Guidance for Industry

Uncomplicated Gonorrhea — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

Uncomplicated Gonorrhea: Cervical, Urethral, Rectal, and/or Pharyngeal — 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 antimicrobial drugs for the treatment of uncomplicated cervical, urethral, rectal and/or pharyngeal gonorrhea.

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

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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 the development of antimicrobial drugs for the treatment of uncomplicated gonorrhea. 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.

one location. Where appropriate, this guidance contains relevant information from several 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. UNCOMPLICATED GONORRHEA — CERVICAL, URETHRAL, RECTAL, AND/OR PHARYNGEAL

A. Regulatory Synonyms

A number of synonyms have been used in the past in discussions of uncomplicated gonorrhea, including *gonorrhea*, *uncomplicated gonorrhea* or *acute uncomplicated gonorrhea*. A search of the PDR for labeling of approved products revealed that on many labels, the actual site of the infection (endocervical/cervical, urethral, rectal, pharyngeal) is specified, and there are labels in which the gender (male, female) is specifically mentioned. In addition, for most beta-lactam type antimicrobials, the labeling specifies whether approval is granted for beta-lactamase positive isolates as well as beta-lactamase negative isolates.

Uncomplicated gonorrhea is a sexually transmitted disease (STD) caused by *Neisseria gonorrhoeae.* The disease involves mucosal sites such as the urethra, rectum, and pharynx in the male, and the urethra, cervix, (endocervix), rectum, and pharynx in the female.

Note: Pelvic inflammatory disease in the female, gonococcal arthritis, and neonatal gonorrhea involving the eye are separate entities not covered in this guidance.

The primary efficacy endpoint is site specific (i.e., urethral, endocervical, rectal, pharyngeal) eradication of *Neisseria gonorrhoeae.*

B. Study Considerations

Effectiveness against this disease entity should be established in both men and women by conducting a trial involving at least 100 men and 100 women per treatment regimen.

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

Bacterial eradication rate should be the primary effectiveness endpoint, and at least 95% bacterial eradication should be expected in both genders (gonococcal cervicitis and gonococcal urethritis) to support the claim for this infection. Initial resistance of a given isolate to the investigative agent should not ordinarily make that patient nonevaluable. Patients could be stratified by the presence or absence of resistance to the pathogen and then analyzed. Such an approach may result in a restricted indication, depending on the data outcome.

When beta-lactamase production is not a factor (i.e., in non-beta-lactam antimicrobial drug products), evaluation of infections caused by beta-lactamase-producing microorganisms should not be needed. If beta-lactamase production is a factor, greater than 95% bacterial eradication should be demonstrated in a subset analysis of at least 40 patients (at least 20 men and 20 women) from these two trials to support specific wording in the INDICATIONS AND USAGE section that states the product is indicated in the treatment of uncomplicated gonococcal urethritis/cervicitis due to beta-lactamase-positive and beta-lactamase-negative strains of *Neisseria gonorrhoeae.* Without such data, the labeling should be restricted to beta-lactamase-negative *N. gonorrhoeae,* and the labeling should also have a "not first line therapy" restriction, depending on the level of beta-lactamase-positive *N. gonorrhoeae* in the country at the time of approval of the final product labeling.

Once effectiveness in uncomplicated gonococcal urethritis/cervicitis has been established, effectiveness in gonococcal pharyngitis or proctitis may be established by scanning databases from the critical studies and from similar uncomplicated gonococcal urethritis/cervicitis studies recognized by the division as adequate studies. All patients with gonococcal pharyngitis or proctitis should be pooled, and all patients with these diagnoses should be included in the analyzed data. A minimum of 20 patients each of each gender for each additional body site (i.e., rectum, pharynx) where at least 90% bacterial eradication is demonstrated should be sufficient to establish effectiveness in these additional infections. Applicants should be encouraged to study these additional body sites in both men and women; however, individual gender-specific labeling claims could be approved by the division if the above criteria are met.

- Because of the public health significance of this indication, consideration should be given to enrollment of pregnant women to study the effectiveness of a drug for the treatment of gonorrhea.

- Since many patients with gonorrhea may have other STDs concurrently (e.g., chlamydia, syphilis), it is customary and expected in clinical practice to perform cultures (or rapid diagnostic tests) and treat for these infections concurrently with another agent, usually a 7-day course of doxycycline. For purposes of clinical studies of single-dose gonorrhea therapy, however, these patients may be excluded or, if the patients are retained in the study, treatment of these other STDs should be started after the post-treatment culture specimens have been taken to assess the eradication of *Neisseria gonorrhoeae*.

C. Inclusion Criteria

Postpubertal, usually adult male and female patients are enrolled.

The primary efficacy parameter in this indication is the eradication of the pathogen, *Neisseria gonorrhoeae,* from the specific site of infection; therefore, the microbiological criteria are listed first.

To be microbiologically evaluable, the patients should have a microbiological diagnosis of gonorrhea based on the isolation of the organism from the infected site. Documentation should include the site cultured, isolation of *N. gonorrhoeae*, beta-lactamase status (when applicable) and susceptibility to both the study and control drugs. However, even if the susceptibility is unknown or the isolate is resistant to the study drug(s) in this indication, the eradication rate for all isolates without regard to susceptibility results should be performed (analyzed).

A Gram's stain of the culture specimen may be used as preliminary evidence to enroll patients in the study; however, a confirmatory culture should be done to consider a patient evaluable.

As a general rule, the urethra should be cultured in all men, urethra and rectum in all female patients. Depending on the history of sexual exposure, the rectum in males or the pharynx in either gender should be cultured. All sites cultured at the entry visit should be recultured at the post-treatment visit.

For the reasons of patient management and public health issues stated earlier, results of chlamydia and syphilis testing are important, but their absence is not a reason to disqualify a patient.

- In men, characteristic symptoms of acute urethritis are mucoid or purulent urethral discharge and dysuria (generally without urgency or frequency). In women, symptoms may include vaginal discharge, intermenstrual spotting and bleeding, urethral discharge, or dysuria (generally without urgency or frequency).

- Many women and some men have asymptomatic infections with *N. gonorrhoeae*.

- Gonococcal proctitis may be asymptomatic. If symptomatic, the patient has pruritus, tenesmus, purulent discharge and/or rectal bleeding.

- Gonococcal pharyngitis is usually asymptomatic, but in symptomatic patients, erythema and exudate may be observed.

D. Exclusion Criteria

(See *General Considerations*.)

Patients with complicated or systemic gonococcal infections such as pelvic inflammatory disease, arthritis, and endocarditis should be excluded.

Patients with other symptomatic STDs may be excluded because they may confound clinical evaluation.

E. Drugs and Dosing Regimen

The drug and dose taken should be documented. Although a minimum target efficacy rate (pathogen eradication) of 95% for uretheral and endocervical gonorrhea, and a 90% target efficacy rate for rectal and pharyngeal gonorrhea has been established, controlled clinical trials are nevertheless desirable to assess safety and efficacy of the product.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: Any drug and dose approved by the FDA for uncomplicated gonorrhea that has a 95% microbiological efficacy.

F. Evaluation

There are only two visits in the evaluation of this disease entity.

1. Entry Visit

Documentation should include date of visit, signs and symptoms identified, physical examination, including genital examination, Gram's stain (if done), culture antimicrobial susceptibility testing, and laboratory testing.

2. Post-therapy (Test-of-Cure) Visit

This visit should occur approximately 3 to 7 days after drug administration. Drugs with long half-lives should have later follow-up; this issue should have been addressed at the time of the protocol discussion with the division. Patients should have documentation of the date of the visit, site(s) cultured, culture and antimicrobial susceptibility testing results, any reexposure history, use of other antimicrobials, and clinical symptoms or signs.

G. Outcome, Including Statistical Considerations

Microbiological outcome by site of infection (e.g., urethritis, cervicitis, proctitis, pharyngitis) is the primary efficacy endpoint. In this indication, an eradication rate of 95% for urethral and cervical (90% for rectal and pharyngeal) gonorrhea should be demonstrated for all baseline pathogens for approval to be supported. Clinical outcome is important to assess resolution of clinical signs and symptoms because these are the evidence of disease that patients can identify.

While the isolation of a pathogen resistant to the study drug is typically a reason for considering a patient nonevaluable in other infectious disease studies, these patients should be included in the efficacy population in gonorrhea studies because of the public health implications of failing to eradicate *N. gonorrhoeae* in a patient.

1. Primary Efficacy End Point

   Microbiological Outcome/by Site

   - *Eradication*: Absence of the pathogen from the site-specific 3- to 7-day post-therapy culture.
   - *Persistence*: Presence of the pathogen in site-specific 3- to 7-day post-therapy culture.

2. Other Efficacy Endpoints

   a. Microbiological Outcome by Patient

   - *Eradication*: Absence of the pathogen from all the 3- to 7-day post-therapy cultures.
   - *Persistence*: Presence of the pathogen from any site at 3- to 7-day post-therapy culture.

   b. Clinical Outcome by Patient

   - *Asymptomatic*: A patient who is asymptomatic at entry and asymptomatic at follow-up (and meets all other evaluability criteria).
   - *Clinical Cure*: Patient meets above evaluability criteria and has resolution of signs and symptoms at all infected sites at the test-of-cure visit. No other antimicrobial (other than per protocol) were given.

- *Clinical Failure*: Patient who meets evaluability criteria and has persistent signs and symptoms of *N. gonorrhoeae* at one or more sites of infection, or the appearance of any new signs or symptoms. Patients who receive additional antimicrobials are also considered failures.

3. Clinical Outcome by Site

Clinical results from the urethra, endocervix, rectum, or pharynx:

- *Asymptomatic:* A patient who is asymptomatic at entry and asymptomatic at follow-up (and meets all other evaluability criteria, including a positive culture at the site).

- *Clinical Cure*: Patient meets above evaluability criteria and has resolution of signs and symptoms at the specified site at the test-of-cure visit. No other antimicrobial (other than per protocol) was given.

- *Clinical Failure*: Patient who meets evaluability criteria and has persistent signs and symptoms of *N. gonorrhoeae* at the specified site of infection, or the appearance of any new signs or symptoms. Patients who receive additional antimicrobials are also considered failures.

H. Statistical Considerations

(See Section G above.)

I. Labeling

It is the current practice to label drug products approved for the treatment of gonorrhea with the following information:

a. *Site of infection*: Urethral, cervical/endocervical, rectal, and pharyngeal.

b. *Gender:* Cervical involvement is synonymous with female patients and urethritis implies men; for rectal or pharyngeal approval, the gender of the patients in whom approval is granted is specified.

c. *Organism*: For beta-lactam drugs, the labeling specifies whether beta-lactamase positive *N. gonorrhoeae,* beta-lactamase negative isolates or both were studied and garnered approval.