A Report for the ODAC

Clinical Pharmacology and Biopharmaceutics Issues for sNDA 20-726/006 Femara

Tamofen (European formulation) tablets used in the pivotal clinical trials are bioequivalent to Nolvadex (US formulation) tablets.

I. BACKGROUND:

During the clinical trial for the new indication: first-line treatment of postmenopausal women with advanced breast cancer, the applicant requested the use of a generic tamoxifen formulation (Tamofen) as the active comparator in the pivotal studies. In section 6 of this sNDA, the applicant submitted a bioequivalence study report (Protocol 102) comparing Tamofen to the US approved formulation (Nolvadex). In addition, Study P015, P036, AR/ET1, and AR/PK1 are cross-referenced to their previous submissions. These studies address Phase 4 commitments, and the studies are not directly related to the new indication. Therefore, this report focuses on the bioequivalence study to validate the use of generic tamoxifen (Tamofen) as the active comparator in the pivotal clinical trial.

II. STUDY REPORTS:

Title:

A Single-Dose, Randomized, Open-Label, Crossover Study Comparing Generic Tamoxifen Citrate Tablets and Nolvadex® Tablets in Postmenopausal Women

Subjects: Thirty-six postmenopausal women volunteers.

Design:

- Open-label, randomized
- Single oral dose 20 mg
- Two-period
- Two-way crossover
- Washout period: 13-week

Plasma tamoxifen and the major metabolite, N-desmethyltamoxifen, concentrations were monitored to evaluate the comparative pharmacokinetics of the two formulations. The pharmacokinetic analyses were descriptive statistics for log-transformed and untransformed C_{max}, AUC_{last}, $AUC_{0-\infty}$, and $t_{1/2}$ as well as untransformed t_{max}. ANOVA (analysis of variance) was used to assess the pharmacokinetic comparisons among formulations for C_{max}, $AUC_{0-\infty}$ and AUC_{last}. The effects due to sequence, subject within sequence, period, and treatment were evaluated. Bioequivalence was concluded if the 90% confidence intervals of C_{max} and AUC for the ratio of geometric means of test and reference intervals fell within the standard bioequivalence range of 80-125%.

The criteria for evaluation for safety were physical examination, vital signs, ECG, laboratory test results and reported adverse events.

Results:

The pharmacokinetic results of the study showed that treatment with the generic tamoxifen tablet formulation (Tamofen) leads to similar plasma concentration profiles for both tamoxifen and desmethyltamoxifen, as seen with those of the US innovator formulation (Nolvadex). The statistical analysis of the pharmacokinetic parameters, C_{max} and AUC, showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range for both tamoxifen and desmethyltamoxifen as shown in the Table below.

Parameters	Compound	Ratio (B/A)	90% confidence interval	
			Lower	Upper
AUC_{inf}	Tamoxifen	95.5	90.3	101.1
C_{max}	Tamoxifen	98.3	92.8	105.1
AUC_{inf}	N-desmethyltamoxifen	95.6	88.1	103.8
C_{max}	N-desmethyltamoxifen	99.3	93.6	105.3

There were no serious adverse events reported during the conduct of this study.

III. CONCLUSION:

1. The generic tamoxifen formulation (Tamofen) and the US approved formulation (Nolvadex) are bioequivalent.
2. Since this study is critical for evaluating the clinical results, the on-site investigation is ongoing. The results will be available soon.

Briefing Document for the ODAC
Single Patient Use of Investigational Anticancer Agents

I. Introduction

At the meeting of the Oncologic Drugs Advisory Committee (ODAC) on the afternoon of December 14, 2000 we will discuss single patient use of investigational cancer drugs[1], also called single patient INDs (Investigational New Drug Application), special exception use and sometimes referred to outside of FDA as compassionate use. Single patient use generally refers to treatment use of an investigational drug for an individual patient that is not part of the overall development. Single patient use may be requested by a commercial sponsor under an existing IND or by a physician-investigator under a new IND. This is distinct from more expanded access protocols that allow access to large numbers of patients, including Treatment INDs, that allow wide use prior to marketing late in development for a drug that has demonstrated promising results in an area without satisfactory available therapies.

The primary objectives of this meeting are to:

- solicit advice from ODAC on the evaluation of requests for single patient treatment with investigational cancer drugs;
- educate the public, physicians, and ODAC on the issues surrounding access to investigational cancer drugs for single patient treatment use.

The FDA will ask experts in biomedical ethics, representatives from the pharmaceutical industry, and patient advocates to provide their perspective on the issues involved in single patient treatment with investigational therapy.

II. Investigational Use versus Treatment Use of an Investigational Drug

FDA's responsibilities for oversight for the use of investigational drugs are described in part 312 of the *Code of Federal Regulations* (21 CFR part 312—Investigational New Drug Application (IND)). Most clinical trials conducted under an IND

[1]In this document *cancer drugs* refers to drug or biologic products for treating cancer.

are designed to evaluate some aspect of the safety or effectiveness of the drug (See Appendix (i) for an overview of the cancer drug development process). The FDA strongly endorses participation in clinical trials because it is in the best interest of the patient and the American public to determine whether a drug is safe and effective for the proposed use. There are situations, however, in which it is appropriate to make an investigational drug available under an IND where the primary purpose is to treat a disease or condition rather than evaluate the drug's safety and effectiveness. Generally, the unusual step of authorizing use of an investigational drug for what is primarily a treatment purpose is warranted only for patients with serious diseases or conditions who are without satisfactory therapeutic alternatives.

Particularly when a drug is being developed to treat a serious or life-threatening condition, FDA will receive requests for individual patient treatment use throughout the development program. Thus, the amount of information about safety and effectiveness that the agency has available at the time of a treatment use request can vary considerably but is often very limited. Therefore, safeguards are needed to protect patients and to ensure that treatment use does not interfere with development of critical safety and effectiveness information.

III. Single patient treatment use of an investigational drug

Treatment use of experimental drugs can generally be grouped into two broad categories according to the number of people treated: *expanded access* and *single patient treatment.* Regardless of the category of treatment use, all applications for investigational treatment *require* an *investigator, informed consent,* a *sponsor* who accepts responsibility for the study and communicates with the FDA, a *drug supplier* (who may also be the sponsor), and oversight by an *Institutional Review Board.*

A. Expanded access protocols

Expanded access protocols outline a treatment regimen that will be used for a predefined patient group. Since the early 1970s, FDA has facilitated access to drug under investigation for serious and life-threatening diseases, including cardiovascular, antiviral, and oncology drugs to thousands of patients. Two specific types of expanded access programs are Treatment INDs and Group C.

In 1987, the agency promulgated regulations formalizing the Treatment IND mechanism that permits widespread access to an investigational drug if there is no comparable or satisfactory alternative, if the sponsor is pursuing marketing approval with due diligence, if the drug is nearing the end of its development, and if the data support the conclusion that the drug may be effective for the intended use in the intended population.

In the field of oncology, through an agreement with FDA, NCI has provided provided expanded access to approximately 20 investigation agents through a mechanism called *Group C*.

B. Single patient treatment use of investigational cancer drugs

Single patient use is a treatment use of experimental drugs for an individual patient rather than a group of patients and this can occur in one of several ways. FDA can grant a single patient exception to receive drug under an existing IND when a patient is ineligible for the specified protocol. Under a single patient exception, the existing commercial IND sponsor provides drug and is responsible for reporting to the FDA.

If the commercial sponsor is unwilling to assume responsibility for a special exception, an investigator may perform the role of sponsor for a single patient treatment use. Under this model, the investigator must obtain the drug from a willing manufacturer and must apply directly to the FDA for an IND. This application should include a completed 1571 form (http://www.fda.gov/cder/cancer/singleind.htm, an outline of the patient's history, a treatment plan, and a commitment to obtain informed consent and IRB approval.

At times, FDA has granted hundreds of such INDs per year, for instance 435 for aerosolized talc in 1996 and 515 for Thalidomide in 1998. In general, however, we believe that a single protocol covering such uses is preferable and it provides a better opportunity to obtain data useful to the drug's development.

While evaluating requests for single patient use of investigational drugs, FDA often receives telephone calls from

investigators or patients. FDA staff in the Office of Special Health Issues are available to help address patient questions. However, because the information contained in the IND is confidential, proprietary material, the FDA is limited in the information that may be communicated to the investigator or public. It is also important to remember that the process of requesting single patient use of a drug cannot begin with the FDA. The first step is for a qualified investigator to contact a manufacturer or commercial sponsor that is willing to supply the drug for this use.

IV. Legal Authority

Prior to 1997, there were no express regulatory criteria for assessing whether an individual patient should have access to an investigational drug for treatment use. The regulations described only procedures for obtaining an emergency IND for a single patient (21 CFR 312.36 permits authorization by telephone before the agency has received the IND submission) if the situation does not allow time for submission of an IND in accordance with 21 CFR 312.23 or 24.

The Food and Drug Administration Modernization Act (FDAMA) of 1997 sought to address the concern that because there were no guiding criteria there could be inconsistent or arbitrary implementation of individual treatment access. FDAMA identifies specific criteria for determining whether an individual patient should have access to an investigational drug for treatment use that, for the most part, formalize the general criteria FDA had been using to evaluate individual patient treatment use requests. FDAMA makes clear that any individual patient, acting through a licensed physician, is empowered to seek to obtain an investigational drug for treatment use. The expanded access provisions in FDAMA (Section 561) specify that an individual patient may obtain an investigational drug for treatment use when:

(1) The patient's physician determines that the patient has no comparable or satisfactory alternative therapy;

(2) FDA determines that there is sufficient evidence of safety and effectiveness to support use of the investigational drug;

(3) FDA determines that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and

(4) The sponsor or clinical investigator submits information sufficient to satisfy the IND requirements.

Sponsors and investigators must also comply with reporting IND requirements (e.g., safety reports), obtain the informed consent of the patient, and obtain IRB approval.

The stated criteria are necessarily general, and subject to some interpretation. In applying these criteria to individual patient treatment use in the oncology setting, the following questions commonly arise:

- How much evidence of anti-tumor activity or efficacy is required to support single patient use of an investigational drug? Does this depend upon the degree of observed or expected toxicity?

- How strongly should the effectiveness of standard therapy be weighed in deciding whether single patient use of an investigational drug is appropriate? What if standard therapy is moderately effective (giving an advantage in median survival) or very effective (with cure in some patients)?

Other issues, not unique to oncology, arise as single patient use increases for a particular investigational drug. These issues include:

- whether an expanded access protocol should be developed,

- whether treatment use is adversely affecting the development of the drug, and

- whether lack of evidence of efficacy in ongoing studies should lead to discontinuation of treatment use of the drug.

V. FDA's Analysis of Safety and Possible Benefit

In patients for whom no curative therapy exists, the usual practice in oncology is to approve requests for single patient treatment use that are reasonably safe with little regard for the evidence for potential benefit. The safety question can be framed as whether the drug would present an unreasonable risk compared to non-treatment in the clinical situation for which use is contemplated. The evidence for potential benefit may be only theoretical.

In patients for whom there is proven curative therapy, the safety analysis must consider the alternative therapy. Patients can be indirectly harmed by an experimental therapy that does not by itself cause injury if the experimental drug is used in lieu of a proven curative therapy. For example, if an unproven therapy is used instead of a proven curative therapy, and the unproven therapy turns out not to work, a patient could be irretrievably harmed if there disease had advanced to a point where the proven curative therapy could no longer help.

There have been two well publicized cases where FDA refused to allow patients access to an unproven cancer therapy prior to receiving the standard of care that was likely to cure the disease. There were, in addition, no clinical data to suggest a benefit from the investigational product requested. The standard of care for these two diseases was considered "CURATIVE THERAPY," a rare opportunity in cancer treatment.

As long as a curative treatment for a disease is available, and particularly where there is evidence that the unproven therapy is likely to be no more effective than a placebo, FDA believes strongly that use the unproven agent would be unethical, is unsafe and can not be permitted.

VI. Issues and examples

The following is a list of issues and examples (grouped by category) often encountered by the FDA when reviewing requests for treatment use of investigational cancer drugs.

Decision making

- Local or individual autonomy: patients, physicians and IRBs may feel that the decision about patient treatment should be theirs alone. Further, may not understand that our statue and regulations do not permit FDA to permit use of an investigational agent if we believe that the potential risks outweigh the potential benefits.

- Access to information: a patient may wish to forego or delay effective or even curative therapy to receive treatment use of a investigational drug. Statements in the news media and on websites may present overoptimistic accounts of efficacy that the FDA knows not to be supported by existing data or to be otherwise misleading.

- When to stop when the therapy is unlikely to help: A patient with metastatic cancer has failed all standard therapy and has very poor performance status, and the physician wishes to treat the patient with experimental therapy. Even proven therapy seldom has any benefit in such circumstances. Should FDA accede to the wishes of the physician?

The fate of drug development

- Unbridled treatment use of investigational drugs may interfere with enrollment in clinical trials to evaluate the safety and effectiveness of new drugs. Sponsors and FDA may be concerned that patients may refuse to enroll in a randomized trial designed to compare standard treatment to experimental treatment if the experimental treatment is available outside of trials.

- Sponsors may not have sufficient drug supply to support widespread treatment use.

- Meaningful data collection is difficult in the context of single patient use of investigational therapy.

- Sponsors may worry that adverse events from treatment use reported in patients who have a poor performance will have an adverse impact on drug development.

Draft Questions for ODAC
Single Patient Treatment Use of Investigational Drugs

As discussed in the briefing document, the FDA strongly endorses participation in clinical trials because it is in the best interest of the patient and the American public. Individual patients benefit by receiving the best available treatment and the American public benefits by sound development of new therapies. However, sometimes patients are ineligible for clinical trials or are unable or unwilling to participate.

The FDA is seeking advice from the committee to help FDA in its role of assessing the risk to benefit ratio of treatment use with an experimental drug in an individual patient.

When determining the apparent risk to benefit ratio, the following are important considerations:

- How thoroughly has the drug been studied in humans?[2]
- What do the preliminary results from these studies suggest about the safety and efficacy (or activity) of the drug?
- What are the other therapeutic options available to the patient?

At any stage of development, evidence from ongoing trials may suggest that the drug is effective or ineffective, or that it is toxic or non-toxic.

The appropriateness of treatment use of experimental therapy also depends upon the patient's medical history, especially whether the patient has already received standard therapy. The following are scenarios that FDA may encounter. They are listed

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[2] For the purpose of our discussion, the degree to which a drug has been studied may be categorized as follows:

0: The drug has not yet been tested in humans.

1: The drug has been tested in Phase 1 studies to evaluate toxicity.

2: The drug has been tested in Phase 2 studies to evaluate whether it can reduce tumor size in some patients.

3: The drug has been tested in Phase 3 studies and we have some knowledge about whether it affects survival or other endpoints indicating clinical benefit.

according to the benefit available from standard therapy in the particular clinical situation.

Questions

The following are draft questions. The final questions may change as we explore other question formats to guide discussion of these multi-dimensional issues.

1. **For each of the following clinical scenarios describing standard therapy, please discuss the following question:**

   FDA receives a request from an investigator to use Drug X under a single patient IND. The commercial sponsor (manufacturer) of drug X has granted permission for the investigator to use the drug and also has provided written permission for FDA to refer to the commercial IND. The patient's medical history is outlined in each of the scenarios below.

   The investigator states that the patient is aware of the benefits of standard therapy but wants to receive investigational treatment with Drug X instead. The patient is ineligible or unable to participate in a clinical trial using Drug X.

   When would single patient treatment with Drug X be appropriate?

   In your discussion consider:

   - The drug's **stage of development** (0-3 above), and
   - The **level of efficacy and toxicity** of Drug X that would be acceptable in the following standard therapy cases.

Standard Therapy Cases

A. There is no standard therapy available.

EXAMPLE:
A patient with metastatic nonsmall cell lung cancer has received all available therapy.

B. Available treatment shows a marginal survival benefit.

EXAMPLE:
A patient has metastatic nonsmall cell lung cancer. Standard chemotherapy produces a 1-2 month median survival benefit and produces moderate toxicity.

C. Standard therapy provides a substantial prolongation of median survival.

EXAMPLE:
A patient has advanced ovarian cancer. Standard chemotherapy produces a 1 to 2 year median survival benefit but is generally not curative.

D. Standard therapy provides a substantial rate of cure.

EXAMPLE:
A 40 year old patient with acute leukemia does not want to receive chemotherapy that is associated with a 40-50% rate of cure with substantial acute toxicity but that produces few lasting toxic effects.

E. Available therapy provides cure in most patients, but treatment involves permanent morbidity.

EXAMPLE:
A 60 year old man has recurrent superficial bladder cancer that has recurred despite treatment with all available intravesical chemotherapy agents. Recently, a muscle-invading bladder tumor (Stage T2) was removed during cystoscopy. Cystectomy (surgical removal of the bladder) is standard therapy and is associated with a high cure rate. The patient does not want to undergo cystectomy despite counseling about various surgical techniques that can be used to provide a substitute for the urinary bladder after it is removed. He also refuses radiation therapy.

2. As noted above, FDA strongly endorses participation in clinical trials. Patients should first consider entering a clinical trial before pursuing treatment under a single patient IND. If a patient is eligible and able to receive drug X as part of a clinical trial but is unwilling to do so, should that patient be allowed to receive drug X under a single patient IND?

3. If FDA has sufficient evidence to conclude that a drug is ineffective for treatment of a particular cancer, discuss under what circumstances, if any, single patient treatment use should be permitted.

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[1]In this document *cancer drugs* refers to drug or biologic products for treating cancer.
[4]A marketing application for a drug is a New Drug Application (NDA) and for a Biologic product is a Biologics License Applications (BLA).

Appendix i.

Overview of Cancer Drug Development

The responsibilities of the FDA and of sponsors of investigational drug applications are outlined in the *Code of Federal Regulations (CFR)* 21 part 312.

Any use of an investigational drug that is not marketed must be done under an *IND*. The CFR defines *IND* as Notice of Claimed Investigational Exemption for a New Drug. The IND provides permission to use an investigational drug according to a plan (a protocol) filed with the FDA.

- The *sponsor* of an IND initiates and assumes responsibility for the clinical investigation. The sponsor may be a pharmaceutical company, but individuals or academic institutions may also serve as IND sponsors.

- The *investigator* is the individual that actually performs the trial. The regulations stipulate that a sponsor shall "select only investigators qualified by training and experience as appropriate experts to investigate the drug." In most cases we expect the investigator to be a licensed physician and have training and experience in treating cancer.

Single patient use of investigational cancer drugs outside of a clinical trial may be requested at any time during drug development. The stage of drug development, which is related to the amount of knowledge we have about a drug's effectiveness or safety, is an important consideration when evaluating such a request for single patient use of an investigational drug. The following is a brief overview of the traditional drug-development process for cancer drugs.

The formal role of the FDA begins with receiving the IND submission. Prior to submitting the IND, the sponsor analyzes the drug's main physical and chemical properties and studies its pharamacologic and toxic effects in pre-clinical studies. Sponsors are encouraged to meet with FDA at pre-IND meetings. These meeting assure that the FDA and sponsor agree upon the proper preclinical tests prior to submission of the IND.

The sponsor subsequently files an IND. Among other things, this application describes the drug's identity, the manufacturing process, and the toxic effects of the drug in preclinical

studies. The *clinical protocol*, a carefully written clinical plan that describes how the drug will be studied in humans, must also be submitted with the IND. In the IND submission, the sponsor must provide data from preclinical tests supporting a safe starting dose and administration schedule.

After the IND is submitted, a team of FDA reviewers has 30 days to determine whether the IND can proceed. The FDA review team includes PhD chemists who evaluate the drug's chemistry and manufacturing, PhD toxicologists who evaluate the drug's toxic effects in animals, and oncologists who evaluate the clinical protocol. The research proposal must be approved by an Institutional Review Board. Finally, patients must be informed of the risks and potential benefits of the study.

The IND process, i.e., the time it takes to fully test the drug's safety and effectiveness, generally lasts several years while the sponsor conducts trials in different diseases. The earliest clinical study is a Phase 1 study. In oncology, these are usually small trials to evaluate toxicity at a range of doses. Subsequently, the sponsor may perform Phase 2 studies, preliminary investigations of drug activity at a selected dose. Traditionally, in oncology, Phase 2 studies are single-arm trials to see whether the drug can cause tumor size reduction, but, especially if tumor shrinkage is not anticipated, studies may be concurrently controlled trials. For diseases where the drug shows evidence of antitumor activity, the sponsor then designs larger randomized trials (Phase 3 trials) that usually compare the drug's effect to a standard therapy, if it exists. The objective of these studies is to demonstrate whether the drug produces clinical benefit, such as improvement in survival or improvement in disease-related symptoms.

Finally, if studies suggest that a drug is efficacious, these studies and the data that support them are submitted to the FDA in a marketing application[5]. Depending upon the priority of the application, FDA has 6 or 10 months to review and act on the marketing application.

Marketing applications are large applications that contain all the information learned about the drug during IND investigations. The application includes chemistry and

[5] A marketing application for a drug is a New Drug Application (NDA) and for a Biologic product is a Biologics License Applications (BLA).

manufacturing data, animal data, and human clinical trials data. A larger team of FDA reviewers evaluates a sample of these applications. In addition, a field team evaluates the investigational sites where the clinical data were generated to assure the validity of the submitted data. The results of the FDA review of the data submitted in the marketing application are often presented to an advisory committee. Based upon the results of FDA review of the data and on advice from the advisory committee, FDA renders a decision: an Approval Letter, an Approvable Letter, or a Non-Approval letter. If the drug is approved, the sponsor may distribute and market the drug for the approved indication.

Appendix ii

National Cancer Institute's Treatment Referral Center and Non-Research (Compassionate) Use of Investigational Anticancer Agents. Am. J. Health-Syst. Pharm. 55:651-660, 1998.

Appendix iii Excerpt from IND Regulations

TITLE 21—CFR Part 312

Sec. 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in Sec. 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.