Guidance for Industry

Empiric Therapy of Febrile Neutropenia — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

For questions on the content of the draft document contact Renata Albrecht, 301-827-2336.

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GUIDANCE FOR INDUSTRY[1]

Empiric Therapy of Febrile Neutropenia — Developing Antimicrobial Drugs for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials* (*General Considerations*).

This guidance for industry focuses on developing antimicrobials for the empiric therapy of febrile neutropenia.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in one location. Where appropriate, this guidance contains relevant information from several

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[1] This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobials for empiric therapy of febrile neutropenia. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);[2] *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. EMPIRIC THERAPY OF FEBRILE NEUTROPENIA

A. Regulatory synonyms

The indication of *empiric therapy in febrile neutropenic patients* was formally recognized as an indication in the 1992 *Points to Consider* document and has been granted as a labeled indication. In the past, some agents included statements in parts of their labeling stating what type of experience was submitted to the Agency to demonstrate the role of the particular antimicrobial in the treatment and management of patients who were immunocompromised, who had fever, and who had neutropenia. The information to support these statements was generally not based on adequate and well-controlled trials designed to address the role of the antimicrobial in patients with febrile neutropenia but rather were obtained from patients that were enrolled in various protocols intended for the treatment of site-specific infections.

1. Disease Definition

Fever is present, defined as an oral temperature of at least 38.0°C on at least two occasions within 24 hours, or a single oral temperature of at least 38.3°C, in the presence of neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/µL. Fever may be also be defined as a rectal temperature of 38.6°C on at least two occasions within 24 hours, or a single rectal temperature of 39°C.

Less well-defined terms, such as *fever in the immunocompromised host* or *fever in the cancer patient*, are not synonymous with the term *febrile neutropenia.*

[2] This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases.*

2. Febrile Neutropenia Categories:

a. Microbiologically defined infection (MDI) with bacteremia

This includes infection at an anatomically defined site or bacteremia alone. For review purposes, any blood culture that grows a Gram-negative organism may be regarded as evidence of bacteremia in a febrile neutropenic patient. The diagnosis of a Gram-positive bacteremia in such patients may be made if one positive culture is obtained for a normally pathogenic Gram-positive organism (e.g., *Staphylococcus aureus)*. For organisms that might represent a contaminant (e.g., *Staphylococcus epidermidis* or *Bacillus* species), at least two positive cultures, with all isolates showing the same antibiotic susceptibilities, within a 48-hour period should ordinarily be obtained for this diagnosis, or a blood culture and a catheter tip culture, obtained within a 48-hour period, positive for the same organism, with all isolates showing the same antibiotic susceptibilities.

b. MDI without bacteremia

For review purposes, this diagnosis should be based on a positive culture that either grows a pathogenic organism in a clinical setting consistent with infection at a specific anatomic site, or a culture growing a normally nonpathogenic organism (e.g., *S. epidermidis* in a clinical setting consistent with the isolate representing true infection at a specific anatomic site, rather than contamination).

c. Clinically diagnosed infection (CDI)

This diagnosis should be based on a set of clinical findings compatible with infection at a specific anatomic site, but without confirmatory microbiologic data.

d. Fever of uncertain origin (FUO)

This consists of any febrile episode that does not meet the criteria in sections a through c and is not considered noninfectious (see e., below). This is synonymous with the term *unexplained fever in the neutropenic patient*; the term *fever of unknown origin* should not be used because of the potential for confusion with the classical entity of the same name.

e. Non-infectious fever (NIF)

Fever should be present in patients who have convincing evidence of a noninfectious source of fever (e.g., deep venous thrombosis). Convincing

evidence may include pathologic or radiologic data consistent with this diagnosis or an investigator's statement that provides a clinical rationale for this diagnosis.

For purposes of classification, protocols should define the criteria used to make the diagnosis of infection at a specific anatomic site.

B. Study Considerations

If the compound has established effectiveness in at least three of the following infections (nosocomial pneumonia; complicated intra-abdominal infections; complicated urinary tract infections; complicated skin, skin structure, and soft tissue infections; acute osteomyelitis; or acute bacterial arthritis), evidence of effectiveness for this indication may be demonstrated in a statistically adequate and well-controlled multicenter trial. This trial should use rigorous prospective clinical, radiographic (as appropriate), and microbiologic entry criteria and evaluability criteria.

C. Inclusion Criteria

1. Fever

Fever should be documented by oral or rectal thermometry. Because of concerns over their sensitivity, axillary or infrared tympanic thermometry should not be used in clinical trials enrolling febrile neutropenic patients to document fever.

2. Neutropenia

Neutropenia should be documented by a manual differential count by an experienced hematology technologist. Febrile patients with an ANC greater than 500 cells/µL may be enrolled if their ANC is expected to fall below 500 cells/µL within 48 hours after the onset of fever. However, such patients will only be considered evaluable for efficacy if their ANC does in fact fall below 500 cells/µL.

3. Primary Disease

A primary disease entity known to lead to neutropenia, or recent administration of at least one chemotherapeutic agent known to consistently induce neutropenia, should be documented.

In addition, the following background information should be provided on patients to allow

full evaluation by the reviewer:

- Severity of neutropenia
- Duration of neutropenia
- Underlying disease
- Disease status (induction/relapse)
- Prior steroid therapy
- Use of hematopoietic growth factors
- Presence of indwelling catheter
- Use of prophylactic antibiotics
- History of bone marrow transplant
- Transplant type
- Location at time of initial fever (inpatient vs. outpatient)

D. Exclusion Criteria

(See also *General Considerations*.)

Specific exclusion criteria for this indication include:

1. Febrile neutropenia in the setting of human immunodeficiency virus infection, unless the study is specifically designed to address questions concerning infections in such patients

2. Neutropenia associated with syndromes that are not associated with a high risk of bacterial infection (e.g., chronic benign neutropenia)

3. Death from the underlying disease expected within 14 days or less

4. Administration of antibiotics within 72 hours of study entry. This includes prophylactic antibiotics, unless use of specific ***oral*** agents is explicitly provided for in the study protocol. For patients receiving prophylaxis, the same prophylactic regimen should be used, and patients should be stratified prior to randomization according to whether or not they are receiving prophylaxis. Use of systemic prophylactic parenteral antibiotics is strongly discouraged; protocols including such prophylactic regimens should be discussed with the division in advance.

5. Identification of a specific pathogen responsible for fever prior to study entry

E. Drugs and Dosage Regimen

Treatment should normally continue for at least 7 days after defervescence or until neutropenia has resolved. The control agent should be one approved for the indication. However, because of the limited number of approved choices, the variety of regimens described in the literature, and the evolving nature of this field, the choice of a comparator agent should be discussed with the division in advance. If oral antibiotics are to be used to complete a course of therapy, such use should be clearly explained and justified in the protocol and presented to the division.

F. Evaluation

The following set of assessments assumes that patients will ordinarily be admitted to an inpatient facility for initial management. Protocols in which patients will primarily be managed on an outpatient basis should include a complete discussion of how this will be accomplished and specifically how the patient's course will be monitored, how all necessary testing will be performed and recorded in the case report form, and how assurances will be made that the protocol is correctly implemented.

Because decisions regarding modification of the original regimen may be based solely on subtle clinical changes, double-blind assessment is recommended to minimize introduction of bias. At a minimum, any and all individuals responsible for making any treatment decisions should be blinded.

1. Entry Visit and Pretherapy Assessments

Assessment should include a history; review of systems for relevant symptoms; physical examination, including vital signs; at least two blood cultures, of which at least one was obtained from a peripheral site; cultures of other sites suspected on clinical grounds to be infected, chest radiography and other diagnostic studies designed to identify a specific site of infection. Results of all these tests should be recorded in the case report form.

2. On-Therapy Visits

On-therapy visits should normally be conducted on a daily basis for hospitalized patients. For those being managed on an outpatient basis, the schedule of planned visits and assessments should be spelled out in the protocol and presented in advance to the division.

The initial assessment of efficacy on therapy should be performed at 72 hours. This will allow sufficient time for a treatment effect to be detected, as well as for preliminary identification and susceptibility determinations of any bacterial organisms isolated from pretherapy cultures.

On-therapy assessments should include review of systems for relevant symptoms, physical

examination and vital signs, repeat blood cultures, cultures of other sites, and radiographic examinations felt to be clinically necessary due to persistent fever or other symptoms.

3. End-of-Therapy Visit

End of therapy assessments should include review of systems for relevant symptoms; physical examination and vital signs; repeat blood cultures; cultures of other sites; and radiographic examinations felt to be clinically necessary due to persistent fever or other symptoms.

4. Test-of-Cure or Post-Therapy Visit

The test-of-cure assessment should be at least seven days after completion of therapy. Post-therapy assessment should include review of systems for relevant symptoms, physical examination and vital signs, repeat blood cultures, cultures of other sites, and radiographic examinations felt to be clinically necessary due to persistent fever or other symptoms.

G. Outcome

1. Clinical Outcome

The following should be used in assessing patients; patients will be considered evaluable if all of the following apply (only the first three factors should be used to define an intent-to-treat population):

- Febrile at study entry
- Neutropenic within 48 hours of study entry
- Absence of a well-documented noninfectious cause of fever
- Original regimen administered without modification for at least 72 hours
- In cases of FUO, no addition of an antifungal, antiviral, or antiparasitic agent prior to defervescence
- No systemic antiinfective agents within 72 hours of study entry
- Absence of infection due to virus, fungus, mycobacteria, or parasites
- In cases of MDI, susceptibilities and final microbiologic outcome documented

- Final clinical outcome at post-therapy assessment available
- No discontinuation for an adverse drug reaction
- No concomitant use of antibacterial agents in the absence of failure
- No mortality due to a noninfectious cause prior to test-of-cure assessment
- Presence of all inclusion criteria/absence of all exclusion criteria

Patients who die of infection or have a change in antibacterial therapy prior to 72 hours should be considered unevaluable in the primary analysis and failures in the intent-to-treat analysis.

The primary endpoint is the clinical outcome at the end of the follow-up period. Patients can be scored as failures at any point after the initial efficacy assessment at 72 hours; a successful outcome can only be assigned at the end of the follow-up period.

- *Cure*: All signs and symptoms resolved, and cultures negative for MDIs with the initial therapy (i.e., no modification of the original empiric regimen). No recurrence of infection apparent for at least 7 days after drug discontinuation.
- *Failure*: Death attributed to infection; clinical deterioration or microbiologic failure on initial regimen; persistence of symptoms; addition of new anti-bacterial for persistent symptoms or new infection; resistant isolate.
- *Unevaluable*: Absence of any evaluability criterion.

2. Microbiological Outcome

This assessment can be made in patients where a bacterial pathogen is identified from a blood culture or other specimen obtained at the entry visit. The outcome determination of eradication or persistence would be based on whether or not the pathogen could be isolated from a repeat specimen taken from the previously positive site. The criteria for either documented eradication or persistence, or presumed eradication or persistence, would be determined by the site of infection from which the original pathogen(s) was isolated at entry.

H. Statistical Considerations

The specific definitions of clinical outcome described below for primary efficacy analyses represent composite endpoints. Therefore, applicants are *strongly* encouraged to perform secondary analyses using different component definitions of outcome, such as mortality or occurrence of new febrile episodes, as well as analyses using an intent-to-treat principle. In addition, analyses of subgroups at high risk for severe infection (e.g., patients with prolonged or severe neutropenia) should also be performed. Information sufficient to permit reviewers to determine outcomes for all individual components of the primary endpoint should be submitted as part of the NDA.

I. Labeling

As part of the approval of an agent for the empiric therapy of febrile neutropenia, the Agency may request that a description of the clinical trial performance and results be provided in the labeling to advise physicians about the particular conditions of the studies and provide information about the expected usefulness and limitations of the drug.