CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022578Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

DATE: August 27, 2010

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

FROM: Abhijit Raha, Ph.D.
Martin K. Yau, Ph.D.
Pharmacologists
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 8/27/10
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-578, Zyrtec® Orally Disintegrating Tablets, 10 mg, Sponsored by McNeil Consumer Healthcare

At the request of DNCE, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: CETALY1003

Study Title: "A Randomized, Open-Label, Single-Dose, Five-Way Crossover Study to Evaluate Bioequivalence and Food-Effect of a New Orally Disintegrating Tablet Formulation of Cetirizine HCl"

The audits of the clinical and analytical portions of Study CETALY1003 were conducted at Celerion, Inc. (formerly MDS Pharma Services), Neptune, NJ and (b) (4) , respectively.

Clinical Site: Celerion, Inc., Neptune, NJ (FEI No. 3003583366)

Following inspection of the clinical site (June 8-23, 2010), Form FDA-483 was not issued, and no significant clinical findings were noted.

Analytical Site: (b) (4)

Following inspection at the analytical site (August 2-5, 2010), a 4-item Form FDA-483 was issued **(Attachment 1).** DSI received the written response (dated August 25, 2010) from (b) (4) electronically on August 26, 2010 **(Attachment 2).** Our evaluations of the Form FDA-483 observations **(in bold type)**, and the firm's responses to the 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.**

(b) (4) acknowledged the above observation during the inspection. In their response, (b) (4) conducted additional validation experiments to evaluate the stability of cetirizine in the stock solution, un-extracted QC samples, and extracted QC samples under normal light conditions. The stability samples were evaluated against freshly-prepared calibration standards. Cetirizine stock solution was found to be stable for 9 hours, un-extracted QC samples for 6 hours, and extracted QC samples for 69 hours (Report No. (b) (4), **Attachment 3, pages 6, 18, 15, and 17, respectively**). The time frames cover the sample assay period for this study. Furthermore, the firm will revise their validation SOP to include the light sensitivity test.

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

Following the inspection, an ISR assessment for study CETALY1003 was conducted by (b)(4) under protected light conditions. The results provided in the written response show that there is no ISR issue for the cetirizine LC/MS/MS method used in the study **(see Attachment 4, pages 9, 13-15).**

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

   a. **Freshly prepared standard curves were not used in the freeze-thaw stability study and long-term frozen stability study at -20°C.**

(b)(4) conducted additional validation experiments after the inspection to assess freeze-thaw stability and long-term frozen storage stability at -20°C against freshly-prepared calibration standards under protected light conditions. QC samples were found to be stable for three freeze-thaw cycles and for 545 days at -20°C **(see Attachment 3, pages 6, 7, 16, and 19).** Also, the firm promised revision of their validation SOP to emphasize that all stability testing must be performed against freshly-prepared calibration standards.

   b. **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.**

Following the inspection, (b)(4) conducted an experiment to validate the precision and accuracy of the assay on MDX Sciex API-5000 and submitted the data in the written response **(Attachment 3, pages 6 and 14).** The results demonstrate that the method is robust and can be run on both the API-4000 and API-5000.

Conclusion:

Following the inspections at the clinical and analytical study sites, and after evaluating the response to the 483 observations submitted by (b) (4) DSI recommends that the data from study CETALY1003 be accepted for review.

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

Abhijit Raha, Ph.D.

Martin K. Yau, Ph.D.

Final Classification:

Celerion, Inc., Neptune, NJ (Clinical)—NAI
(FEI Number: 3003583366)

(b) (4)

cc: DARRTS

CDER DSI PM TRACK
OND/ODE IV/DNCE/Andrea Segal, Janice Adams-King (HFD-560)
HFD-48/Ball/Haidar/Yau/Rivera-Lopez/Raha/CF
HFR-CE1505/Joseph Despins
HFR-CE1515/Daniel Tammariello (BIMO)
HFR-CE100/Karyn Campbell (DIB)
Draft: AR 8/10/10; 8/26/10; 8/27/10
Edit: MKY 8/25/10; 8/26/10
DSI: (b) (4); O:\BE\EIRCover\22578 (b) (4) .zyr.doc
FACTS (b) (4)

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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

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/s/

ABHIJIT RAHA
08/27/2010

Addendum Labeling Review for Zyrtec Allergy *Draft Labeling*

SUBMISSION DATES:	July 12, 2010 and July 29, 2010
NDA/SUBMISSION TYPE:	22-578
ACTIVE INGREDIENTS:	10 mg cetirizine
DOSAGE FORMS:	Orally Disintegrating Tablet
SPONSOR:	McNeil Consumer Healthcare Elizabeth H. Finn (215) 273-7469
REVIEWER:	Ayana K. Rowley, Pharm.D.; ODEIV/DNRD
TEAM LEADER:	Marina Y. Chang. RPh; ODEIV/DNRD

I. BACKGROUND

This is a labeling amendment to the review completed on May 4, 2010 for the new drug application Zyrtec Allergy 10 mg strength orally disintegrating tablets indicated for allergy relief. The sponsor has submitted final draft labeling in response to on-going labeling negotiations with the agency.

Submitted Labeling	Representative of Following SKUs
6-count immediate container (blister card)	N/A
6-count outer carton	N/A
12-count outer carton	N/A
24-count outer carton	N/A
66-count outer carton	N/A

REVIEWER'S COMMENTS

A. 6-count, 12-count, 24-count, and 66- count carton labels

i. Outer Carton Label Outside Drug Facts

a. Promotional Statements and Graphics

(a) The sponsor has revised the statement (b) (4) to "Dissolve Tabs" and has chosen to retain the "Melts in Your Mouth" statement. These are acceptable.

Reviewer's Comment: The agency finds the promotional "Dissolve Tabs" acceptable. The sponsor's revision to replace (b) (4) with "Dissolve Tabs" on the PDP, side panels and background layout on the carton label are acceptable.
In regards to the "Melts in Your Mouth" statement, after additional internal discussion with the Division of Nonprescription Clinical Evaluation (DNCE) and the Division of Nonprescription Regulation Development (DNRD) labeling review team it was determined that the "Melts in Your Mouth" statement is acceptable because this is a truthful statement and is not misleading to the consumer.

b. Established Name

The sponsor has revised the established name from Cetirizine HCl to Cetirizine HCl orally disintegrating tablets. This is acceptable.

Reviewer's Comments: DNCE and DNRD held an internal policy meeting and decided to revise the established name layout. It was recommended to the sponsor via an email correspondence on July 12, 2010 to revise the established name as follows: "active ingredient" followed by "dosage form". The sponsor revised the label as in accordance to the new office policy which follows the USP/NF format in naming for established name of a finished dosage form.

c. Propriety Name

The proprietary name for this application is Zyrtec Allergy, which is consistent with the trade name branding for this product line. In email correspondence on August 3, 2010 the agency requested that the sponsor aligned their trade dress so that the trade name "Zyrtec Allergy" would have the same font size. Currently the trade name "Zyrtec" is in prominently display on the top half of the PDP and the trade name "Allergy" is offset as a smaller trade dress (similar to a flag). It is the view of the sponsor that the proprietary name for this product is "Zyrtec" followed by the modifier "Allergy". The agency intends to allow the sponsor to retain their current

trade dress until further clarification as to whether the word "Allergy" should be part of the trade name or as a modifier on the PDP. The current presentation of "Zyrtec Allergy" is acceptable.

II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for Zyrtec Allergy carton and immediate container (6- count blister card) labels and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 6-count immediate container (blister card submitted on July 12, 2010) and 6-, 12- 24-, and 66- count carton labels submitted on July 29, 2010.

Remind the sponsor to remove the "New Form" flag from the carton labels after 180 days of marketing.

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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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

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/s/

AYANA K ROWLEY
08/12/2010

MARINA Y CHANG
08/12/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 30, 2010
To:	Andrea Leonard-Segal, MD, Director Office of Nonprescription Drugs Division of Nonprescription Clinical Evaluation (DNCE)
Through:	Kellie Taylor, PharmD., Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Zachary Oleszczuk, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Addendum to May 13, 2010, Label and Labeling Review
Drug Name(s):	Zyrtec Allergy (Cetirizine HCl) Orally Disintegrating Tablets 10 mg
Application Type/Number:	NDA 022578
Applicant:	McNeil Consumer Healthcare
OSE RCM #:	2009-2312

1 INTRODUCTION

OSE Review #2009-2312, dated May 13, 2010 summarizes DMEPA's evaluation of the container labels and carton labeling for Zyrtec Allergy (Cetirizine HCl) Orally Disintegrating Tablets, 10 mg submitted by the Applicant on November 6, 2009. The review provides comments to help minimize the risk of wrong product selection. However, we did not comment on the acceptability of the proposed name, Zyrtec Allergy, for this product at the time of this review. Thus, per request from the Division of Nonprescription Clinical Evaluation, we provide the following comments on the proposed proprietary name for the administrative record.

2 DISCUSSION

DMEPA found the name Zyrtec Allergy acceptable in OSE Review #2007-400, dated November 7, 2007. In that review DMEPA described post-marketing reports of confusion between the root name 'Zyrtec', 'Zantac', and 'Zyprexa'. We considered this confusion in our evaluation of Zyrtec Allergy and concluded that while the possibility for confusion still exists between the root name Zyrtec and other drug products, the modifier 'Allergy' should provide some differentiation between these products and thereby reduce on going confusion. Although, there is known name confusion with the root name 'Zyrtec', DMEPA notes that the reported name confusion was only identified when Zyrtec was marketed as a prescription drug product and we did not identify any reports of confusion during marketing as an over-the-counter product (AERS search for OSE Review #2009-2312, dated May 13, 2010).

In OSE Review #2009-2312, DMEPA evaluated the proposed labels and labeling, for NDA 022578, and noted the use of the proprietary approved name, *Zyrtec Allergy* with the dosage form descriptor (b) (4) The Applicant did not request an evaluation of the proprietary name since *Zyrtec Allergy* exists in the market place for the same active ingredient (certirizine), strength (10 mg), and frequency of administration (once daily). This proposed product differs from the currently marketed product only in regard to dosage form (tablet vs. orally disintegrating tablet). Given that the dosage form is the only difference between the products we find that it is appropriate to mange the proposed products under the name *Zyrtec Allergy* and highlight the differences in dosage form on the principal display panel of the carton labeling

As currently proposed, the principal display panel of the carton labeling adequately highlights the differences of these products and thus supports the use of the same proprietary name. However, at the filing meeting for this application on January 5, 2010, the Division voiced concerns with the phrase (b) (4) and whether not it is an accurate statement for this product. We deferred to the Division on the accuracy of this statement. However, if the dosage form descriptor (b) (4) is not allowed on the carton labeling, we recommended revising the principle display panel to prominently state the this is an orally disintegrating product. We recommended this be accomplished by increasing the statement 'orally disintegrating tablets' and increasing the size of the statement 'Melts in your mouth'.

3 CONCLUSION

DMEPA finds the use of the proprietary name, Zyrtec Allergy, with an appropriate dosage form descriptor suitable for use with this product. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Catherine Carr, at 301-796-2311.

4 REFERECNES

1. Duffy, F. OSE Review #2007-400: Proprietary Name, Label, and Labeling Review for Zyrtec Allergy. November 7, 2007.

2. Duffy, F. OSE Review #2009-2312: Label, and Labeling Review for Zyrtec Allergy Orally Disintegrating Tablets. November 7, 2007.

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

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/s/

ZACHARY A OLESZCZUK
06/30/2010

KELLIE A TAYLOR
06/30/2010

CAROL A HOLQUIST
06/30/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 13, 2010
To:	Andrea Leonard-Segal, MD, MS Director, Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Through:	Zachary Oleszczuk, PharmD, Acting Team Leader Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Zyrtec Allergy (Cetirizine HCl) Orally Disintegrating Tablets 10 mg
Application Numbers:	NDA 022578
Applicant:	McNeil Consumer Healthcare
OSE RCM #s:	2009-2312

1 BACKGROUND

1.1 INTRODUCTION

This review summarizes DMEPA's evaluation of the proposed blister label, carton and drug facts labeling for Zyrtec Allergy (Cetirizine HCl) Orally Disintegrating Tablets. The Applicant has added the dosage form descriptor (b) (4)' as well as the statement copy 'Melts in your mouth' to the principle display panel.

1.2 REGULATORY HISTORY

On November 16, 2007, Zyrtec Allergy was approved for over-the-counter use as 5 mg and 10 mg tablets. Although Zyrtec Allergy is approved in 5 mg and 10 mg tablets, this application is applicable only to the 10 mg tablets.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Because Zyrtec is a currently marketed product, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on March 17, 2010 for any medication errors relevant to the labels or labeling of Zyrtec using the following criteria: Trade Name "Zyrtec Allergy" and "Zyrtec Hives Relief", Verbatim Substance "Zyrtec%" and the MedDRA reaction terms "Medication Errors" (HGLT) and "Product Quality Issue" (PT). Since Zyrtec went from Rx to OTC on November 16, 2007, DMEPA conducted the AERS search limiting cases to the reported dates between November 16, 2007 and March 17, 2010.

The reports were manually reviewed to determine if medication errors occurred involving factors related to either the packaging or labeling. Those cases that did not describe a medication error, and those that were determined to be irrelevant, were excluded from further analysis. Duplicate reports were grouped together into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) uses the principles of Human Factors and Failure Mode and Analysis (FMEA) in our evaluation of the blister labels and carton labeling submitted November 6, 2009 (see Appendices A and B).

3 RESULTS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS)

On March 17, 2010, the AERS search retrieved a total of 41 reports involving Zyrtec.

Twenty-three cases (n=23) pertained to adverse events that were not caused by a medication error (e.g., anaphylaxis, shortness of breath, hypertension, nose bleeds). These cases were excluded from further analysis. Two cases (n=2) were foreign cases that were also excluded from further analysis.

The remaining 16 cases were related to medication errors involving Zyrtec (see Appendix C). Thirteen (n=13) of the 16 cases pertained to overdose. Seven cases of overdose were intentional. Two cases (n=2) pertained to the wrong patient receiving Zyrtec, and one case (n=1) pertained to the wrong technique (i.e., cutting the tablet in thirds). We determined that the medication errors that these 16 cases were not the result of inadequate labeling.

3.2 LABELING

The three issues identified with the proposed labels and labeling are as follows.

The carton labeling for this orally disintegrating product is similar to the currently marketed Zyrtec over-the-counter products that are not orally disintegrating tablets.

The product strength is not prominent on the blister label and carton labeling, and the net quantity appears more prominent than the product strength.

The presentation of the statement of identity and dosage form is not consistent with currently marketed Zyrtec products.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the blister labels and carton labeling can be improved to minimize the potential for medication errors. *Section 4.2 Comments to the Applicant* contains our recommendations for the blister labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Catherine Carr, Regulatory Project Manager, at 301-796-2311.

4.1 COMMENTS TO THE DIVISION

1. On the Drug Facts label 'Active Ingredient' section, it is not clear that the statement "in each tablet" pertains to the orally disintegrating tablet dosage form. We recognize that other over-the-counter orally disintegrating products (e.g., Claritin Reditabs) use the language "in each tablet" to describe the dosage form in the 'Active Ingredient' section of Drug Facts. Therefore, we defer to the Division for the proper designation of this section.

2. A filing meeting for this application was held on January 5, 2010. We note that the Division voiced concerns with the phrase (b) (4) and whether not it is an accurate statement for this product. We defer to the Division on the accuracy of this statement. However, if ' (b) (4) (b) (4) is not allowed on the carton labeling, then we recommend revising the principle display panel to clearly differentiate this orally disintegrating product from the other Zyrtec dosage forms to avoid potential administration errors. This may be achieved by increasing the statement 'orally disintegrating tablets' and increasing the size of the statement 'Melts in your mouth'.

3. The directions on the Drug Facts labeling do not clearly indicate that the orally disintegrating tablets should be placed on the tongue and allowed to dissolve. As currently presented, consumers may swallow the orally disintegrating tablet rather than placing it on their tongue. Revise the directions to indicate the appropriate administration directions. For example:

   Place 1 tablet on tongue, tablet disintegrates, with or without water.

4.2 COMMENTS TO THE APPLICANT

A. Blister Label

Increase the prominence of the product strength in order to improve readability and identification on the label. We recommend you relocate the product strength from within the established name to appear near the proprietary name.

B. Carton Labeling (6 count, 12 count, 24 count, 66 count)

1. The “New Form!” flag adjacent to the proprietary name should remain on the carton labeling no more than 6 months.

2. We recommend that the established name should be increased in size as it is small in comparison to the proprietary name.

3. Increase the prominence and size of the product strength because “24 Hour” appears more prominent on the carton labeling than the product strength.

4. Decrease the prominence of the net quantity located on the bottom right side of the carton labeling as it appears more prominent than the product strength.

5. We note that the dosage form does not appear in close proximity to the active ingredient. Since this is a new dosage form in the Zyrtec product line and the administration of this product is different than currently marketed Zyrtec products, we recommend you revise the labeling so that the dosage form appears in closer proximity to the active ingredient. For example:

    Cetirizine HCl 10 mg/antihistamine
    Orally disintegrating tablets

5 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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Appendix C: Zyrtec medication error ISR numbers

Overdose (n=13) ISR #s
5942246-7, 6054256-2, 6075612-2, 6082719-2, 6099627-3, 6173417-5, 6200070-4, 6200763-9, 6200779-2, 6215538-4, 6264525-9, 6435604-8, 6484393-X
Wrong patient (n=2) ISR #s
6215025-3, 6434393-0
Wrong technique (n=1) ISR
6420701-3

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

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/s/

FELICIA DUFFY
05/13/2010

ZACHARY A OLESZCZUK
05/13/2010

KELLIE A TAYLOR
05/13/2010

CAROL A HOLQUIST
05/14/2010

Labeling Review for
Zyrtec ODT
Draft Labeling

SUBMISSION DATES:	November 6, 2009 and March 11, 2010
NDA/SUBMISSION TYPE:	22-578
ACTIVE INGREDIENTS:	10 mg cetirizine
DOSAGE FORMS:	Orally Disintegrating Tablet
SPONSOR:	McNeil Consumer Healthcare Hina Harlow (215) 273-4810
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Y. Chang. RPh

I. BACKGROUND

This is a new drug application for Zyrtec 10 mg strength orally disintegrating tablets indicated for allergy relief. The annotated font specifications were not included in the November 6, 2009 submission. An information request was sent to the sponsor and revised labels were submitted on March 11, 2010. This is a preliminary draft labeling review; additional revisions or labeling changes may be required upon the completion of the team reviews.

Submitted Labeling	Representative of Following SKUs
6-count immediate container (blister card)	N/A
6-count outer carton	N/A
12-count outer carton	N/A
24-count outer carton	N/A
66-count outer carton	N/A

REVIEWER'S COMMENTS

A. 6-count, 12-count, 24-count, and 66- count carton labels

i. Outer Carton Label Outside Drug Facts

a. Flags

(a) Original Prescription Strength- The sponsor has included the phrase “original prescription strength” on the principal display panel. This is acceptable.

Reviewer’s Comments: The Division of Nonprescription Development only allows this statement as a flag on the principal display panel for complete prescription to nonprescription switches as in accordance with current Office of Drug Evaluation IV (ODE IV) policy. The orally disintegrating tablet (ODT) is a new dosage form for the Zyrtec product line and has not been marketed under a prescription. The inclusion of this flag was cleared by the ODE IV immediate office. The ODE IV immediate office agrees that the product can carry the "original prescription strength" flag since it is a truthful statement based on the strength of the tablet even though the dosage form is new.

(b) New Form- The sponsor has included the flag “New Form”. This is acceptable.

Reviewer’s Comments: As stated above, ODT is a new dosage form that has not been previously marketed; therefore, the “New Form” flag is appropriate. This flag must be removed following 180 days of marketing.

b. Promotional Statements and Graphics

(a) (b) (4) and “Melts in Your Mouth”. The sponsor has included the following promotional statements and/or graphics on the principal display panel and side panels. This is not acceptable; these promotional statements/graphics must be revised or removed.

Reviewer’s Comment: The agency is concerned that the promotional statement (b) (4) and “Melts in Your Mouth” can be potentially misleading to consumers because these statements can have various interpretations. The (b) (4) statement implies a comparative claim, which may or may not be accurate depending upon the basis used for comparison. The agency discourages the use of such comparative statements as a part of the promotional statement because the agency is concern that consumers may think (b) (4) than other products that are currently on the market. In regards to the statement, “Melts in Your Mouth” the agency, recommends that this statement be revised (or removed) to indicate to the consumer the expected time the drug product will melt in their mouth.

ii. Outer Carton Drug Facts Label

a. Under the heading, "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 be included in this section.).

Reviewer's Comments: It is recommended that the submitted labels be revised as in accordance with 21 CFR 201.66 (c)(9).

b. The annotated font specifications are acceptable.

iii. Immediate Container Label (Blister card)

The immediate container label for this application is a 6-count blister card. The information provided on the blister card is in accordance with the current regulations. This is acceptable.

iv. Consumer Information Leaflet or Package Insert

The sponsor did not submit a consumer information leaflet or a package insert. The review team concurs that there is no additional information that needs to be conveyed to the consumer that is not already presented on the drug facts panel. This is acceptable.

II. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

- The sponsor has included the promotional statements/graphics (b) (4) and "Melts in Your Mouth" on the principal display panel and side panels; these are not acceptable and must be revised or removed. The agency is concerned that the promotional statement (b) (4) and "Melts in Your Mouth" can be potentially misleading to consumers because these statements can have various interpretations. The (b) (4) statement implies a comparative claim, which may or may not be accurate depending upon the basis used for comparison. The agency discourages the use of such comparative statements as a part of any promotional statement because the agency is concern that consumers may think that the drug product (b) (4) than other products that are currently on the market. In regards to the statement, "Melts in Your Mouth" the agency, recommends that this statement be revised (or removed) to indicate to the consumer the expected time the drug product will melt in their mouth.

- Inform the sponsor that the agency recommends that they include the days of the week and times of the day when a person is available to respond to questions under the heading, "Questions or comments?". This recommendation is in accordance with 21 CFR 201.66(c)(9).

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

5 pages have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

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/s/

AYANA K ROWLEY
05/04/2010

MARINA Y CHANG
05/04/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22578 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zyrtec® Established/Proper Name: cetirizine Dosage Form: tablets (orally disintegrating) Strengths: 10mg		
Applicant: McNeil Consumer Healthcare Agent for Applicant (if applicable):		
Date of Application: November 6, 2009 Date of Receipt: November 9, 2009 Date clock started after UN:		
PDUFA Goal Date: September 9, 2010	Action Goal Date (if different):	
Filing Date: January 8, 2010	Date of Filing Meeting: January 6, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Temporary relief of symptoms of hay fever and other upper respiratory allergies		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☒ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☒ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (*if OTC product*): DPAP				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☒ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	Labeling			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).			**X**	
Index: Does the submission contain an accurate comprehensive index?				
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			(new formulation; partial pediatric waiver requested (birth to 6 months; 6 months to 23 months; 2 to 5 years)
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***				
Is the PI submitted in PLR format?				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				
REMS consulted to OSE/DRISK?				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?				
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☐ Immediate container label ☒ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***		X		Annotated font specifications are missing
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 6, 2010

BLA/NDA/Supp #:

PROPRIETARY NAME: Zyrtec®

ESTABLISHED/PROPER NAME: cetirizine

DOSAGE FORM/STRENGTH: oral disintegrating tablets, 10 mg

APPLICANT: McNeil Consumer Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): temporary relief of symptoms of hay fever and other respiratory allergies

BACKGROUND: Cetirizine HCl was first approved by FDA as a prescription product in 1995 and approved for OTC use in 2007 for temporary relief of symptoms of hay fever or other upper respiratory allergies and for the relief of urticaria in adults and children 6 years of age and older. The syrup formulation was approved for children 2 to 5 years of age for temporary relief of symptoms of hay fever and other respiratory allergies. This application, NDA 505(b)(1), proposes a new formulation developed by McNeil to provide consumers a convenient option for dosing that does not require swallowing a tablet whole and may be dosed with or without water. The application seeks approval for temporary relief of hay fever and upper respiratory allergy symptoms; relief of itching due to hives, urticaria, is not being sought for this application. Partial pediatric waiver requested for those ages birth to 5 years.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Janice Adams-King	Y
	CPMS/TL:	Melissa Furness	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Ryan Raffaelli	Y
	TL:	Lesley-Anne Furlong	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:	Ayana Rowley	Y
	TL:	Marina Chang	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Arun Agrawal	Y
	TL:	Partha Roy	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul C. Brown	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rao Puttagunta	Y
	TL:	Shulin Ding	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Felicia Duffy	Y
	TL:	Zachary Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(1) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: The pivotal study was a single bioequivalence/ PK trial. The Clinical Pharmacology review team requested a DSI audit of the labs where samples were analyzed	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	
PRODUCT QUALITY (CMC) **Comments**: one-year stability update for drug product	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: EIC < 1ppb	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Andrea Leonard-Segal, M.D. **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/

JANICE Adams
02/03/2010

Filing Checklist for Zyrtec (orally disintegrating tablets)

SUBMISSION DATES:	November 6, 2009
NDA/SUBMISSION TYPE:	22-578
ACTIVE INGREDIENTS:	Cetirizine 10 mg tablets
SPONSOR:	McNeil Consumer Healthcare Hina S. Harlow Director, Global Regulatory Affairs 7050 Camp Hill Road Fort Washington, PA 19034-2299 215-273-4810
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Chang, R.Ph

Submitted Labeling	Representative of Following SKUs
6 - count blister card for Allergy Relief	
6 – count carton for Allergy Relief	
12- count carton for Allergy Relief	
24 – count carton for Allergy Relief	
66 – count carton for Allergy Relief	

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	Original Application
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	No	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	No	Annotated font specifications are needed
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	Yes	"Original Prescription Strength"
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	No	
Does a medical officer need to review any clinical issues?	Yes	New Application
If SLR, should ONDQA also review?	N/A	

Information Request:

Project Manager: An information request is necessary; please inform the sponsor that the annotated font specifications are missing.

Internal Comments:

Project Manager: The sponsor has included the phrase "original prescription strength". DNRD only allows this statement as a flag on the PDP for complete Rx to OTC switches. The ODT (orally disintegrating tablet) is a new dosage form and has not been marketed under a prescription. The inclusion of this flag must be cleared by the ONP immediate office. Please request the ONP immediate office to provide comments regarding the acceptability of this statement.

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/

AYANA K ROWLEY
01/05/2010

MARINA Y CHANG
01/05/2010