CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-155

CHEMISTRY REVIEW(S)

NDA 22-155

Children's Zyrtec ®
(Cetirizine HCl 1mg/ml, oral solution)

Pfizer Inc.

Yubing Tang, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC Review of NDA 22-155
For the Division of Nonprescription Product

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-155

2. REVIEW: #1

3. REVIEW DATE : Nov. 01, 2007

4. REVIEWER: Yubing Tang, Ph.D.

5. PREVIOUS DOCUMENTS:
Not applicable

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	January 15, 2007
Amendment[1]	March 02, 2007
Amendment[2]	May 15, 2007
Amendment[2]	June 06, 2007
Amendment[3]	June 13, 2007
Amendment[3]	June 25, 2007
Amendment[4]	September 26, 2007

1. Response to IR letter on February 12, 2007
2. Response to IR letter on April 02, 2007
3. Response to IR letter on June 04, 2007
4. Response to IR letter on September 12, 2007

1. NAME & ADDRESS OF APPLICANT

Name: Pfizer Inc

Address: 235 E. 42nd Street
New York, NY 10017

Chemistry Review Data Sheet

Representative: McNeil Consumer Healthcare
Division of McNeil-PPC, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Telephone: 973-385-5419

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Children's Zyrtec Allergy; Children's Zyrtec Hives Relief
b) Non-Proprietary Name (USAN) : Cetirizine hydrochloride
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 8
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-allergic Agent, Antihistamine

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5mg/5ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _X_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

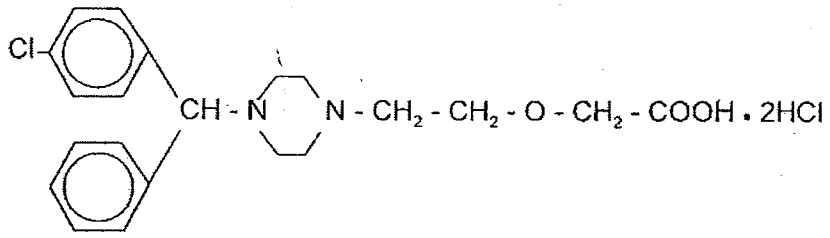
__X___Not a SPOTS product

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

- CHEMICAL NAME:

(±) – [2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]ethoxy]acetic acid dihydrochloride

- CAS NUMBER: 83881-52-1
- MOLECULAR FORMULAR: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$



- MOLECULAR WEIGHT: 461.8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
6853	II	UCB Pharma SA	Drug Substance	1	Adequate	Aug. 23, 2007	Reviewed by Y. Tang
	IV			4	Adequate	N/A	Food grade flavors
	III			3	Adequate	April 10, 2007	Reviewed by Craig Bertha
	III			3	Adequate	August 13, 1999 Sept. 21, 2004	Reviewed by James Vidra (1999) and by Yvonne Yang

						(2004)
	III		3	Adequate	March 23, 2000	Reviewed by Don Klein
	III		3	Adequate	Aug. 08, 1996	Reviewed by Craig Bertha
	III		1	Adequate	Aug. 24, 2007	Reviewed by Y. Tang

[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:

APPLICATION NUMBER	DESCRIPTION
NDA 19-835	Approved prescription drugs using the same active ingredient by the same sponsor
NDA 21-621	

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1 (18-Feb.-93)	NDA 20-346	Approved prescription of Zyrtec™ syrup.
CMC Review #2 (11-May-95)	NDA 20-346	
CMC Review #3 (02-July-96)	NDA 20-346	
CMC Review #4 (24-Sept.-96)	NDA 20-346	

18. CONSULTS/CMC-RELATED REVIEWS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Oct., 2007	See EES Inspection Report in review

Pharm/Tox			N/A
Biopharm			N/A
Division of Non-prescription products			N/A
Methods Validation	N/A		
Labeling			Martin, Cazemiro (for OTC drugs)
EA	Acceptable	Aug. 2007	Tang, Yubing
Microbiology	N/A		No consult needed

19. ORDER OF REVIEW (OGD Only): N/A

Appears This Way
On Original

The Chemistry Review for NDA 22-155

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **APPROVAL** from the CMC standpoint.

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

Not applicable.

II. Summary of Chemistry Assessments

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

1) Drug Product

The proposed drug product, *Children Zyrtec®* (Cetirizine HCl 1mg/ml,oral solution), is an OTC switch of the prescription product *Zyrtec®* Syrup. The prescription *Zyrtec®* Syrup was approved in September 26, 1996 under NDA 20-346 for the indications of perennial allergic rhinitis (6 months of age and above), seasonal allergic rhinitis (2 years of age and above) and chronic idiopathic urticaria (6 months of age and above).

The NDA holder, Pfizer, Inc , is now seeking OTC marketing of the drug product under the proposed name of *Children's Zyrtec® Allergy* oral solution and *Children's Zyrtec® Hives Reief* oral solution. Other than the proposed indications and population for the OTC marketing (see two bullets below), the rest of indications and targeting population (perennial allergic rhinitis 6 to under 24 months of age and relief of itching due to hives for 6 months to under 6 years) will remain in the prescription drug. In addition, the OTC product will have the same strength, doses, duration of use, dosage form, and route of administration as the existing already approved prescription drug. The proposal for the OTC product is shown as follow.

- *Children's Zyrtec® Allergy* oral solution -- for seasonal allergic rhinitis and perennial allergic rhinitis and for 2 years of age and above;
- *Children's Zyrtec® Hives Reief* oral solution -- for chronic idiopathic urticaria and for 6 years of age and above.

Children's Zyrtec® is an oral solution containing cetirizine hydrochloride as an active pharmaceutical ingredient in the concentration of 5mg/5 ml. Purified water, propylene glycol, glycerin, glacial acetic acid, sodium acetate, ——— sugar, sodium hydroxide, artificial grape

and banana flavors are present as excipients and they are compendial or of food grades. Methylparaben and Propylparaben (both USP grade) are present as the preservatives.

The sponsor proposed to market *Children's Zyrtec®* in a 4 fl ounce retail size. The packaging system for the retail product will consist of a glass bottle as the primary packaging with tamper evident neckband. Accompanied the bottle are a package insert and a dosing cup with three marks calibrated to deliver 2.5 ml, 5 ml and 15 ml of the oral solution. A carton functioning as the secondary packaging holds the primary container and the dosing cup. In comparison with the already approved prescription drug, the sponsor proposed a change _____ _____ . Dosing cup is the new item introduced in this application. The information regarding the material suitability and the accuracy of the cup dimension provided in DMF —— and in the application has been reviewed and found acceptable.

The sponsor proposed 24-month expiry period for *Children's Zyrtec®*, the same as that labeled for the already approved prescription drug product. The storage temperature is proposed to range from 20° – 25°C (68° – 77°C). The sponsor will conduct a long-term stability study using the first commercial batch under the condition of 25°C /60%RH; and the study result will be submitted in Annual Report.

Since this is the OTC product, also referenced is the labeling review of the Division of Non-prescription Products for other content of the insert and the labeling.

2) Drug Substance

The drug substance, cetirizine hydrochloride, is the same drug substance used in the already approved drug product under NDA 20-346. The sponsor references to DMF#6853 for the drug substance. This DMF has been reviewed and found to be adequate.

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

The drug product is 1 mg/1 ml cetirizine hydrochloride oral solution. It is intended to be used for relief of seasonal and perennial allergic rhinitis for 2 year of age and older; and chronic idiopathic urticaria for 6 years of age and older. The drug product is a partial OTC switch from an existing approved prescription drug product. The dosing is age and symptom dependent, ranging from 2.5 ml to 10 ml daily.

The commercial drug product is contained in a 4 fl ounce glass bottle with child resistance cap, which, along with a dosing cup, is packaged in a carton as the secondary packaging container. The storage condition is proposed for 20° – 25°C (68° – 77°C) and the expiration period is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC perspective, the application is recommended for approval based on the following.

- The drug substance is the same as used in the approved existing prescription drug products. The CMC information of the drug substance in DMF #6853 is recently reviewed and found to be adequate.
- The drug product is an OTC switch of the existing approved prescription drug product. The only change proposed by the sponsor is that, in comparison with the existing prescription drug product, the primary container has smaller bottle finish to allow the dosing cup to fit on the container. This change is considered acceptable since the construction materials of the bottle and the cap are identical to the existing prescription drug product; and the smaller headspace generally improves the stability of the drug product. The sponsor will conduct tests to verify that the primary glass bottle complies with USP <661> requirement; and to confirm that the moisture permeation rate is comparable to the existing prescription drug product.
- The sponsor will conduct post-approval stability study using the drug product of the first commercial batch in the commercial container/closure system. The sponsor will submit the stability result in Annual Report. These stability results are expected to support two-year expiration period, which is the same as that for the existing approved prescription drug.
- cGMP status of all facilities are satisfactory.

III. Administrative

A. Reviewer's Signature

Yubing Tang, Ph.D.
Branch III/DPAII/ONDQA

B. Endorsement Block: in DFS

C. CC Block: in DFS

19 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Yubing Tang
11/2/2007 02:29:40 PM
CHEMIST

Moo-Jhong Rhee
11/2/2007 02:36:06 PM
CHEMIST
Chief, Branch III