CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022578Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-578

Zyrtec® (cetirizine HCl) Orally Disintegrating Tablets 10 mg

McNeil Consumer Healthcare

Rao Puttagunta, Ph.D.
Branch IV/Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Reviewed for
The Division of Nonprescription Clinical Evaluation (DNCE), HFD-560

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 22-578

2. REVIEW #: 1

3. REVIEW DATE: 09-AUG-2010

4. REVIEWER: Rao Puttagunta, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-NOV-2009
Amendment (BC)	17-MAR-2010
Amendment (BC)	22-JUL-2010
Amendment (BC)	29-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	McNeil Consumer Healthcare (division of McNIEL-PPC, Inc.)
Address:	7050 Camp Hill Road Fort Washington, PA 19034-2299
Representative:	Hina S. Harlow Director, Global Regulatory Affairs
Telephone:	215-273-4810

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ZYRTEC®
b) Non-Proprietary Name (USAN): Cetirizine Hydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Antihistamine (temporary relief of symptoms of hay fever and other upper respiratory allergies)

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 10 mg cetirizine HCl/tablet

13. ROUTE OF ADMINISTRATION: Oral

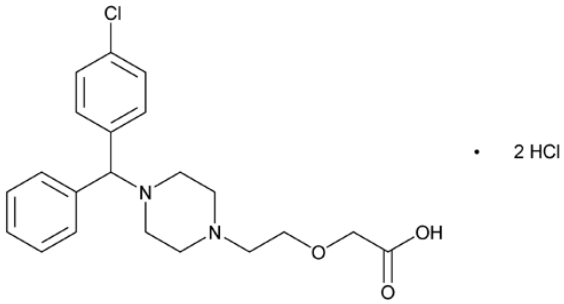
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name: (RS)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1piperazinyl]ethoxy]acetic acid dihydrochloride

Molecular Formula: $C_{12}H_{25}ClN_2O_3 \cdot 2HCl$ **Molecular Weight:** 461.81

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4) 5	Cetirizine HCl	1	Adequate	R. Puttagunta 7/23/10	---
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	R. Puttagunta 8/06/10	---
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	7/28/10	CFR & FEMA listed GRAS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	---	21 CFR §170-199 & §175.300

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3/16/10	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A per new ONDQA policy		
DMEPA	N/A		
DDMAC	N/A		
EA	Categorical Exclusion		Rao Puttagunta
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-578

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An overall "Acceptable" recommendation from the Office of Compliance has been made.

Therefore, from the CMC standpoint this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance cetirizine HCl is an antihistamine. Cetirizine hydrochloride is a white or almost white powder that is freely soluble in water. It was sated that according to the drug substance supplier cetirizine HCl does not exhibit polymorphism.

Cetrizine HCl is manufactured by (b) (4) Switzerland. The CMC information on Cetrizine HCl was referenced to DMF (b) (4). The DMF has been recently reviewed and found to be adequate.

2. Drug Product:

The Zyrtec ODT (cetrizine HCl) orally disintegrating tablets contain 10 mg of cetrizine HCl per tablet. The orally disintegrating tablets were formulated with (b) (4) (b) (4) cetrizine HCl (b) (4). The (b) (4) is insoluble in saliva, but readily soluble in stomach.

All ingredients in the drug product are of USP/NF grade except for the (b) (4) Citrus (b) (4) Flavor. However, the flavor ingredients are GRAS listed items.

The manufacturing process for Zyrtec ODT consisted of [redacted]. The drug product is tested for appearance, identity, assay, degradation products, content uniformity, loss on drying, disintegration time, dissolution, and microbial limits for release. The drug product specification was considered adequate as amended.

Zyrtec ODT 10 mg tablets are packaged in 6 count child-resistant unit dose blisters. The packaging materials were found to be adequate. The blister system is a [redacted] foil blister material [redacted] material consisting of foil laminate with paper backing. The container closure materials were acceptable.

The submitted stability data included a total of 4 full-scale batches of Zyrtec ODT, 10 mg tablets at long-term (25°C/60%RH), and accelerated (40°C/75%RH) storage conditions for up to 12, and 6 months respectively (as amended).

The drug product is labeled for storage at controlled room temperature of 20-25°C (68-77°F).

The proposed expiration dating period of 24 months is granted based on the submitted satisfactory drug product stability data.

B. Description of How the Drug Product is Intended to be Used

The Zyrtec ODT tablets are indicated for temporary relief of symptoms of hay fever and other upper respiratory allergies (sneezing; runny nose; itchy, watery eyes; and itchy throat or nose). Each tablet contains 10 mg of cetirizine HCl, to be taken orally one tablet once daily.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided adequate CMC information for Zyrtec ODT (cetrizine HCl) tablets:

- The submitted raw material controls are adequate.
- The manufacturing process and process controls are robust to ensure consistent product quality in conformance with the established specification.
- The proposed drug substance and drug product specifications are adequate.

- The submitted stability data, as updated, is adequate to support the proposed expiration dating period of 24 months.
- The packaging information is adequate to ensure the drug product quality during storage, transportation, and use.
- The overall "Acceptable" recommendation from the Office of Compliance has been made.

III. Administrative

A. Reviewer's Signature

Rao Puttagunta, Ph.D. {electronic signature}

B. Endorsement Block

Moo-Jhong Rhee, Ph.D. {electronic signature}
Branch Chief, DNDQAII, ONDQA

C. CC Block

N/A

33 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

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

/s/

RAO PUTTAGUNTA
08/27/2010

SHULIN DING on behalf of MOO JHONG RHEE
08/27/2010
on behalf of Moo-Jhong Rhee

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	22-578
Applicant:	McNeil Consumer Healthcare
Stamp Date:	Nov. 9, 2009
PDUFA Date	Sep. 9, 2010
Trademark:	Zyrtec®
Established Name:	Cetirizine hydrochloride
Dosage Form:	Orally disintegrating tablet
Route of Administration:	Oral
Indication:	Temporary relief of symptoms of hay fever and other upper respiratory allergies
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

McNeil Consumer Healthcare is submitting a 505(b) (1) New Drug Application (NDA) for the nonprescription use of cetirizine hydrochloride orally disintegrating tablet 10 mg. This is a new oral dosage form for cetirizine hydrochloride. It is developed for pediatric administration and as an alternative for individuals who have difficulty swallowing solid dosage forms. NcNeil Consumer Healthcare has marketed cetirizine hydrochloride as Zyrtec® tablets, chewable tablets, and syrup formulations.

The applicant references to DMF (b) (4) held by (b) (4) for the CMC information of the drug substance, cetirizine hydrochloride. DMF (b) (4) was most recently reviewed in May 2007 for NDA 19-835/SCM-19 Zyrtec tablet, and deemed adequate to support the supplement. As a result of the supplemental review, (b) (4) has been approved as an alternative drug substance manufacturer for NDA 19-835.

The proposed drug product is a citrus flavored, white to off-white, round, flat-faced, beveled edge tablet with "Z10" debossed on one side. It is formulated as an immediate release, (b) (4), orally disintegrating tablet. The (b) (4). The CMC information of the (b) (4) cetirizine HCl (b) (4) is referenced to DMF (b) (4). Each tablet (weighing 325 mg) contains (b) (4) (b) (4) that contains 10 mg of cetirizine hydrochloride (b) (4), the tablet also contains the following excipients: mannitol, USP; microcrystalline cellulose, NF; sucralose, NF; crospovidone, NF; colloidal silicon dioxide, NF; sodium bicarbonate, USP; anhydrous citric acid, USP; (b) (4) citrus (b) (4) flavor (b) (4), and

magnesium stearate, NF. The components and compositions of cetirizine HCl (b) (4) and the (b) (4) citrus flavor are referenced to DMFs and not provided in the NDA. The applicant claims no novel excipients and no excipients of human or animal origin. The claim can not be verified until an in-depth review on the referenced DMFs.

The drug product is packaged in 6-count child-resistant, peelable blister cards in folding cartons of 6, 12, 24, and 66 tablet counts. The blister system is a (b) (4) foil blister material with (b) (4) (b) (4) foil/paper backing.

The proposed product is manufactured by (b) (4) (b) (4) cetirizine HCl (b) (4) with other ingredients. Process development work was conducted, including full scale process optimizing and ranging studies, and process ranges have been established for critical process parameters. Content uniformity, disintegration, and dissolution have been identified as critical quality attributes for the proposed product. The manufacturing process and process controls of the (b) (4) cetirizine HCl (b) (4) is referenced to DMF (b) (4).

Registration stability data provided in the initial submission to support a proposed expiration dating period of 24 months at the storage temperature of 20-25°C include 3-6 months at 25°C/60% RH and 40°C/75% from four stability batches. All four registration stability batches are full scale (b) (4)) in batch size. One of them, Batch C12909, is the batch used in the pivotal bioequivalent study. The to-be-marketed formulation is the same formulation used in the pivotal bioequivalent study and registration stability batches.

Photostability study results from one batch are also provided in the NDA.

B. Critical issues for review

DMFs (b) (4)

- CMC information for the (b) (4) cetirizine HCl (b) (4) and the (b) (4) citrus (b) (4) flavor (b) (4) is referenced to DMFs (b) (4), respectively, and not provided in the NDA. An in-depth review of the referenced DMFs will need to be conducted to determine whether the referenced DMFs are adequate to support the NDA and whether the two DMFs contain novel excipients and/or excipients of human or animal origin.

Residual Solvents in Drug Product

- The applicant does not address this issue in the NDA. The proposed drug product specification does not include a test on residual solvent. An information request should be made to the applicant regarding residual solvents present in excipients and (b) (4) if a test on residual solvents is not going to be performed on the drug product.

Drug Product Manufacturing

- Process development work was conducted, including full scale process optimizing and ranging studies, and process ranges have been established for critical process parameters. The process studies and the acceptability of the proposed process ranges for critical process parameters need to be critically reviewed.

- The age of the (b) (4) cetirizine HCl (b) (4) used in the manufacture of registration stability batches should be factored in the review and approval of the hold time for the (b) (4)

Drug Product Stability and Expiration Dating Period

- Drug product stability data provided in the initial submission are too few to support a viable expiration dating period for commercialization. Since the stability batches were made in November, 2008, the batches are older than one year now. A request of one-year stability update is recommended so that the Agency can grant a viable expiration dating period.

C. Comments for 74-Day Letter:

Update drug product stability as soon as possible to provide at least one year of stability data from registration stability batches.

D. Comments/Recommendation:

The application is fileable from CMC perspective. The major CMC review issues with this NDA are the adequacy of DMF (b) (4) for cetirizine HCl (b) (4) and the (b) (4) citrus (b) (4) flavor (b) (4), any novel excipients, residual solvents in drug product, the acceptability of the proposed process ranges for critical process parameters, and drug product stability.

The drug substance manufacturing site is located in Switzerland. The drug product manufacturing sites are located in U.S. GMP inspection has been requested for each manufacturing/testing site.

The CMC review of this NDA is recommended to be a team-review. Rao Puttagunta is the primary CMC reviewer, and Tapash Ghosh is the BioPharm reviewer.

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch III

NDA Number: 22-578	**Supplement Number and Type:**	**Established/Proper Name: Cetirizine hydrochloride**
Applicant: McNeil Consumer Healthcare	**Letter Date: 11/6/09**	**Stamp Date: 11/9/09**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			n/a

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	Referenced to DMF (b) (4).
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4).
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to DMF (b) (4).
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (b) (4).
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		CMC information for cetirizine (b) (4) is referenced to DMF (b) (4).
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		CMC information for cetirizine (b) (4) is referenced to DMF (b) (4).
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4) (b) (4)	Drug substance	6/15/2009	
(b) (4)	II	(b) (4)	(b) (4)	9/28/2009	
(b) (4)	IV	(b) (4)	(b) (4)	7/14/2009	
(b) (4)	III	(b) (4)	(b) (4)	4/24/2009	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See page 3 of IQA.

{See appended electronic signature page}

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

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/

SHULIN DING
01/07/2010

MOO JHONG RHEE
01/07/2010
Chief, Branch III