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APPLICATION NUMBER:

22-429

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	6/1/09
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-429 N-000
Applicant Name	Banner Pharmacaps
Date of Submission	July 31, 2008
PDUFA Goal Date	June 1, 2009
Proprietary Name / **Established (USAN) Name**	[redacted] Cetirizine hydrochloride
Dosage Forms / Strength	capsule
Proposed Indication(s)	1. relief of allergic rhinitis 2. relief of itching due to hives
Action/Recommended Action for NME:	*Approval*

b(4)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lolita Lopez/Daiva Shetty/Anthony Dermowicz
Statistical Review	
Pharmacology Toxicology Review	Cindy Li/Wafa Harrouk
CMC Review/OBP Review	Christopher Hough/Shulin Ding
Microbiology Review	
Clinical Pharmacology Review	Yun Xu/Sally Choe
DDMAC	
DSI	Hyojong Kwon
CDTL Review	
OSE/DMETS	
OSE/DDRE	
OSE/DSRCS	
OtherDMEPA/DNRD	Zachary Oleszczuk/Ayana Rowley/Marina Chang

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Banner Pharmacaps is seeking approval to market their proposed products, cetirizine hydrochloride (HCl) 5 and 10 mg softgel capsules for over-the-counter (OTC) use. The indications will be the same as the already approved OTC indications for cetirizine HCl which are: temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat due to hay fever or other upper respiratory allergies, and relief of itching due to hives.

This NDA is submitted under a 505(b)(2) application and relies on the Agency's previous finding of safety and efficacy for cetirizine HCl tablets. Reference is made to NDA 19-835 (Zyrtec tablets) marketed by Pfizer.

In support of this NDA, the sponsor conducted two bioavailability studies, 20-219-SA under fasting conditions and 20-220-SA under fed conditions, comparing the pharmacokinetics (PK) of a single dose of the proposed cetirizine HCl 10 mg softgel capsule and the currently marketed Zyrtec 10 mg tablet, the reference listed drug (RLD).

2. Background

The sponsor submitted NDA 22-429 as a 505(b)(2) application to seek approval for Cetirizine HCl Capsules, 10 mg & 5 mg. This application relies on the Agency's finding of safety and effectiveness for the reference listed drug (RLD), Zyrtec HCl Tablets, 10 mg & 5 mg, the subject of NDA 19-835, held by Pfizer.

Cetirizine hydrochloride was initially approved for prescription use on December 8, 1995 for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) and treatment of chronic idiopathic urticaria (CIU) in adults & children ages $\geq$ 12 years, and later in children ages $\geq$ 6 years. In May 1998, use in children down to two years old was approved. In October 2002, it was approved for the indication of perennial allergic rhinitis (PAR) and CIU in children as young as 6 months old.

In November 2007, cetirizine was switched from prescription to nonprescription (OTC) use. The currently approved OTC indications for cetirizine are: 1) temporary relief of allergic rhinitis symptoms due to hay fever or other upper respiratory allergies; runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat in adults and children $\geq$ 2 years of age; 2) relief of itching due to hives in adults and children $\geq$ 6 years of age.

In this submission, Banner Pharmacaps is seeking approval of cetirizine HCl 5 and

10 mg capsules for OTC use in adults and children ≥ 6 years of age for the same indications as the currently approved cetirizine tablets for OTC use.

3. CMC/Device

The chemistry reviewer comments:

The sponsor has provided adequate information on raw material controls, manufacturing processes, process controls, specifications and analytical methods to assure consistent drug substance and drug product quality. The NDA also has provided sufficient drug product stability data to assure its strength, purity and quality for the duration of its proposed 24-month expiration dating period. All facilities have acceptable site recommendations.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The toxicology reviewer comments :

This is a 505(b)(2) application. The applicant is relying on the Agency's finding of safety and efficacy for the reference listed drug (RLD), Zyrtec® Tablets, 10 mg & 5 mg, which is the subject of NDA 19-835 held by McNeil Consumer Healthcare. Based on the Agency's previous finding of safety for Zyrtec, NDA 22-429 can be approved from the pharmacology/toxicology perspective provided the clinical and clinical pharmacology/biopharmaceutics reviewers find that an adequate clinical bridge has been established between the two products.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There are no clinical safety and/or efficacy studies supporting this NDA. Two single oral dose bioequivalence (BE) studies (Study 20-219-SA and 20-220-SA) were conducted to compare the new formulation and the approved and marketed formulation of cetirizine hydrochloride at 10 mg in healthy subjects under both fasted (20-219-SA) and fed (20-220-SA) conditions. The sponsor requested a biowaiver for 5 mg strength and in support of this biowaiver request, an *in vitro* dissolution study was conducted to compare the dissolution of cetirizine hydrochloride 10 mg versus 5 mg soft gelatin capsules.

The Division of Scientific Investigations (DSI) conducted an audit of Study 20-219-SA and Study 20-220-SA. In the inspection memorandum dated March 11, 2009, the reviewer comments:

An aberrant internal standard response was identified in runs 6 and 7 in study 1001659 (20-219-SA). Consequently, accuracy of runs 6 and 7 in 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, which included data from subjects 217, 218, 219, 220, 221, 222, 223, and 224, should be excluded from the BE determination. The rest of the study data are deemed to be acceptable for review.

Therefore, the data from runs 6 and 7 were excluded from the BE determination in the clinical pharmacology review. Tables 1 and 2 in the appendix present the results of the BE studies under fed and fasted conditions excluding the samples listed above.

Based on the results, the clinical pharmacology reviewer concluded that bioequivalence between the test formulation and the reference formulation is demonstrated.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

There are no clinical microbiology issues for this NDA submission.

7. Clinical/Statistical-Efficacy

There were no efficacy trials conducted for this application. Efficacy is based on demonstrating bioequivalence to the RLD. See the clinical pharmacology section for the results of these studies.

8. Safety

Cetirizine hydrochloride has been marketed since 1995. In November 2007, the Rx-to-OTC switch of cetirizine hydrochloride (Zyrtec) was approved, and the safety of cetirizine for OTC use was reviewed in detail. This present submission is a 505(b)(2) application and the applicant is relying on the findings of safety for the RLD, Zyrtec. In addition the applicant

provided safety data from the 2 PK trials and an integrated summary of safety that included the following:

1) A report summarizing adverse event reporting to the FDA Adverse Event Reporting System (AERS) (June 1, 2007 to July 31, 2008)
2) American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) database (June 1, 2007 to July 31, 2008)
3) A report of the Drug Abuse Warning Reports (DAWN) (June 6, 2007 to July 31, 2008)
4) A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program (June 1, 2007 to July 31, 2008)
5) A review of medical literature relevant to the safety of cetirizine (June 1, 2007 to July 31, 2008)

Previously, in controlled (15) and uncontrolled (10) clinical efficacy trials conducted for the marketing of prescription cetirizine, and which included more than 6,000 patients aged 12 years and older (more than 3,900 patients received cetirizine at doses of 5 to 20 mg per day), most adverse reactions reported during therapy with cetirizine were mild or moderate.

Pediatric studies were also conducted in more than 1,300 pediatric patients aged 6 to 11 years of age, and more than 900 patients were treated with cetirizine at doses of 1.25 to 10 mg per day (controlled and uncontrolled clinical trials). The majority of adverse reactions reported were mild or moderate and the most common AEs in this age group were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea and vomiting.

In the bioavailability studies conducted by the sponsor, a total of 47 subjects were exposed to both the proposed cetirizine HCl capsule and Zyrtec tablet formulations, 10 mg. There were no deaths or serious adverse events (SAEs) reported from these studies, and no subject was withdrawn due to an adverse event (AE). In the combined PK studies, the most common AEs experienced for both treatments were headache (6/48, 12.5%); somnolence (2/48, 4%); and nausea (2/48, 4%). One subject was dropped from the study due to non-compliance (i.e., positive urine drug screen).

The postmarketing safety databases FDA AERS, WHO, and DAWN submitted with the Safety Update during the reporting period June 1, 2007 to July 31, 2008 did not reveal any specific trend or signal detected with the use of cetirizine.

In the FDA AERS database, there were a total of 233 cases with 902 associated AE terms during the reporting period. Overall, the most frequently reported AEs were: convulsion (24, 2.7%); hypersensitivity (14, 1.6%); somnolence (12, 1.3%); drug exposure during pregnancy (12, 1.3%); depression (11, 1.2%); drug ineffective (11, 1.2%); pruritus (11, 1.2%); abnormal behavior (10, 1.1%); feeling abnormal (10, 1.1%), dizziness (9, 1%), and fatigue (9, 1%). These do not differ from AEs identified during the prescription to OTC switch.

In the WHO database, there were 274 cases reported involving 854 AEs. The most common AEs reported were: dizziness (24, 2.8%); drug ineffective (24, 2.8%), somnolence (22, 2.6%),

drug dispensing error (21, 2.4%) medication error (21, 2.4%), fatigue (17, 1.9%), urticaria (15, 1.7%), convulsion (14, 1.6%), pruritus (14, 1.6%), and wrong drug administered (14, 1.6%).

The DAWN data did not reveal any signal that cetirizine is being abused or misused. A review the medical literature did not reveal any new significant safety concerns with the use of cetirizine.

The combination of postmarketing information from safety databases, previous clinical trials, literature review, and adverse events from the relative bioavailability studies conducted by the applicant, do not raise any new safety concern.

I concur with the medical officer's assessment that there are no new safety concerns, and that the product can be approved. The reader is referred to the medical officer's review for additional details regarding the safety analysis.

9. Advisory Committee Meeting

There were no issues raised in this submission that required discussion at an Advisory Committee meeting.

10. Pediatrics

Pediatric patients were not evaluated in this NDA. Cetirizine is approved for OTC use for the treatment of allergic rhinitis symptoms in adults and children ≥ 2 years of age; it is available for prescription use in children 6 months old to <2 years of age. Cetirizine is also approved for OTC use for hives relief in adults and children ≥ 6 years of age; it is available for prescription use for children < 6 years of age. The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established and it is not labeled for use in this population.

This submission triggers the Pediatric Research Equity Act (PREA) because it is a new dosage formulation. This cetirizine softgel capsule formulation will only be labeled in adults and children ≥ 6 years old. For children < 6 years of age, the label directs a consumer to ask a doctor. The sponsor is requesting a waiver for pediatric studies below 6 years of age, and states that the proposed softgel capsule formulation does not represent a meaningful therapeutic benefit over existing therapies, and it is not likely to be used in a substantial number of children below 6 years of age. There are in fact more appropriate age related (<6 years) formulations already available.

I agree with the medical officer that a waiver is appropriate.

PeRC also agreed with granting a partial waiver for less than 6 years of age, and that the product is otherwise appropriately labeled for use by children.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The Drug Facts label will be the same as Zyrtec and there are no labeling issues in this regard. The PDP is acceptable and will use the name "Cetirizine."

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The reader is referred to the labeling review for additional details.

13. Decision/Action/Risk Benefit Assessment

This is a 505(b)(2) application and the applicant is relying on the demonstration of bioequivalence to support the efficacy and safety of this new formulation. The applicant submitted 2 PK studies, which demonstrate that this cetirizine capsule is bioequivalent to the RLD.

From a clinical safety standpoint, the safety information provided to support Banner's proposed cetirizine softgel capsules 5 and 10 mg for the requested indications, demonstrates that cetirizine has an acceptable safety profile for OTC marketing.

Therefore, approval of this application is recommended.

APPENDIX

Statistical Summary of the Comparative Bioavailability Data (Studies 20-219-SA and 20-220-SA)

Table 1. Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single oral dose administration of a 10 mg new capsule formulation (test) and currently-marketed 10 mg Zyrtec® tablet (reference) in healthy subjects under fasted condition.

PK parameters	Geometric Least Squares Mean		Test: Reference ratio	
	Test: 10 mg Capsule	Reference: 10 mg Zyrtec® tablet	Point estimate	90% Confidence Intervals
C_{max} (ng/mL)	347.73	329.83	1.05	96.28 – 115.48
$AUC_{0\text{-last}}$ (ng.hr/mL)	2607.71	2618.82	1.00	94.89 – 104.81
$AUC_{0\text{-inf}}$(ng.hr/mL)	2663.06	2672.64	1.00	94.97 – 104.84

Table 2. Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single oral dose administration of a 10 mg new capsule formulation (test) and currently-marketed 10 mg Zyrtec® tablet (reference) in healthy subjects under fed condition

PK parameters	Geometric Least Squares Mean		Test: Reference ratio	
	Test: 10 mg Capsule	Reference: 10 mg Zyrtec® tablet	Point estimate	90% Confidence Intervals
C_{max} (ng/mL)	279.73	276.09	1.01	92.90 – 110.50
$AUC_{0\text{-last}}$ (ng.hr/mL)	2655.94	2678.12	0.99	96.28 – 102.15
$AUC_{0\text{-inf}}$(ng.hr/mL)	2713.63	2733.66	0.99	96.37 – 102.25

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