CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022578Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 1, 2010
From	Andrea Leonard-Segal, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 22-578
Applicant Name	McNeil Consumer Healthcare
Date of Submission	November 6, 2010
PDUFA Goal Date	September 9, 2010
Proprietary Name / **Established (USAN) Name**	Zyrtec® Allergy / cetirizine HCl
Dosage Forms / Strength	Orally Disintegrating tablet / 10 mg
Proposed Indication(s)	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: 1. Runny nose 2. Sneezing 3. Itchy, watery eyes 4. Itching of the nose or throat
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ryan Raffaelli, MD
Pharmacology Toxicology Review	Wafa Harrouk, PhD; Paul Brown, PhD
CMC Review/OBP Review	Rao Puttagunta, PhD and Shulin Ding PhD /Tapash Ghosh, PhD and Patrick Marroum, PhD
Clinical Pharmacology Review	Arun Agrawal, PhD; Yun Xu, PhD
Labeling	Ayana Rowley, PharmD; Marina Chang, RPh
DSI	Abhijit Raha, PhD and Martin Yau, PhD
CDTL Review	Lesley-Anne Furlong, MD
OSE/DMEPA	Zachary Oleszczuk, PharmD; Kellie Taylor, PharmD; Carol Holquist, RPh

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

McNeil submitted this 505(b)(1) NDA for a new nonprescription orally disintegrating tablet (ODT) formulation for cetirizine HCl 10 mg. The product temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- Runny nose
- Sneezing
- Itchy, watery eyes
- Itching of the nose or throat

Cetirizine HCl is metabolite of hydroxyzine. It is a second generation antihistamine (selective inhibitor of peripheral H_1 receptors) which is currently marketed as a nonprescription product for adults and children 2 years and older for this indication in several formulations (5 mg and 10 mg tablets and chewable tablets and 1 mg/mL syrup). This new ODT formulation is intended to provide an alternative dosing option for consumers that does not necessitate swallowing a tablet and that allows for consumption with or without water.

Cetirizine HCl is also approved OTC for the temporary relief of the itching due to hives in adults and children ages 6 years and older. The applicant does not seek this indication for the orally disintegrating tablet. The Agency has approved second generation antihistamines for each of the two nonprescription indications as separate products (either labeled for upper respiratory allergies or for itching due to hives) because of concerns over the complexity of the resultant Drug Facts if all of the information for each indication were to be crammed into one product label.

Cetirizine HCl has not been labeled for children < 2 years of age as a nonprescription product because of concern that caregivers may not be able to properly diagnose allergic rhinitis in younger children. Also, conventional medical thinking is that seasonal allergic rhinitis (such as hay fever) does not actually exist in children until they have had at least two seasons to be exposed and sensitized to an allergen.

2. Background

Cetirizine HCl was approved for prescription use in 1995 for seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria. It was approved for nonprescription use in 2007 for the upper respiratory allergies and itching due to hives indications. It has been marketed internationally for two decades and is available worldwide for nonprescription use in children down to the age of two years.

For this NDA, the sponsor sought approval based upon the demonstration of bioequivalence to a reference drug rather than providing clinical efficacy and safety studies on the new formulation. During the drug development process, the agency told the sponsor that this would be an acceptable approach if bioequivalence was actually demonstrated. The sponsor provided a summary of postmarketing safety data starting from January 16, 2007 which was the end date of the four-month safety update submitted in support of the OTC switch of cetirizine HCl in 2007.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. The dissolution rate for cetirizine ODT is slower in water than the dissolution rate for the tablet formulation to which it was compared. The reviewers suggest that this difference may be attributed to (b) (4) in the ODT formulation that is used (b) (4). The biopharmaceutics reviewers and the sponsor agreed on the following dissolution specification using a pH 6.5 phosphate buffer that differed from what the sponsor originally proposed:

Q = (b) (4) in 10 minutes.

Stability testing supports an expiry of 24 months. An overall "acceptable" recommendation from the Office of Compliance has been made. There are no outstanding chemistry issues and the chemistry reviewers recommended that from the CMC standpoint the NDA is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

To support this application, the sponsor submitted one combined bioequivalence and food effect study (CETALY1003). This was a two-part, open-label, single dose, four-way randomized and five-way crossover study in 28 healthy male and female adults. The reference listed drug (RLD) for this study was the U.S. currently approved cetirizine 10 mg tablet taken with 240 mL of water.

Refer to Figure I for the study outline. In Study Part I, subjects received Treatments A, B, C, and D under fasting conditions during the first four periods.
Part I:

- Treatment A: A single 10 mg dose of cetirizine ODT with 240 mL water

- Treatment B: A single 10 mg dose of cetirizine ODT without water
- Treatment C: (U.S. marketed product): A single 10 mg dose of the currently marketed US cetirizine tablet (ZYRTEC®) with 240 mL water
- Treatment D (Canadian marketed product): a single 10 mg dose of the currently marketed Canadian cetirizine tablet (REACTINE®) with 240 mL water

All study subjects received Treatment E under fed condition in Period 5. (This was Study Part II).

Study Part II:

- Treatment E: A single 10 mg dose of cetirizine ODT administered approximately 30 minutes after the start of a high-fat breakfast with 240 mL water

Each period was separated by a 4 – 7 day washout.

Figure I

Results:
Refer to Tables I and II.
The results of the bioequivalence study demonstrate that under fasted conditions, Zyrtec ODT, taken with or without water is bioequivalent to the RLD. A high fat breakfast decreased the plasma C_{MAX} by 27% and delayed the T_{MAX} by three hours. The delay in Tmax and decrease in Cmax when the ODT is taken with food is greater than that seen with the tablet, but similar to that seen with the approved chewable tablet formulation, which is not labeled for a food effect. Thus, the extent of change in these two parameters with food is consistent with that seen with other previously approved cetirizine products, for which the labeling does not place dietary restrictions.

Table 1. Arithmetic mean (SD) pharmacokinetic parameters for total plasma cetirizine

Pharmacokinetic Parameters	Treatment A Mean ± SD (CV%) (N=28)	Treatment B Mean ± SD (CV%) (N=28)	Treatment C Mean ± SD (CV%) (N=28)	Treatment D Mean ± SD (CV%) (N=28)	Treatment E Mean ± SD (CV%) (N=27)
C_{MAX} (ng/mL)	292 ± 53.5 (18.3)	288 ± 55.7 (19.3)	303 ± 60.4 (19.9)	303 ± 53.4 (17.6)	182 ± 30.5 (16.8)
T_{MAX} (hr)[1]	1.00 (0.50,2.01)	1.13 (0.50,4.00)	1.00 (0.50,2.01)	0.89 (0.52,2.00)	4.01 (2.50,12.00)
AUC_{LAST} (ng*hr/mL)	2597 ± 402 (15.5)	2556 ± 453 (17.7)	2522 ± 575 (22.8)	2593 ± 449 (17.3)	2415 ± 360 (14.9)
AUC_{INF} (ng*hr/mL)	2787 ± 455 (16.3)	2722 ± 525 [2] (19.3)	2706 ± 635 (23.5)	2792 ± 515 (18.5)	2653 ± 439 (16.5)
K_{EL} (1/hr)	0.0844 ± 0.0143 (16.9)	0.0855 ± 0.0155 [2] (18.1)	0.0842 ± 0.0138 (16.4)	0.0847 ± 0.0151 (17.8)	0.0807 ± 0.0134 (16.6)
$T_{1/2}$ (hr)	8.4 ± 1.3 (15.6)	8.3 ± 1.4 (16.8)[2]	8.4 ± 1.3 (15.0)	8.4 ± 1.5 (17.2)	8.8 ± 1.4 (16.3)
$\%AUC_{extrap}$ (%)	6.63 ± 2.71 (40.9)	6.69 ± 2.94 [2] (43.9)	6.58 ± 2.69 (40.9)	6.89 ± 3.15 (45.8)	8.68 ± 3.10 (35.7)

Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted
Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted
Treatment C: cetirizine HCl (ZYRTEC®, McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted
Treatment D: cetirizine HCl (REACTINE®, Keata Pharma Inc.) 1 x 10 mg [with water] fasted
Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed

[1] T_{MAX} is presented as Median (Minimum, Maximum)
[2] N=27

Source: Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4, and Table 14.2.2.5.

Table 2. Statistical comparisons of pharmacokinetic parameters for total plasma cetirizine*

		Treatment LS Means			
Treatment Comparison (Test vs Reference)	Parameter	Test	Reference	% Mean Ratio	Confidence Intervals (90% Confidence)
A vs C	AUC_{LAST} (ng*hr/mL)	2566	2468	103.96	100.48 - 107.56
	C_{MAX} (ng/mL)	287	298	96.34	91.77 - 101.13
	AUC_{INF} (ng*hr/mL)	2749	2643	104.02	100.28 - 107.90
B vs C	AUC_{LAST} (ng*hr/mL)	2519	2468	102.07	98.66 - 105.61
	C_{MAX} (ng/mL)	283	298	95.16	90.65 - 99.90
	AUC_{INF} (ng*hr/mL)	2708	2643	102.46	98.73 - 106.33
E vs A	AUC_{LAST} (ng*hr/mL)	2389	2570	92.97	89.23 - 96.87
	C_{MAX} (ng/mL)	179	287	62.55	58.95 - 66.36
	AUC_{INF} (ng*hr/mL)	2618	2753	95.11	91.13 - 99.27

Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted
Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted
Treatment C: cetirizine HCl (ZYRTEC®, McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted
Treatment D: cetirizine HCl (REACTINE®, Keata Pharma Inc.) 1 x 10 mg [with water] fasted
Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed

Parameters were ln-transformed prior to analysis. The LS means for treatment A are not the same for each comparison since different statistical models were used.

Source: Table 14.2.2.7, Table 14.2.2.8, and Table 14.2.2.9.

*28 subjects for Treatments A-D and 27 subjects for Treatment E. (One subject was discontinued from the trial due to a positive alcohol screen before dosing at period 5 of part 2 of the trial. The subject's fasting BE data were included in the final analysis. The remaining 27 subjects completed period 5 of the trial, the fed study.)

The Division of Scientific Investigations (DSI) completed their inspections of cetirizine study CETALY1003. At the clinical site (Celerion, Inc., Neptune, NJ), they did not issue a Form FDA-483 as they did not identify significant findings. However, DSI issued a Form FDA-483 following the inspection at the analytical site ((b) (4)).

The Form FDA-483 observations follow:

1. Failure to protect study plasma samples from light. Specifically, the label on the container and the certificate of analysis for reference standard material both state that cetirizine should be protected from light but study samples were unprotected from light during processing.

2. Incurred Sample Reproducibility (ISR) assessment for the LC/MS/MS assay was not conducted.

3. Failure to fully validate the cetirizine LC/MS/MS assay:

- Freshly prepared standard curves were not used in the freeze-thaw stability study, and long-term frozen storage stability study at -20 degrees C.
- Partial re-validation of assay precision and accuracy was not conducted when a different mass spectrometer (i.e., MDX Sciex API 5000) was used in the cetirizine assay.

DSI received the written response to the Form-483 from (b) (4) The response addressed each of the observations. After evaluating the response to the Form-483 observations, DSI recommended that the data from the study CETALY1003 be accepted for review.

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

Not applicable.

7. Clinical/Statistical-Efficacy

No clinical efficacy studies were conducted for this NDA. Efficacy was supported by clinical pharmacology study CETALY1003, described above, which demonstrated bioequivalence to the RLD, cetirizine HCl 10 mg tablets (NDA 19-835/S-022).

The clinical team agreed that the changes in the clinical pharmacology profile when taken with food (which were not seen in the AUC) were not likely to impact the overall efficacy of cetirizine, a once-daily use product, and so no admonitions against using with food were recommended for the labeling. I think that this is acceptable.

8. Safety

Dr. Raffaelli performed an excellent, detailed review of the safety data for this Pregnancy Category B drug. This section summarizes his findings but, for more detail, refer to his review.

McNeil estimated that during the two years comprising the submitted postmarketing safety database, there were approximately (b) (4) doses of cetirizine consumed, representing about 36 million patient-years of use. Approximately one third of cetirizine use was in the United States.

Safety was supported by the demonstration of bioequivalence of the new ODT to the RLD. Additionally, the sponsor provided safety data from the bioequivalence study CETALY1003 and postmarketing safety data from the following sources:

- Safety data from McNeil's database accumulated since the most recent safety update report for Zyrtec® sNDA 19-835 (01/17/07 – 01/16/09)

  There were 4778 case reports in this database of which 52 were deaths. Dr. Raffaelli found that most deaths were of unknown cause or associated with confounding factors. Refer to page 34 of his review. In two of the deaths cetirizine may or may not have played a role. One patient, a 23-year-old male, took cetirizine, clemastine, and alcohol and died after an 8-story fall. Cetirizine and clemastine are labeled not to be taken with

alcohol because each of these three agents has sedating properties. The second patient had several miscarriages while taking cetirizine, a few of which were linked to lethal chromosomal abnormalities; however, since miscarriage is common on or off medication, it is hard to know if there was any relationship to the drug.

Among the serious reports, those most commonly reported were:

- Drug exposure during pregnancy (2.1%)
- Convulsion (2%): Many of these subjects had a history of an underlying seizure disorder.
- Hypersensitivity (1.7%)
- Somnolence (1.7%)
- Death (1.7%)

Regarding hypersensitivity, the OTC cetirizine product labels already have a warning not to use if the consumer has had a previous allergic reaction to cetirizine or hydroxyzine. The labels also have the standard OTC Drug Facts pregnancy warning to ask a health professional before use (21 CFR 201.63). Cetirizine product labels state that drowsiness may occur and that alcohol and sedatives should be avoided.

The relationship of cetirizine with convulsions, cardiac arrhythmias, and thrombocytopenia, has been explored in many reviews, including at the time of the prescription to OTC switch, when new NDAs have been reviewed, and also in 2001 for a response to a Citizen Petition requesting that 3 nonsedating antihistamines (including cetirizine) be switched from prescription to OTC. Convulsions are common medical occurrences with a high background rate and the reviews, including Dr. Raffaelli's, have been unable to draw a clear association between cetirizine and convulsions. Prescription cetirizine labeling does include the adverse event terms "convulsion," "thrombocytopenia," and "tachycardia" but, even if there is a possible association with these events, this association has been considered too rare to appear on the OTC labeling.

I agree with Drs. Furlong and Raffaelli that the data do not support changing the current OTC adverse event labeling for cetirizine. OTC labels should list the most important drug associated AEs and cannot list every conceivable possible rare adverse event. If they did, the labels would be so long and complex as to make them incomprehensible and unreadable for the OTC consumer.

- FDA Adverse Event Reporting System (AERS) data (01/01/01 – 12/31/08)

No new safety signals for cetirizine were noted in this database, which substantially overlapped McNeil's database.

- World Health Organization (WHO) database (01/01/07 – 05-20/09)

No new safety signals were noted.

- American Association of Poison Control Centers (AAPCC) (01/01/07 – 06/15/09)

No new signals of abuse or misuse were noted. As Dr. Raffaelli describes, FDA safety reviews conducted over the years have noted sparse reports of suicide in people who took cetirizine and the prescription label reports this. The relationship with suicide is uncertain and incidents are rare. The current OTC labeling does not list this as an adverse event and I agree with the clinical reviewers that this is reasonable considering the ambiguous nature of the data.

- Drug Abuse Warning Network (DAWN) (01/01/07 – 06/22/09)

No new signals of abuse or misuse were noted.

- Safety update (four-month) during the review cycle

No new safety signals were identified.

In study CETALY1003, somnolence was reported in half of the subjects. As stated above, somnolence is a known adverse effect for cetirizine and OTC cetirizine products are currently labeled to state that drowsiness may occur. No deaths, serious adverse events (AEs), or AEs leading to discontinuation occurred during study CETALY1003.

In addition to providing safety data from the above databases, McNeil provided literature from an online literature search related to clinical trials using cetirizine. Dr. Raffaelli also performed his own literature search. His review of the literature did not identify new safety concerns with cetirizine.

In summary, Dr. Raffaelli did not identify unexpected safety signals in the postmarketing data, published literature, or in study CETALY1003. I agree with him and with Dr. Furlong that the safety data on cetirizine continue to support OTC marketing of this drug and support the approval of this new NDA. The safety database does not suggest the need to change the warnings as they exist currently on the OTC cetirizine products.

9. Advisory Committee Meeting

It was not necessary to convene an advisory committee meeting to discuss this new formulation of cetirizine HCl.

10. Pediatrics

The sponsor requested a waiver of pediatric studies for children < 6 years of age. DNCE and the PeRC agreed with the regulatory rationale for this waiver, the reasons being:

- Seasonal allergic rhinitis does not exist in children < 2 years of age. (Further, FDA has previously determined that dosing of antihistamines for this age group should remain via prescription, independent of the formulation. This would be, for example, because of the difficulty nonprofessional caregivers could have in making an appropriate allergic rhinitis diagnosis in these young children.)

- For children 2 - < 6 years of age, the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of these children.
- For children 6 – 17 years old, the product is appropriately labeled based on studies and extrapolation

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues associated with this NDA.

12. Labeling

Trade Name:
The trade name for this ODT product will be Zyrtec® Allergy. This is the name which DMEPA found suitable in their review dated 06/10/10. (There was communication with the sponsor over the trade name, which, by contrast, they thought was Zyrtec®.) The ODT is a new dosage form for an already approved product line with the trade name appearing on the Principal Display Panel as "Zyrtec®" and with the term "Allergy" appearing as a modifier. Specifically, there are many approved OTC Zyrtec® products with different dosage forms (liquid, tablets and chewable tablets) and strengths (5 mg and 10 mg) in the market with "Zyrtec®" appearing as the trade name and "Allergy" appearing as a modifier (in that the two words are of different font specifications/color and do not necessarily appear right next to each other).

To avoid consumer confusion, we plan to send a supplement request letter to the sponsor to give the sponsor time to reconfigure the labels across the entire product line to properly account for the two-word trade name, which should apply to all OTC Zyrtec® products labeled to treat allergy. It is important to note that the sponsor did not request the “itching due to hives” indication for the ODT formulation, but an analogous trade name situation exists for the Zyrtec® Hives Relief products.

Other Labeling Issues:
After the sponsor made several modifications to their proposed labeling, which FDA requested and which are discussed in the labeling reviews, the labeling reviewers recommended that the labeling could be approved in their review dated 08/12/10. There are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The efficacy and safety for this product were demonstrated based upon the demonstration of bioequivalence with the RLD in study CETALY1003 and the absence of new safety signals in the postmarketing safety data. The data support that this new cetirizine ODT product will be safe and effective for the OTC consumer for the temporary relief these symptoms due to hay fever or other upper respiratory allergies:

- Runny nose
- Sneezing
- Itchy, watery eyes
- Itching of the nose or throat

There are no postmarketing commitments needed. There are no pediatric study requirements.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22578	ORIG-1	MCNEIL CONSUMER HEALTHCARE DIV MCNEIL PPC INC	CETIRIZINE HCL ORALLY 10MG TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREA LEONARD SEGAL
09/01/2010