CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-429

OTHER REVIEW(S)

30 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

OTC Drug Labeling Review
2nd Addendum

Office of Nonprescription Drug Products
Center for Drug Evaluation and Research • Food and Drug Administration

RE-SUBMISSION DATE: May 22, 2009

REVIEW DATE: June 12, 2009

NDA: 22-429

SUBMISSION TYPE: BL 000

SPONSOR/CONTACT: Dana S. Toops, Executive Director
Banner Pharmacaps Inc.
4125 Premier Drive, High Point, NC 27265

DRUG PRODUCT (BRAND NAME): Cetirizine HCL Capsules, 5 mg and 10 mg

ACTIVE INGREDIENT(S) [ESTABLISHED NAME(S)]: Cetirizine HCL

PHARMACOLOGICAL CATEGORY: Antihistamine

LABELING SUBMITTED (SKU)
The following labels are the basis for regulatory action:

1. 5 and 10 mg ALLERGY: - 20 and 200-count carton and container labels
2. 5 and 10 mg Hives Relief: - 20 and 200-count carton and container labels

PROJECT MANAGER: Janice Adams-King, RN

REVIEWER'S NAME: Ayana K. Rowley, Pharm.D

BACKGROUND

On May 19, 2009, the agency sent a letter to the sponsor giving them a preliminary notice of labeling issues identified during the review cycle. The sponsor responded on May 22, 2009 by re-submitting a labeling amendment with the revised labels.

REVIEWER'S COMMENT

Only the "Cetirizine Hydrochloride Capsules, 5 or 10 mg" labels are the basis for this review and regulatory action:

I. Carton Label
   a. Principal Display Panel (PDP)
      i. For the "Hives Relief" products - the sponsor is using upper case for the first word (i.e., "Hives Relief") in all packaging sizes. **This is acceptable.**
      ii. For the "ALLERGY" products - the sponsor is using all upper case (i.e., "ALLERGY") in all packaging sizes. **This is acceptable.**
      iii. For both "Hives Relief" and "ALLERGY" products – the sponsor is using different color schemes to distinguish the potency (i.e. 5 mg and 10 mg) of different strengths as recommended. **This is acceptable.**

II. Drug Facts Panel
   a. The sponsor is requesting an exemption from the required Drug Facts format information in accordance to 21 CFR 201.66(d)(4) for the 20 count SKUs for both product lines and strengths. Reference is being made to 21 CFR 201.66 (d)(10)(iv) which states that bulleted statements can appear on the same line as a heading or subheading, except for the "Warning heading", if the required information appears to be more than 60 % of the total surface area. The area percentage utilized by the current text is 65%. **This is acceptable.**

   b. The sponsor acknowledges the Agency's recommendation to include the days of the week and times of the day on all the carton labels. However, at this time the sponsor does not wish to include the recommendation. **This is acceptable because including the days of the week and times of the day is a recommendation, not a requirement, according to the CFR 201.66(c)(9).**

RECOMMENDATIONS

1. An approved letter can be issued to the sponsor for the Cetirizine Hydrochloride Capsules, 5 mg and 10 mg liquid filled capsules for the 20 and 200 count SKUs indicated for "ALLERGY" and for "Hives Relief". Request final printed carton and container labels identical to the draft carton and container labels submitted on 5/20/09 for both "Hives Relief" and "ALLERGY" 5 and 10 mg, when available.

2. Inform the sponsor that the "New" flag should be removed from the carton label 180 days following approval.

Ayana K. Rowley, Pharm.D.
Reviewer's name

Marina Chang R.Ph.
Team Leader concurrence

16 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Ayana Rowley
6/23/2009 11:46:12 AM
PHARMACIST

Marina Chang
6/23/2009 12:48:32 PM
INTERDISCIPLINARY

OTC Drug Labeling Review

Office of Nonprescription Drug Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE: September 26, 2008 and April 14, 2009

REVIEW DATE: April 20, 2009

NDA: 22-429

SUBMISSION TYPE: BL 000

SPONSOR/CONTACT: Dana S. Toops, Executive Director
Banner Pharmacaps Inc.
4125 Premier Drive, High Point, NC 27265

DRUG PRODUCT (BRAND NAME): Cetirizine HCL Capsules, 5 mg and 10 mg

ACTIVE INGREDIENT(S) [ESTABLISHED NAME(S)]: Cetirizine HCL

PHARMACOLOGICAL CATEGORY: Antihistamine

LABELING SUBMITTED (SKU)
The following labels are the basis for regulatory action:

1. Cetirizine 5 mg (Allergy) 20 and 200-count carton and container labels
2. Cetirizine 10 mg (Allergy) 20 and 200-count carton and container labels
3. Cetirizine 5 mg (Hives Relief) 20 and 200-count carton and container labels
4. Cetirizine 10 mg (Hives Relief) 20 and 200-count carton and container labels

The following labels are for review and comment only:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

b(4)

PROJECT MANAGER: Janice Adams-King, RN

REVIEWER'S NAME: Ayana K. Rowley, Pharm.D

BACKGROUND

In this submission, the sponsor seeks approval of cetirizine 5 mg and 10 mg liquid filled capsules for the 20 and 200 count SKUs indicated for "Allergy" and for "Hives Relief". The sponsor has requested that the established name will be used in place of a trade name and has submitted generic carton and container labels. These labels will be the sponsor's primary labeling for each count (20 and 200 count), strength (5 mg and 10 mg) and indication ("Allergy" or "Hives Relief").

In the mid-cycle review, an information request letter (dated February 9, 2009) was sent to the sponsor requesting minor editorial adjustments to the initially submitted labels. The following changes occurred:

1. Removal of [redacted] subheading on the principal display panel for the "Hives Relief" 5 mg (20- and 200- count) and 10 mg (20- and 200- count) carton labels. b(4)
2. Font specifications were added to the draft carton label for the 10 mg "Hives Relief" (20-count).
3. Recertification of draft carton labels for the 200-count 5 and 10 mg "Allergy" and "Hives Relief" since the font size for the labeled text seemed smaller than indicated.
4. A telephone number was provided under the subheading "Questions or comments" as in accordance with 21 CFR 201.66 (c)(9).
5. The removal of the title '[redacted]' on the draft immediate container labels for the 5 mg and 10 mg (20- count "Allergy" bottle labels) and the 5 mg and 10 mg (200-count "Hives Relief" bottle labels) because [redacted]' labeling is not required on the immediate container if there is an outer carton that bears the "Drug Facts" label. It the sponsor wishes to include a '[redacted]' title on the container label, then, the entire [redacted] must be included in accordance with 21 CFR 201.66. b(4) b(4)

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REVIEWER'S COMMENT

Primary Cetirizine Labels as the basis for regulatory action:

Of note, drug products in the same therapeutic drug class with the same active ingredient are currently available OTC (this NDA includes a new dosage form). The Drug Facts label is the same as the currently approved products.

Carton and Container labels for the 5 and 10 mg cetirizine ("Allergy" or "Hives Relief") drug products are based on the currently approved OTC drug product with the same active ingredient (cetirizine).

I. Carton Label
   a. Principal Display Panel (PDP)
      i. For consistency in labeling, the phrase "Hives Relief" should be either all upper cases or using upper case for the first word in all packaging sizes (i.e. "HIVES RELIEF" versus "Hives Relief").

      ii. The potency (i.e., 5 mg and 10 mg) for different strengths must be distinct from each other. We encourage to use a larger font (i.e., at least 5 size larger) and different color schemes to distinguish the two different strengths.

II. Drug Facts Panel
   a. For the 5 mg and 10 mg 20-count "Allergy" carton labels under the subheading, "Other Information", the bullets in this section must be left aligned in accordance to 21 CFR 201.66(d)(4).

   b. For all carton labels submitted under the subheading, "Questions or comments?"; it is recommended that the days of the week and times of the day when a person is available to respond to questions should stated as in 21 CFR 201.66(c)(9).

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RECOMMENDATIONS

1. This application cannot be approved. The sponsor must revise the carton and container labels, and resubmit for our review and comment, prior to the regulatory action due date as follows:

Principal Display Panel

a. For consistency in labeling, the phrase "Hives Relief" should be either all upper cases or using upper case for the first word in all packaging sizes. (i.e. "HIVES RELIEF" versus "Hives Relief").

b. The potency (i.e., 5 mg and 10 mg) for different strengths must be distinct from each other. We encourage to use a larger font (i.e., at least 5 size larger) and different color schemes to distinguish the two different strengths.

Drug Facts Panel

a. For the cetirizine 5 mg and 10 mg (Allergy) 20-count carton labels. The bullets in the "Drug Facts" label under the heading, "Other Information" must be left aligned in accordance to 21 CFR 201.66(d)(4).

2. Inform the sponsor that we recommend the following:
   a. For all carton labels - under the subheading, "Questions or comments?"; it is recommended that the days of the week and times of the day when a person is available to respond to questions should stated as in 21 CFR 201.66(c)(9).

3. [redacted] b(4)

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b(4)

[ ]

b(4)

Ayana K. Rowley, Pharm.D.
Reviewer's name

Marina Chang R.Ph.
Team Leader concurrence

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/s/

Ayana Rowley
4/30/2009 02:38:17 PM
PHARMACIST

Marina Chang
4/30/2009 02:42:37 PM
INTERDISCIPLINARY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 11, 2009

FROM: Hyojong Kwon, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 3/11/09
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-429, Cetirizine HCl Capsules, Sponsored by Banner Pharmacaps, Inc.

TO: Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation (DNCE)

At the request of DNCE, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study Number: 20-219-SA

Study Title: A Single Dose, 2-Period, 2-Treatment, 2-Way Crossover Comparative Bioavailability Study of 10 mg Cetirizine HCl capsules (investigational product/ Banner Pharmacaps Inc.) and Zyrtec 10 mg Tablets (Cetirizine 10 mg, Pfizer Inc.) under Fasting Conditions.

Study Number: 20-220-SA

Study Title: A Single Dose, 2-Period, 2-Treatment, 2-Way Crossover Comparative Bioavailability Study of 10 mg Cetirizine HCl capsules (investigational product/ Banner Pharmacaps Inc.) and Zyrtec 10 mg Tablets (Cetirizine 10 mg, Pfizer Inc.) under Fed Conditions.

The clinical and analytical portions of the study were conducted at [redacted] b(4) and [redacted] respectively.

Following the inspections at [redacted] b(4) (1/29-2/4/09) and at [redacted] (12/16-19/08), Form 483 was issued for the bioanalytical portion of Studies 20-219-SA (DCN 1001659) and 20-220-SA (DCN 1001660) (Attachment 1); there were no significant findings concerning the clinical conduct. The objectionable items and our evaluation of them follow:

Analytical Site: [redacted] b(4)

Analytical observations for Studies 20-219-SA (DCN 1001659) and 20-220-SA (DCN 1001660):

1. Failed to use the same objective criteria for accepting/rejecting QCs/Standard Calibrators (SCs) and study samples.

a) The quality control samples (QCs) in runs 2 and 3 in Study 1660 would have been rejected according to the criteria used for study samples, in that the internal standard (IS) chromatographic areas of QCs were less than 50% of the mean for the runs.
b) Run 9 of Study 1660 also displayed the low IS for QCs; this run was repeated without investigation of the cause.
c) Different criteria to evaluate IS variation, although undocumented, were used for QC acceptance/rejection in Studies 1659 and 1660.

The IS chromatographic areas of all QCs in runs 1, 2 and 3 of study 1001660 (referred to as 1660) were out of the acceptable range used for study samples (50% $\leq$ or $\geq$ 175% of the mean of the non-zero IS for the run). QC's for run 1 failed, but QCs of runs 2 and 3 met the run acceptance criteria specified in the SOP. The firm's investigation did not find the cause of the unusual IS responses. All the samples from runs 2 and 3 were repeated and the repeat values were reported.

In run 9 (study 1660), IS responses of all QCs/SCs were lower than 50% of the mean of non-zero IS but, as with runs 2 and 3, the QCs/SCs met the run acceptance criteria. Run 9 was rejected without any investigation based on the results from run 2 and 3.

In contrast, in study 1001659 (referred to as 1659), runs 6 and 7 with aberrant IS responses (4 of 12 QCs and 2 SCs for run 6 and 3 of 6 QCs for run 7) were accepted because the QCs and SCs met the run acceptance criteria. In the firm's response dated 1/8/2009, the firm explained that the different conclusions regarding IS variation in 1660 and 1659 was that in 1659 there was no clear trend of low IS response compared to runs in study 1660. However, the firm lacked a definition of trend to clarify what number of QCs/SCs with unusual IS response would be grounds to reject a run. Furthermore, when the firm investigated the variable IS response in study 1660 runs 2 and 3, subject sample concentrations from these runs were not reproducible on repeat analysis although the QCs passed the run acceptance criteria (see item 2 below). In light of this finding, the accuracy of data of runs 6 and 7 can not be assured.

The firm's response is attached (Attachment 2).

2. Failed to demonstrate incurred sample reproducibility (ISR).

a) Runs 2 and 3 of Study 1660 did not meet the specification[1].
b) The firm claimed ISR for the study was subsequently demonstrated using other reanalyzed samples from the run. There was no documentation of how the firm performed this demonstration of ISR for the study or which data they used to support this conclusion.
c) There was no documentation of how the firm demonstrated ISR for the study, after they observed this failure of ISR in the investigation of runs 2 and 3.

In study 1660, the firm investigated the lower IS responses of QCs/SCs in runs 2 and 3 by randomly repeating 10% of the samples in singlet in run 7 to assess if the difference in response was significant. This investigation did not demonstrate reproducibility of the randomly selected samples and failed to determine the cause of IS variations.

The firm responded that the investigation was not conducted to demonstrate ISR, but to find the cause of unusual IS variation. It is noted that study 1660 was conducted before the firm established an SOP to demonstrate ISR. The firm

[1] The response difference is not significant would be 2/3 of all the repeats must be <15% different from original value.

decided to reject runs 2 and 3 after the 10% of samples repeated in run 7 failed to demonstrate reproducibility. Run 2 and 3 samples were reassyed in their entirety in later runs. The results for the 10% of samples from the investigation in run 7 were compared and found similar to the later run results for these same samples. The firm claims that the consistency of the data in run 7 and the re-assay data of runs 2 and 3 demonstrates that the study is reproducible.

3. Failed to resolve or correct the out-of-specification results for IS areas.

Unusual responses of IS occurred more than once, but the firm failed to identify the source of IS variation. Instead of conducting further assessment to resolve this issue, the firm decided to reject runs with the out-of-specification results for IS areas. The unusual IS response indicates that some aspect of the bioanalytical method is not performing consistently. Without clarifying the source of the unusual IS response, its potential impact on the accuracy and integrity of the study data can not be evaluated.

Conclusion:

The Division of Scientific Investigations recommends the following:

- Runs 6 and 7 had an aberrant IS response that was correlated with an observed failure to demonstrate reproducibility in other runs with IS variation (see discussion under item 1). Consequently, accuracy of runs 6 and 7 of study 1001659 can not be assured and samples in runs 6 and 7 should have been re-assayed. As these samples have not been re-assayed, data generated in runs 6 and 7 should be excluded from the BE determination. The rest of the study data can be acceptable for review.

Study 1001659 (20-219-SA)	
Run 6	Subject 217, 218, 219, 220, 221
Run 7	Subject 222, 223, 224

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Hyojong Kwon 3/11/09
Hyojong Kwon, Ph.D.

Final Classifications:

NAI: [redacted] b(4)
vAI: [redacted] b(4)

cc:
OC DSI/RF
OC DSI/Rivera-lopez/Patague
OC DSI/Kwon/CF
OND/ONP/DNCE/Adams-king
HFR-SW1540
Draft: HK 02/12/09
Edits: JAO 02/18/09, SS 03/09/09, MKY 03/10/09 b(4)
DSI: [redacted], O:\BE\EIRCOVER\22429[redacted]doc
FACTS: [redacted]

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_____ § 552(b)(5) Deliberative Process

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/s/

Hyojong Kwon
3/11/2009 12:41:17 PM
BIOPHARMACEUTICS
Dr.Yau (acting for Dr. Viswanathan) signed the paper copy on 3/11/2009.