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April 3, 2003

**VIA FEDERAL EXPRESS**

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 01P-0470 -- Citizen Petition To Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products

Dear Sir or Madam:

Enclosed for filing in this docket is a request for a meeting that we have submitted with respect this matter.

Respectfully submitted,

Donald O. Beers

Enclosure

cc: Gary J. Buehler

01P0470

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March 3, 2003

VIA FEDERAL EXPRESS

Mr. Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
United States Food and Drug Administration
Metro Park North 2 (Room 286)
7500 Standish Place
Rockville, MD 20855

Re: ANDAs for Generic Versions of Catapres-TTS®

Dear Mr. Buehler:

As you know, we have submitted a citizen petition on behalf of Boehringer Ingelheim Pharmaceuticals, Inc., which markets the Catapres-TTS system. That petition addresses a number of issues with respect to the standards for approval of generic versions of the Catapres-TTS system. One issue that Boehringer believes would benefit from scientific discussion relates to the difference between the design of products covered by pending applications and that of the innovator product. I am writing now to ask for a meeting of scientific experts, from FDA and from Boehringer, to address this issue and our proposed solution to it.

The Catapres-TTS system has, as an integral part of its drug delivery system, an internal rate-controlling membrane. Our understanding, based on the information provided in connection with paragraph IV notices, is that two products covered by pending ANDAs do not contain such a rate-controlling membrane. (The patent covering Catapres-TTS expires on May 4, 2003, so there may be additional ANDA applicants of which we are unaware because they have made paragraph III certifications with respect to that patent. To the extent that the products covered by any such applications have in fact duplicated the design and rate-controlling membrane of Catapres-TTS, then this issue would not apply to them.)

Boehringer is well aware that the skin itself is a rate-limiting barrier that limits the permeation of drug from a transdermal patch. The Catapres-TTS system was designed with an internal rate-controlling membrane, however, because of the understanding that there is significant variation in skin permeability among patients. Thus, while a generic

product might be shown to be bioequivalent to Catapres-TTS in a bioequivalence test utilizing subjects with average skin permeability, those patients with relatively high skin permeability would be put at risk from a patch that does not have an effective internal rate-limiting mechanism.

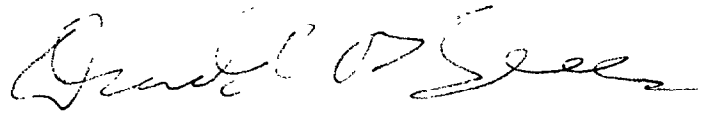
As you know, clonidine is a potent drug and has been identified by FDA as a drug with a narrow therapeutic ratio. Boehringer feels strongly that the potential approval of generic versions of Catapres-TTS that lack an internal rate-controlling membrane would create a public health problem and put some patients at risk. As a matter of law, it is the generic applicant, not the innovator, that has the responsibility to resolve scientific issues of this type. Boehringer has, however, itself commissioned the design of a study that would resolve, one way or the other, the scientific issue Boehringer has raised. We enclose a summary of such a study. Boehringer cannot, of course, perform this study, as it does not have samples of the generic products at issue. The generic companies, if they think that their products would adequately protect patients with high skin permeability, could perform such a test.

We have been communicating with FDA on this issue through the means of a citizen petition. Whatever virtues the petition process may have in other contexts, the submission of written statements in the petition file does not allow for an easy exchange of scientific views. We would like, therefore, to ask that you set up a meeting with the FDA's experts at which the experts advising Boehringer could lay out their concerns and discuss the enclosed test protocol. Specifically, Boehringer would invite Dr. Howard Maibach and Dr. Harold Hopfenberg to present their views at such a meeting. We ask that the meeting involve experts not only from the Office of Generic Drugs but also from the Cardio-Renal Drug Products Division, which was responsible for the initial approval of Catapres-TTS, and the Dermatologic and Dental Drug Products Division, which has special experience with issues involving skin permeability.

If there is a way to address Boehringer's concerns on a scientific basis – and we are prepared to discuss all options in that regard – we believe that would be preferable for all involved. While an in-house Boehringer attorney and I would expect to attend this meeting, this would be in no sense a legal meeting and our roles will be limited. We had earlier offered to meet with Dan Troy to discuss the legal issues involved, but he suggests that, with respect to the proposed study, we should request a scientist-to-scientist meeting. We would, of course, have no objection to having Mr. Troy, or another representative of his office, attend the meeting we are requesting.

We enclose a proposed agenda for the meeting. Please let me know when such a meeting can be scheduled. Ideally, from our standpoint, we would like to schedule the meeting for a Monday or possibly a Tuesday, as that makes it easier for Dr. Maibach to travel from the West Coast. Any supporting documentation in addition to the enclosed protocol will be provided at least two weeks in advance of the meeting.

Sincerely,



Donald O. Beers

Enclosures

cc: Douglas Throckmorton, M.D.
Jonathan Wilkin, M.D.
Daniel Troy, Esq.

**Proposed Meeting Agenda: ANDAs for Generic Versions of Catapres-TTS®**

Meeting Date: TBD Location: TBD Time: TBD

External participants:

Representatives of Boehringer Ingelheim, including Thomas MacGregor, Ph.D., Steve Marlin,Ph.D., Martin Kaplan, M.D., and Randall Zakreski, Esq.
Howard Maibach, M.D. (University of California Department of Dermatology)
Harold Hopfenberg, Ph.D. (North Carolina State University)
Don Beers, Esq. (Arnold & Porter)

Meeting Chair, (FDA): TBD Sponsor lead: Dr. Steve Marlin

Introductions:

Meeting Objective(s):

1. To seek to resolve on a scientific basis Boehringer Ingelheim's concern about potential generic versions of Catapres-TTS that lack internal rate-limiting barriers
   - to explain clearly Boehringer's concerns
   - to respond to any questions FDA experts have about Boehringer's concerns

2. To present a proposed study that would resolve the Boehringer concerns on a scientific basis
   - to obtain feedback from FDA experts on the proposed study
   - to discuss whether there is a mechanism to resolve this issue on a scientific basis

Meeting Discussion Items:

| | Name of Presenter | Discussion Item | Time Allocated |
|---|---|---|---|
| 1. | Harold Hopfenberg, Ph.D | Catapres-TTS design | 15 minutes |
| 2. | Howard Maibach, M.D. | Variability of skin permeability | 15 minutes |
| 3. | Howard Maibach, M.D. | Proposed study to resolve concerns about generic products lacking an internal rate-limiting barrier | 15 minutes |
| 4. | All participants | Mechanism for resolving this issue on a scientific basis | 15 minutes |

Summarize Agreed-upon Points/Unresolved issues

Discuss any necessary follow-up

Close meeting

**Clonidine Transdermal**
**Bioequivalence Study**

Title

Comparative human bioequivalence of clonidine from Catapres–TTS and generic transdermal products in a patient population including patients with high permeability skin

Protocol Number

(To be assigned)

Investigative Products

Catapres–TTS-2
Generic version

Trial Rationale

To compare relative bioavailability of clonidine from Catapres-TTS-2 and a generic transdermal patch designed to deliver the equivalent amount of clonidine. This will be done as a crossover comparison of plasma and urinary clonidine, as well as the amount of clonidine remaining in the patch. It will be done in a blind fashion in that the analytical data will be processed by people who do not know what product was used by a particular subject, or the relative skin permeability of the subject.

An objective of the study is to determine whether the test and reference patch are bioequivalent in a patient population that would include patients with high skin permeability. To do so requires screening the potential subjects to ensure that such patients are in the study population.

The basic principle in separating a human population into subjects with greater or lesser skin permeability is based upon the observations of Rougier, et al. that there is a direct correlation between permeability and water coming from the skin (transepidermal water loss, or TEWL). This correlation holds true in man, and is relevant regardless of anatomic site studied, gender, or age.

Although numerous instruments exist for measuring TEWL, the most facile is the evaporimeter. This commercially available instrument measures TEWL in terms of water/hour by measuring the difference in water vapor between two sensors placed on the skin. Experience in measuring TEWL is described in *Bioengineering of the Skin: Water and the Stratum Corneum*, edited by Peter Elsner, et al. CRC Press (1994).

The study will be conducted in two parts. The first part is to screen the potential study population and stratify the potential subjects by permeability, as determined by TEWL score. The second part is to conduct a comparative bioavailability test in patients, including those with higher permeability. To maintain objectivity, the analytical laboratory will not be aware of which quartile the subject was in or which product was used by the subject.

Objective

Primary: Comparative bioequivalence in a population including higher permeability subjects

Secondary: General tolerability of systems and drug

Trial Design

Permeability Screening

- Measure TEWL in healthy, normotensive male and female subjects (N = 100). The laboratory should take three measurements within 1 hour.
- Calculate the average of the 3 readings for each subject.
- Separate the subjects into quartiles based on their average TEWL readings.

Bioequivalence

- This is an open label, randomized crossover study.
- Healthy, normotensive male and female subjects (N = 30) will be randomized and selected with the same number of subjects from each of the highest and lowest quartiles determined in the permeability screening
- Each subject will wear a single Catapres-TTS-2 or generic equivalent (as randomly determined) for seven (7) days followed by a seven (7) day washout period. Each subject will then wear the alternate patch for seven (7) days.
- To determine bioequivalence, blood samples and total urine are collected for clonidine determination over days 1 through 10 and 15 through 24.
- Blood and urine samples and used transdermal systems are sent to an analytical laboratory as specified by the sponsor. Subjects will report to the clinic at 0900 for each visit. Pre-dose blood samples and pre-dose urine samples are collected prior to patch application. The subject is observed for patch adhesion and tolerance for 3 hours prior to release from the clinic. No dietary restriction or activity restriction are imposed. Urine containers with instructions are given to each subject.
- The subject returns to the clinic on a daily basis (days 1-10 and 15-24) for blood sample collection, return of the urine container, and receipt of a new urine container.
- Blood pressure will be monitored throughout the study.

End Points

- Clonidine plasma concentrations: AUC (9-day concentration curve), steady state plasma concentrations over days 4-6
- Total unchanged clonidine amount excreted in the urine over 10 days
- Residual clonidine amount in the patch after wear

Statistics

- Calculate means for the results for each end point for the low permeability group for the test product (Test-low), the high permeability group for the test product (Test-high), the low permeability group for Catapres-TTS-2 (Reference-low), and the high permeability group for Catapres-TTS-2 (Reference-high).
- The analysis will be done to test the equivalence of the results for the following groups:
  - Test-low versus Reference-low
  - Test-high versus Reference-high
  - Test-high versus Test-low
  - Reference-high versus Reference-low
- For each assessment, bioequivalence should be considered demonstrated if the 90% confidence interval for the primary variable ratio (first to second parameter in the groups above) is wholly contained in the interval 0.80-1.20 (or 0.80-1.25 for log transformed data) and the point estimate for each variable ratio is within 0.90-1.10.

Inclusion and Exclusion Criteria

Inclusion

- Male or female subjects 18 years of age and older providing consent.
- If female and of childbearing potential, use of reliable contraceptive (e.g., sterilized, oral contraceptive, IUD), and negative pregnancy test within 1 week of active participation with the patch.
- Healthy as determined by medical history.

Exclusion

- Any subject not capable of understanding and following the protocol.
- Any subject not capable of understanding and signing the informed consent.
- Any subject with a history of active dermatologic disease within the prior 6 months.
- Any subject with active dermatologic disease (by physical examination) other than levi, dandruff, actinic keratosis or lentigines.
- Any subject with systemic disease (by history or chosen testing).
- Any subject with any of the following:
  - Sitting blood pressure less than 100 mmHg
  - Sitting diastolic blood pressure less than 60 mmHg
  - Pulse less than 55 beats per minute
  - Examination of history shows clinically significant abnormalities in electrocardiogram, blood or urine chemistries.
- Any subject with a history of hypersensitivity or tolerance to clonidine.

Regimen of Treatment and Data Collection

- Day 1 (0900)
  - Pre-dose blood and urine samples collected
  - Transdermal product (randomly selected) applied
  - Subject observed for 3 hours, then released
- Days 2-10
  - Subject returns each day to clinic for blood sampling, to return urine collector and to get a new urine collector (on day 8, the patch is removed and saved for residual clonidine testing)
- Days 11-14
  - No testing activity
- Day 15 (0900)
  - Pre-dose blood and urine sample collected
  - Other transdermal product applied
  - Subject observed for 3 hours, then released
- Days 16-24
  - Subject returns each day to clinic for blood sampling, to return urine collector and to get a new urine collector (on day 22, the patch is removed and saved for residual clonidine testing)
- Day 25
  - Subject is released from study

Principal Investigator

Associates and Assistants

Study Site

Department of Dermatology
University of California
San Francisco, CA 94143