial conditional approval for the use of an anti-fungal agent in a restricted indication. If, as a last resort, an uncontrolled study design is chosen all possible attempts

should be made to generate a precise and unbiased estimate of efficacy in a clearly defined patient population in order to facilitate the interpretation of the data.

Outcomes

The timing of the test of cure (TOC) assessments on which the primary analysis of outcomes will be based should reflect the type of IFD under study. The timing of the TOC visit should take into account any available recommendations of the EORTC/MSG, the terminal elimination half-lives of the test and reference therapies and any other factors that might affect the course of the IFD (e.g. expected recovery time from neutropenia). The final study visit (i.e. follow-up visit) should be appropriately timed to document recrudescent or new fungal infections. Patients should usually be followed up for three months post-therapy. Subject to discussions with EU Regulators, shorter durations of follow-up may be acceptable in specific types of IFD (e.g. when treatment of the acute IFD is routinely followed by long-term prophylaxis).

Outcomes should be assessed in all randomised and treated patients using the response criteria recommended by the EORTC/MSG. The clinical and mycological components of global outcomes should also be presented separately and any discrepancies should be noted and discussed.

Supplementary assessments of outcomes may be pre-defined in the protocol but these should be considered to be secondary or exploratory. For example, studies may designate serial evaluations of specific clinical criteria or laboratory biomarkers as secondary endpoints of relevance to the types of IFD under study.

If it is anticipated that the study population will include a substantial proportion of subjects infected with HIV it would be appropriate that the analyses should include an assessment of outcomes according to response to anti-retroviral therapy (i.e. maintenance of viral suppression and CD4 count). The incidence of immune reconstitution syndrome should also be described.

It is recommended that all studies (i.e. even if double blind) should include an assessment of clinical, mycological and global outcomes by a panel of experts that is independent of the study and unaware of treatment assignments. It is preferable that the primary analysis should be based on outcomes determined by such an independent panel but both the investigator-assigned and panel judgements of outcome should be presented and compared in the study report.

Outcomes should be presented for all treated patients and for all sub-populations that may be pre-defined in the protocol, including a population that is confined to patients with proven IFD. If appropriate to the patient population under study, sub-groups with proven or probable IFD and with proven, probable or possible IFD may also be derived. The selection of the primary population for analysis will depend on the primary objective of the study (see above). In all instances a full range of sensitivity analyses will be expected with a discussion of any discrepancies that may be apparent.

Advances in pharmacogenomics should be taken into account in the analyses of clinical and mycological outcomes. For example, genetic polymorphisms affecting fungal transporters or specific cytochrome P450 isoenzymes may have a marked effect on the pharmacokinetics and, hence, the clinical safety and efficacy of some antifungal agents. CHMP guidance on this issue should be consulted.

4.3 Salvage therapy in refractory cases

An anti-fungal agent that possess in-vitro activity against certain drug-resistant fungi, favourable pharmacokinetics or a good safety profile may be a suitable salvage therapy for some cases of refractory IFD (i.e. IFD that has not responded adequately to prior treatment). However, refractory IFD may reflect many factors including one or more of drug resistance, inadequate drug concentrations achieved and maintained at the site of infection or inability to continue therapy because of intolerance. Therefore, patients considered to have refractory IFD are potentially a very heterogeneous group in which the reasons for prior inadequate responses to a wide range of previous therapies may not be clearly identifiable.

As a general rule studies of clinical efficacy in refractory IFD should be conducted only after satisfactory efficacy has been shown for an antifungal agent in one or more specific types of IFD and

enrolment should be restricted by IFD type in accordance with results of previous studies. Any plan to conduct studies in refractory IFD early in the clinical development programme, to enrol a wide range of IFDs and/or to include co-administration of antifungal agents in one or both treatment arms would need careful justification and should be discussed in detail with EU regulators before initiation.

Studies of clinical efficacy in refractory IFD should enrol patients with proven IFD that has persisted or progressed despite previous antifungal therapy. Consideration should be given to stratification of patients according to the most likely reason for lack of an adequate response to previous regimens. All previous anti-fungal therapy (agents, regimens and durations) must be documented and the duration of exposure before a judgement of failure is made must be defined and justified. It is usually necessary that the protocol allows for the comparative treatment group to receive a range of antifungal agents that is deemed by investigators to be the best available for individual patients. Studies should not enrol refractory IFD cases that are considered unlikely to respond to any of the the comparative regimens allowed in the protocol.

Studies should aim to demonstrate at least non-inferiority between the investigational regimen versus comparative therapy. Exploratory analyses should compare outcomes according to the most likely reasons for inadequate responses to previous treatment. It is important to appreciate that the wording of any indication for an antifungal agent that might result from a demonstration of non-inferiority against best available therapy in refractory IFD would have to reflect the specific anti-fungal agents that the patients enrolled had previously received for their IFD.

4.4 Studies in patients with febrile neutropenia

Empirical use of antifungal agents in neutropenic patients with fever but without any definite evidence of IFD remains a common practise. Specimens obtained from febrile neutropenic patients before initiation of antifungal therapy generally lead to confirmation of an IFD in less than 5% of cases, suggesting that many patients may be treated unnecessarily. However, the initiation of an antifungal agent on suspicion of an IFD may have a beneficial prophylactic effect during periods of high risk.

In the past, studies have been conducted in which antifungal agents have been initiated in neutropenic patients with fever of specified duration and degree despite a defined period of antimicrobial therapy aimed at known or suspected non-fungal pathogens. The primary endpoint in these studies has often been composite and has included:

- Resolution of fever. However, just as fever may not reflect an ongoing IFD so resolution of fever may occur for many reasons that are not related to treatment of any infectious process.
- Outcomes of any IFD present but not documented at baseline i.e. documented only post-enrolment from baseline specimens. However, it is common that only 1-5% of patients have a confirmed pre-treatment IFD and these are variable in site and pathogen.
- Breakthrough infection rates. However, these represent a summation of failure of the antifungal agent to treat any IFD that may have been present at baseline and failure of antifungal prophylaxis i.e. the two possible roles of the antifungal agent cannot be differentiated.

As a result of the issues mentioned above, these types of studies cannot be used to assess the efficacy of an antifungal agent in the treatment of IFD in neutropenic patients with fever. In addition, an indication for *empiric therapy* is not tenable since it would wrongly imply that the antifungal agent has been shown to be (or could be expected to be) effective in the treatment of any type of IFD that may be present in febrile neutropenic patients.

However, these studies can provide a general assessment of the overall utility of an antifungal agent as part of the management of neutropenic patients with fever. If a sponsor chooses to conduct such a study it is important that the antifungal agents evaluated have suitably broad spectra of activity and have already been shown to be efficacious against several types of IFD in confirmatory studies. Studies should aim to demonstrate at least non-inferiority of an investigational antifungal regimen against a suitable comparative regimen. Nevertheless, sponsors should be aware that only a very guarded reflection of the results of a highly satisfactory study could be allowed in the SPC. Therefore, sponsors who intend to conduct such a study should seek specific advice from EU regulators.

An alternative to empirical antifungal therapy is to implement serial screening of neutropenic patients for possible IFD by means of rapid diagnostic tests and imaging techniques, leading to initiation of pre-emptive treatment regardless of the presence or absence of fever. Since rapid diagnostic tests such as those which detect fungal cell wall elements or use PCR to detect fungal DNA have high negative predictive values some centres now withhold antifungal therapy in febrile neutropenic patients with no other clinical or radiological evidence of IFD while those with positive results are investigated further and treated accordingly. There are insufficient data at present to estimate the proportions of patients that might have antifungal therapy initiated based on such criteria (although probably less than would be treated based on fever) and ultimately have a documented IFD. However, with further experience it is conceivable that sponsors might contemplate such a study, in which case it is strongly recommended that this should be discussed with EU regulators before initiation.

4.5 Prophylaxis of IFD

It is expected that studies that assess the use of an antifungal agent for prophylaxis of IFD would be conducted only after an agent has demonstrated satisfactory clinical efficacy in the treatment of several types of IFD. The general principles outlined in respect of the design of studies for the treatment of IFD are relevant to studies of prophylaxis.

At least one randomised, comparative study with sufficient statistical power to demonstrate superiority or exclude inferiority of the investigational regimen versus an appropriate active comparative regimen would be necessary in order to support the use of an anti-fungal agent for prophylaxis against IFD. If studies are conducted in highly selected patient populations it may be considered appropriate to reflect this fact in indications for prophylactic use or at least in the description of the clinical studies in Section 5.1 of the SPC.

Adequate steps should be taken to exclude patients who may already have an IFD before enrolment. It is essential that the criteria by which patients are defined as being at risk of IFD should be specified in the protocol and documented in the study report. The most common approach is to study patients who are, or are about to become, neutropenic. If sponsors choose to evaluate prophylaxis in non-neutropenic patients it is recommended that a separate study is performed. In either case it may be appropriate to plan for stratification of patients according to the perceived risk of developing an IFD at baseline.

Sponsors may propose prophylactic regimens for antifungal agents that differ from those shown to be effective in the treatment of IFD (e.g. lower total daily dose, less frequent doses of the same or a higher amount). In all instances there should be clear justification for the selected regimens that reflects PK/PD considerations and the theoretical risk for selecting out less susceptible or frankly resistant fungi. The maximum duration of prophylaxis should be stated in the protocol together with clear rules for stopping therapy (e.g. based on recovery from neutropenia).

The primary efficacy analysis should compare the incidences of any proven or probable IFD (using the EORTC/MSG definitions as in treatment studies) between treatments. Incidences of IFD should be compared during the treatment period and for a defined period after cessation of prophylaxis using data from all treated patients. The assessment time point selected for the primary analysis should reflect the patient population and the ongoing risk of infection. Pre-planned secondary analyses may be confined to sub-populations such as those compliant with a minimum duration of treatment. An analysis of time to breakthrough infection should also be included among the secondary analyses.

A further exploratory analysis should be restricted to IFD due to pathogenic fungi that are expected to be susceptible to the assigned treatments. If a study demonstrates superiority or excludes inferiority of the investigational agent versus the comparative regimen only for certain fungi it might still be appropriate to reflect this fact in the SPC provided that these fungi predominate among IFD in at-risk populations.

4.6 Studies in children and adolescents

Serious invasive fungal infections can occur at any age and a paediatric investigation plan will need to be developed. In general, factors that predispose to IFD in children are similar to those in adults and the range of fungal pathogens encountered is the same. Therefore, a demonstration of efficacy in specific circumstances in adults may be extrapolated to use in the same circumstances in children.

In accordance with ICH E 11 it is expected that suitable dose sizes and, if the novel agent is orally available, paediatric formulations will be developed. When sufficient non-clinical and adult data are available to identify a likely suitable dose range for children, studies should aim to evaluate the pharmacokinetics and safety of the novel agent in children with IFD. However, information on clinical and mycological outcomes should be collected as in studies in adults and should be subjected to exploratory analyses.

4.7 Assessment of the safety profile

The evaluation of the safety of anti-fungal agents is not straightforward due to factors such as serious underlying diseases in the majority of patients with IFD, large numbers of concomitant medications, and, in many cases, the considerable potential for clinically significant drug-drug interactions to occur. Safety data derived from comparative studies in which at least one treatment group receives the investigational antifungal agent with no other antifungal agent can help identify adverse reactions and it is essential that such data are generated during the clinical development programme.

The extent of the clinical safety database that would be required before an initial marketing authorisation might be granted must be considered on a case by case basis. The total number of patients that have been exposed is likely to be relatively small in comparison with most other new drugs. Whatever the conditions of the initial approval, supplementation of routine post-marketing safety update reports with specific studies that are designed to evaluate particular issues raised by the pre-authorisation data may be deemed necessary.

5. CONSIDERATIONS FOR THE SPC

It should be noted that the following recommendations are intended to be implemented prospectively.

5.1 Section 4.1 Indications

- In most instances individual studies with antifungal agents for the treatment of IFD are restricted to types associated with specific genera. They may also be restricted to specific infection sites. Therefore, organism-specific indications are usual and organism- and site-specific indications may be necessary.
- Indications for use in Invasive aspergillosis or Invasive candidiasis could be considered to be somewhat unsatisfactory since they imply that the antifungal agent has been demonstrated to be efficacious regardless of any known or unidentified focus of infection. However, these broad indications may be accepted subject to adequate description of the types of infection treated in the SPC. See also below and section 4.3.
- It is not considered appropriate to grant an indication for fungaemia (e.g. Candidaemia) or for catheter-related fungaemia. Patients who only have fungi obtained from blood cultures ± catheter cultures but have identifiable risk factors for invasive infections may be considered to have IFD. Therefore, use in fungaemia, including fungaemia associated with catheters, is considered to be included in terms such as Invasive aspergillosis or Invasive candidiasis. See also the section dealing with ‘Range of IFD to be studied’.
- Efficacy data relevant to some individual species within a genus may be absent (i.e. some species may be inherently resistant to an antifungal agent) or may be limited (e.g. some species may be of intermediate susceptibility or have a high rate of acquired resistance). This should be addressed by a cross-reference to Section 5.1 (e.g. Treatment of invasive aspergillosis; see section 5.1).
- Indications for the treatment of rare but important fungal pathogens should carry a cross-reference to section 5.1, where the limitations of the data should be described. The same approach should apply in any instance in which it is considered pertinent to point out the extent of experience in specific clinical settings.
- Indications for use in salvage therapy should strictly reflect the range of antifungal agents to which patients enrolled with refractory IFD had previously been exposed.

- Indications for prophylaxis should be separated from indications for treatment. If appropriate, indications for prophylaxis may be qualified by specific patient populations and specific fungi.
- If the indications are restricted to adults or to other specified age ranges this should be stated in Section 4.1 and also made clear in the dose recommendations in Section 4.2.
- If the indications are different between age groups it may be appropriate to group them under age-specific sub-headings.

5.2 Section 5.1 In-vitro anti-fungal activity

- The mycological data should precede the description of the salient clinical data in Section 5.1 of the SPC (see 4.3 below).
- A consistent approach to the presentation of the mycological data should be adopted with a layout as follows:

General properties

ATC classification

Mode of action

The section should be strictly confined to what is known about how the agent exerts its antifungal effect.

Note that if the in-vitro data suggest the possibility of antagonism between the antifungal agent and other agents and this has not been refuted by clinical efficacy data then a warning regarding the potential for this to occur should be placed in section 4.4 and the information relevant to this pharmacodynamic interaction should be placed in 4.5.

Information on any indifference or synergy observed in vitro should not be placed in the SPC unless in-vitro data are also supported by animal studies of efficacy and/or clinical data.

PK/PD relationship

This section should describe what is known about the PK/PD relationship, which may need to be considered separately for treatment and prophylaxis.

Mechanism(s) of resistance

The section should cover the known resistance mechanisms in targeted pathogens and the potential for cross-resistance to other antifungal agents in the same class and in other classes.

Breakpoints

The SPC should include any available EUCAST-recommended susceptibility test breakpoints for common Candida species and Cryptococcus species.

If in the future validated methods are derived for determining breakpoints for rare Candida species and for filamentous fungi then available EUCAST-recommended breakpoints for these organisms may also be included.

Table of susceptibility

The genera/species listed in the table should be restricted to those relevant to the indications.

Some fungal genera contain a very large number of species. The list should be restricted to those that are most common. Not all species in a single genus may be susceptible to the antifungal agent. Therefore the common species that are susceptible or resistant should be named in the appropriate category in the table.

Commonly susceptible species
[Species for which acquired resistance may be a problem – if category is deemed appropriate]
Inherently resistant organisms

Data may be very limited regarding estimates of acquired resistance, especially at the time of initial approval, in which case the table should have only two categories and any important information regarding acquired resistance for any genus or species should be highlighted in footnotes. The genera/species listed should not be qualified in the table by mention of resistance to other antifungal agents. Any activity against fungi that are resistant to one or more other antifungal agents and the expected presence/lack of cross-resistance should be covered in the section on resistance above.

The potential variability of study designs and patient populations in clinical efficacy studies with antifungal agents supports the inclusion of short descriptions of the clinical efficacy studies in the SPC (see below). Therefore it is not necessary (and it would be complex to attempt) to place asterisks against certain genera or species to denote that clinical efficacy has been demonstrated.

The table should be updated as necessary in accordance with available data on the emergence of resistance over time.

5.3 Reflecting clinical efficacy data in the SPC

- It is relevant to include some information on the clinical data that support the indications in Section 5.1 since small differences between studies in the exact patient population evaluated may have important implications for the overall demonstration of efficacy. Nevertheless, the section should be kept to a minimum. Details of clinical studies appear in the EPAR and do not belong in the SPC.
- For each indication it should be sufficient to describe the critical features of the study design in a few sentences and then mention or tabulate (but not both) the results of the primary analysis.
- Results of other analyses should only be quoted if these have had an important effect on the wording of the final indication.
- Information on any limitations of the efficacy database (such as the range of infections treated and the extent of experience in individual types of infections) may need to be mentioned if considered highly pertinent in light of the indication(s).
- For limited data against rare species the numbers treated should be given and the success rates quoted.

REFERENCES (scientific and / or legal)

1. Mukherjee PK *et al*. Combination treatment of invasive fungal infections. *Clin Microbial Reviews* 2005;18:163-194.
2. Cenca-Estrella M. Combinations of antifungal agents in therapy – what value are they? *J Antimicrob Chemother* 2004:54:858-869.
3. Baddley JW and Pappas PG. Antifungal combination therapy – clinical potential. *Drugs* 2005;65:1461-1480.
4. Johnson MD *et al*. Combination antifungal therapy. *Antimicrob Agents Chemother* 2004;48:693-715.
5. De Pauw BE and Donnelly PJ. Prophylaxis and Aspergillus – has the principle been proven? *NEJM* 2007:356:409-411.
6. Meletiadis J *et al*. Human pharmacogenomic variations and their implications for antifungal efficacy. *Clin Microbiol Reviews* 2006;19:763-787.
7. De Paiw B *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections co-operative Group and the national Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. *Clin Infect Dis* 2008;46:1813-1821.
8. Segal BH *et al*. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008;47:674-683.
9. Maertens J *et al*. Preemptive antifungal therapy: still a way to go. *Curr Opin Infect Dis* 2006;19:551-556.