

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-621

ADMINISTRATIVE DOCUMENTS

1.4.1 PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient: (+/-)-(2-{4-[(4-chloro-phenyl)-phenyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid, dihydrochloride
2. Strength: 5 mg and 10 mg
3. Trade Name: Zyrtec^R Chewable Tablets
4. Dosage Form/Route of Administration: Tablets/Oral
5. Application Firm Name: Pfizer Inc.
6. NDA Number: 21 - 621
7. Exclusivity Period: 6 month pediatric exclusivity expires December 25, 2007
8. Applicable Patent Numbers And Expiration Dates: U.S. 4,525,358 (June 25, 2007)
U.S. 6,455,533 (July 02, 2018)

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**APPEARS THIS WAY
ON ORIGINAL**

Time Sensitive Patent Information
Pursuant to 21 C.F.R. § 314.53
for
NDA # 21 - 621

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Zyrtec® Chewable Tablets
Active Ingredient(s): cetirizine dihydrochloride
Strength(s): 5 mg and 10 mg
Dosage Form: bilayer tablet
Approval Date:

A. Information for each individual patent:

1. **U.S. Patent Number:** 4,525,358
Expiration Date: June 25, 2007
Type of Patent:
1. Drug Substance(Active Ingredient) yes
 2. Drug Product(Composition/Formulation) yes
 3. Method of Use yes

U.S. 4,525,358 claims methods of use. The specific methods of use for which approval is being sought that are covered by patent: **seasonal/perennial allergic rhinitis.**

Name of Patent Owner: UCB Pharmaceuticals, Inc., Dover, Delaware

2. **U.S. Patent Number:** 6,455,533
Expiration Date: July 02, 2018
Type of Patent:
1. Drug Substance(Active Ingredient) no
 2. Drug Product(Composition/Formulation) yes
 3. Method of Use yes

U.S. 6,455,533 claims methods of use. The specific methods of use for which approval is being sought that are covered by patent: **seasonal/perennial allergic rhinitis.**

Name of Patent Owner: UCB Pharmaceuticals, Inc., Dover, Delaware

B. Declaration Statement for Patents Having Composition/Formulation or Method of Use Claims

The undersigned declares that the above stated United States Patent Number U.S. 4,525,358 covers the composition, formulation and/or method of use of the drug product Zyrtec Chewable Tablet and that United States Patent Number U.S. 6,455,533 covers the composition, formulation and/or method of use of the drug product Zyrtec chewable tablet. This product is the subject of this application for which approval is being sought.

Signed: Robert J. Konan
Date: March 21, 2003
Title: Senior Patent Counsel/Pfizer, Inc.
Telephone Number: (860)441-5910

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EXCLUSIVITY SUMMARY FOR NDA # 21-621

SUPPL # _____

Trade Name Zyrtec Chewable Tablets

Generic Name cetirizine HCl

Applicant Name Pfizer HFD # 570

Approval Date If Known March 16, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO / ___ /

b) Is it an effectiveness supplement?

YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This was a bioequivalence study comparing the approved 10 mg tablet to the 10 mg chewable tablet.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /___/

expires December 25, 2007

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA # _____.

Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade):

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under

consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-835 Zyrtec Tablet
NDA# 20-346 Zyrtec Syrup
NDA# 21-150 Zyrtec D 12-Hour

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !
 !

Investigation #2 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 !
 !
 !
 !

Investigation #2 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 !
 !
 !
 !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not

be credited with having "conducted or sponsored" the study?
(Purchased studies may not be used as the basis for
exclusivity. However, if all rights to the drug are purchased
(not just studies on the drug), the applicant may be
considered to have sponsored or conducted the studies
sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature
Title:

Date

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File

HFD-610 Mary Ann Holovac

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

/s/

Badrul Chowdhury
3/17/04 12:43:16 PM

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NDA 21-621

Zyrtec Chewable Tablet

DEBARMENT STATEMENT

I the undersigned hereby certify that Pfizer Inc. 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.

Denise F. Andrews
Denise F. Andrews

02 April 03
Date

Director, Regulatory Affairs

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 21-621 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: May 16, 2003 Action Date: March 16, 2004

HFD 570 Trade and generic names/dosage form: Zyrtec (cetirizine HCl) Chewable Tablets

Applicant: Pfizer Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indication #1: Seasonal allergic rhinitis

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 2 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Perennial Allergic Rhinitis

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
- NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 2 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Syrup already approved for 6 months to 2 years of age.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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Indication #3: Chronic Idiopathic Urticaria

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

| | | | | |
|-----------|----------|--------------|--------------|--------------------|
| Min _____ | kg _____ | mo. <u>0</u> | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. <u>2</u> | Tanner Stage _____ |

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Syrup already approved for 6 months to 2 years of age

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-621
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT,
HFD-960, 301-594-7337.**

(revised 10-14-03)

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

/s/

Colette Jackson
3/16/04 02:18:04 PM

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DIVISION DIRECTOR'S MEMORANDUM

Date: March 16, 2004

To: NDA 21-621

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Cetirizine (Zyrtec) hydrochloride 5 mg and 10 mg chewable tablets

Applicant: Pfizer Inc.,

Administrative and Introduction

Pfizer Inc., submitted NDA 21-621 for cetirizine (Zyrtec) hydrochloride 5 mg and 10 mg chewable tablets as a 505(b)(1) application. The NDA was received by the Agency on May 16, 2003. The PDUFA due date on this application is March 16, 2004. Zyrtec 5 mg and 10 mg tablets and Zyrtec 1 mg/ml syrup are approved for the treatment of seasonal allergic rhinitis down to the age of 2 years and for the treatment of perennial allergic rhinitis and chronic urticaria down to the age of 6 months. Pfizer is proposing the same indications and same dosing for the chewable tablets, and is proposing to go down to the age of 2 years. The development program for the chewable tablet was a bioequivalence program comparing the Zyrtec 10 mg chewable tablets to the commercial Zyrtec 10 mg tablets. Pfizer did not conduct bioequivalence studies with the 5 mg chewable tablets and is requesting a waiver of bioequivalence study for the 5 mg product by showing similar in vitro dissolution profiles between the 10 mg and the 5 mg products. The clinical pharmacology program and the in vitro dissolution profiles support approval of this application. There are no outstanding issues from other disciplines. There are no issues on the 505(b)(1) regulatory pathway for this application because Pfizer is the NDA holder of all Zyrtec products.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance, cetirizine hydrochloride, is manufactured and supplied by UCB SA, Belgium. The DMF associated with the drug substance is adequate. The drug product is a relatively straightforward formulation, but contains a novel excipient called betacyclodextrin (BCD). The clinical trials and the primary stability batches were manufactured in a site in [redacted]. The commercial batches will be manufactured in Puerto Rico. All manufacturing sites related to this application have acceptable evaluation status. There were some CMC issues that were resolved during review of this application. The CMC team has recommended an approval action on this application, and I concur with that recommendation. Some notable CMC issues are briefly summarized below. Details are available in Dr. Edwin Jao's excellent review.

The formulation contains betacylodextrin (BCD), which is a novel inactive ingredient in a pharmaceutical product, although it is commonly used in food products and is considered to be safe. The concern with BCD is that it may bind to some water-soluble drugs in the gastrointestinal tract and interfere with their absorption. The amount of BCD present in the formulation is considerably small _____, compared to what is considered to be a safe allowable limit in diet (5 mg/kg/day, which is 250 mg/day for a 50 kg person). Another issue surrounding the use of BCD is the use of _____ as a solvent in the isolation stage. The applicant agreed to control the residue of the solvent at _____, which is equal to a maximum daily exposure of _____. Of note the EPA allowable limit of _____ in drinking water is 5 mcg/L. The presence of BCD and _____ was assessed by the CMC team in consultation with the PharmTox Team, and both have concluded that the amount of these substances present in the formulation is not a safety issue, and I concur with that conclusion.

The application contains _____ stability data (under long term, and intermediate term conditions) from _____ (ICH stability lots) for each 10 mg and 5 mg strength. _____ (commercial scale) manufactured in a site in _____, and _____ stability data (under long term, intermediate term, and accelerated conditions) from _____ (site specific lots) for each 10 mg and 5 mg strength, _____ (commercial scale) manufactured in Puerto Rico. Some of the stability data were submitted during review of the application in response to a discipline review letter. Statistical analyses of the stability data support the proposed 24 months expiry. A new degradant _____, was noted during stability. Acceptance criteria for the degradant are adequate.

Clinical Pharmacology and Biopharmaceutics, and Clinical

The applicant submitted results of seven clinical pharmacology studies and a summary of safety data. Of the seven clinical pharmacology studies, three were conducted with the to-be-marketed formulation and were considered relevant to this NDA. The three clinical pharmacology studies were conducted in healthy male and female volunteers between the ages of 18 and 55 years to show bioequivalence of the Zyrtec 10 mg chewable tablets to the commercial Zyrtec 10 mg tablets as the reference product under fasting condition with water (study A 1431019) and without water (study A 1431018). The effect of high fat high calorie diet on the absorption of Zyrtec 10 mg chewable tablets was investigated in study A 1431021. The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Suarez, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Bosken. The OCBP team concluded that the applicant has demonstrated that their 10 mg chewable tablet is bioequivalent to the reference 10 mg tablet, and I concur with that conclusion.

In the two studies conducted under fasting condition, the 90% confidence intervals of the log-transformed C_{max} and AUC values of the test product and reference product were within the 80% and 125% bioequivalence limits. In study A 1431019 (fasting, with water) the point estimates and the 90% confidence intervals were 101.2 and 95.4-107.7 for C_{max}, 93.2 and 89.4-97.1 for AUC_t, and 93.0 and 89.3-96.9 for AUC_{inf}. In study A 1431018 (fasting, without water) the point estimates and the 90% confidence intervals

were 97.3 and 94.3-100.4 for C_{max}, 98.2 and 95.3-101.2 for AUC_t, and 98.3 and 95.4-101.3 for AUC_{inf}.

In the food effect study (study A 1431021) the point estimates and the 90% confidence intervals of the log-transformed values between the fed and fasting condition were 63.1 and 59.8-66.6 for C_{max}, 91.4 and 87.9-94.9 for AUC_t, and 91.4 and 88.0-94.9 for AUC_{inf}. The data indicate that when Zyrtec chewable tablet was taken with high fat meal the C_{max} was decreased by approximately 40% but the overall exposure was essentially unchanged. This difference is clinically not relevant; therefore, Zyrtec chewable tablets can be taken with or without regards to meal.

The applicant requested a waiver of bioequivalence studies for the 5 mg strength based on in vitro dissolution profiles. The OCBP team evaluated the in vitro dissolution profiles of the two strengths and concluded that they were similar ($f_2 > 50$) and that in vivo bioequivalence studies for the 5 mg strength can be waived. I concur with that conclusion.

No clinical efficacy or safety studies were conducted for this NDA.

Review of the safety data in the clinical pharmacology studies did not reveal any new safety signal. The most commonly reported adverse events noted in these studies were somnolence and headache.

Previous post-marketing safety review conducted by the Office of Drug Safety (ODS) noted that convulsions, and psychiatric, emotional, and behavioral disturbances were reported in association with the use of Zyrtec. During review of this NDA, the ODS was consulted to review reports of suicide or suicidal ideation in association with use of Zyrtec. ODS concluded that the reports of suicide or suicidal ideation were probably related to the use of Zyrtec. With this NDA, Pfizer has added convulsions, aggressive reaction, hallucinations, and suicide and suicidal ideation to the post-marketing list of adverse events.

Pharmacology and Toxicology

The applicant did not conduct any new preclinical study for this application because cetirizine is currently approved and marketed product.

Data Quality, Integrity, and Financial Disclosure

There was one study center and one analytical site for the three clinical pharmacology studies considered relevant to this NDA. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues were present. During review of these studies no issues with data quality and integrity were noted. No audit of the study site was requested.

Pediatric Consideration

The applicant is proposing use of Zyrtec chewable tablets down to the age of 2 years, which is appropriate for the formulation. No additional pediatric studies are required for the chewable tablet formulation. Zyrtec is approved down to 6 months of age and a syrup formulation is marketed for use in the very young children.

Product Name

The proprietary name of Zyrtec is approved and used by Pfizer for the product line containing cetirizine. The suffix chewable tablet is appropriate for this dosage form. During the review of this NDA the Division of Medication Errors and Technical Support (DMETS) of the ODS was consulted for comments on the name. DMETS reiterated a previous comment that the name "Zyrtec" is often confused with "Zantac" in the marketplace and that the name "Zyrtec" be changed. Of note, the confusion is mostly with the syrup formulation because of similar appearance of the container closure of the two formulations, and in almost all cases the medication dispensing error was with Zantac (i.e., Zantac being dispensed incorrectly as Zyrtec) and not in the other direction. The Clinical team does not agree that there is enough ground to justify a name change for Zyrtec, and I concur with that assessment. The Division's comments on other minor suggested changes to the labeling and packaging suggested by DMETS are captured on the Medical Team Leader memorandum.

Labeling

Pfizer submitted a product label containing various new sections relevant to the new dosage form. The proposed new label is a unified label inclusive of the three single ingredient cetirizine products – tablets, syrup, and the chewable tablets. The labeling has been extensively reviewed by all relevant disciplines. The Division and Pfizer have agreed on a final labeling text that adequately reflects the data and the new dosage form.

Action

The clinical pharmacology data and clinical safety data are sufficient to support the efficacy and safety of Zyrtec 5 mg and 10 mg chewable tablets for use in patients down to the age of 2 years for treatment of allergic rhinitis and chronic urticaria. Therefore, the action on this application will be APPROVAL.

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this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
3/16/04 01:05:21 PM
MEDICAL OFFICER

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Regulatory Affairs
Pfizer Inc
235 East 42nd Street 150/7/9
New York, NY 10017
Tel 212 573 2241 Fax 212 857 3558
Email samantha.wolfe@pfizer.com

Pfizer Global Pharmaceuticals

Samantha Wolfe
Director
U.S. Regulatory Affairs

March 11, 2004 (sent by e-mail)

Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products (HFD-570)
Document Control Room 8B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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RE: NDA # 21-621 Zyrtec[®] (cetirizine HCl) Chewable Tablets
Submission of Proposed Final Labeling

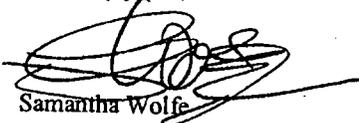
Dear Dr. Chowdhury:

This correspondence is in reference to NDA 21-621 filed on 15May2002 for the Original New Drug Application for Zyrtec (cetirizine HCl) Chewable Tablets.

In follow-up to our 11Mar04 labeling teleconference for above-referenced pending NDA, enclosed please find proposed final labeling reflecting today's agreed-upon changes for Zyrtec (cetirizine HCl).

Please contact me at (212) 573-2241.

Sincerely yours,



Samantha Wolfe

Attachments

- Proposed final labeling

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ON ORIGINAL**

Cover Letter Only:
Ms. Colette Jackson

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Regulatory Affairs
Pfizer Inc
235 East 42nd Street 150/7/9
New York, NY 10017
Tel 212 573 2241 Fax 212 857 3558
Email samantha.wolfe@pfizer.com

Pfizer Global Pharmaceuticals

Samantha Wolfe
Director
U.S. Regulatory Affairs

March 8, 2004 (faxed)

Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products (HFD-570)
Document Control Room 8B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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RE: NDA # 21-621 Zyrtec[®] (cetirizine HCl) Chewable Tablets
Response to Labeling Comments

Dear Dr. Chowdhury:

This submission is in reference to NDA 21-621 filed on 15May2002 for the Original New Drug Application for Zyrtec (cetirizine HCl) Chewable Tablets.

Enclosed please find our response to FDA labeling comments received via fax on 03Mar04. Pfizer requests a teleconference as soon as possible to review FDA comments and Pfizer's response.

Please contact me at (212) 573-2241.

Sincerely yours,

Samantha Wolfe

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ON ORIGINAL

Attachments

- Pfizer's itemized response
- Revised package labeling artwork (not included in fax, sent via hard copy)

Cover Letter Only:
Ms. Colette Jackson

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

| | |
|--|--|
| NAME OF APPLICANT Pfizer Inc | DATE OF SUBMISSION 08Mar04 |
| TELEPHONE NO. (Include Area Code) 212 573-3412 | FACSIMILE (FAX) Number (Include Area Code) 212 857-3558 |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 235 East 42 nd Street New York, NY 10003 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE |

PRODUCT DESCRIPTION

| | | |
|---|---|----------------------------------|
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-621 | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) cetirizine hydrochloride | PROPRIETARY NAME (trade name) IF ANY Zyrtec Chewable Tablets | |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (+/-)-(2-(4 -((4-chlorophenyl)phenylmethyl)-1piperazinyl)ethoxy)acetic acid dihydrochloride | | CODE NAME (If any) |
| DOSAGE FORM: chewable tablets | STRENGTHS: 5mg and 10mg | ROUTE OF ADMINISTRATION: oral |
| (PROPOSED) INDICATION(S) FOR USE: Seasonal Allergic Rhinitis Perennial Allergic Rhinitis Chronic Idiopathic Urticaria | | |

APPLICATION DESCRIPTION

| |
|---|
| APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601) |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____ |
| TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER Response to labeling comments |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) |
| REASON FOR SUBMISSION To provide response to FDA labeling comments for Zyrtec (cetirizine HCl) Chewable Tablet pending NDA. |
| PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) |
| NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC |
| ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. |

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Response to labeling comments

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:

ADDRESS (Street, City, State, and ZIP Code)

Robert Clark, VicePresident, US Regulatory Affairs

08Mar04

235 East 42nd Street, New York, NY 10003

Telephone Number

(212) 573-3412

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Department of Health and Human Services
 Food and Drug Administration
 CDER, HFD-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

Food and Drug Administration
 CDER (HFD-94)
 12229 Wilkins Avenue
 Rockville, MD 20852

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Pfizer's Response to FDA's 03Mar04 Labeling Comments NDA 21-621

FDA comment 1a:

Revise the Professional Sample Blister (5mg and 10mg) One Count as follows:
Front panel: Relocate the strength so that it appears in conjunction with the established name and increase its prominence.

Pfizer response 1a:

The strength designation on the 10mg blister was relocated on the packaging to reside in proximity to the product name. The 10mg designation was increased in size, boldness, and location to increase prominence. We are not planning to launch the 5mg Professional Sample Blister One Count at this time. If we decide to launch this presentation in the future, we will make appropriate changes to the 5mg presentation at that time.

FDA comment 1b:

Revise the Professional Sample Blister (5mg and 10mg) One Count as follows:
Back panel: The product name and website obscure the readability of the stamped lot number and expiration date. Revise accordingly.

Pfizer response 1b:

Please note the lot number and expiration date will be embossed (not stamped) on the front panel of the blister card. This information is intended to be read from the front panel only.

FDA comment 2:

Revise the Professional Sample Carton (5mg and 10mg) 30 cards X 1 tablet and the Individual Folding Carton Professional Sample (10mg) Ten Count. Refer to comment 1a.

Pfizer response 2:

The strength designation (10mg) was added to all panels of the Professional Sample Carton (30 cards x 1 tablet) and resides in proximity to the product name. The 10mg designation was increased in size, boldness, and location to increase prominence. A second strength designation was added to the Individual Folding Carton Professional Sample to reside in closer proximity to the product name. The 10mg designation was increased in size, boldness, and location to increase prominence. We are not planning to launch the 5mg Professional Sample Carton at this time. If we decide to launch this presentation in the future, we will make appropriate changes to the 5mg presentation at that time.

FDA comment 3a:

Revise the Professional Sample Shipping Carton (Early Experience Kit 10mg) (10X10) as follows:

Pfizer response 3a:

FDA comment 3b:

Revise the Professional Sample Shipping Carton (Early Experience Kit 10mg) (10X10) as follows: This carton contains 10 professional sample cartons of 10 tablets each and is referred to as the 'Early Experience Kit'. Explain what is meant by this terminology.

Pfizer response 3b:

The Early Experience Kit is a Pfizer-specific term referring to the set of Professional Samples distributed to select physicians at the time of launch. The Early Experience Kit is intended to introduce the product to select physicians and provide them with an opportunity to experience the product early in the launch of the product. Early Experience Kits have been used previously with other Pfizer products.

FDA comment 3c:

Revise as referenced in 1a.

Pfizer response 3c:

A second strength designation on the 10mg Professional Sample Carton (Early Experience Kit) (10X10) was added on the packaging to reside in proximity to the product name. The 10mg designation was increased in size, boldness, and location to increase prominence.

FDA comment 4:

Revise the Blister Label (5mg and 10mg) 10 count to differentiate between the 5mg and 10mg blister label with the use of contrasting color, boxing or some other means.

Pfizer response 4:

To differentiate between the 5mg (trade) and 10mg (trade and professional sample) blister cards, a prominent '5mg' and '10mg' designation was placed in the center, non-blister section of the cards. Additionally to further help differentiate between 5mg and 10mg blister labeling, the 10mg designation is boxed on each individual blister and on the 10mg in the center of the card, whereas the 5mg presentation does not incorporate boxing.

FDA comment 5a:

Revise the Individual Folding Carton (5mg and 10mg) 3 x 10 count as follows:
The numbers 5 and 10 inside the blue circle have no designation. Delete the blue circle. The blue circle (containing the numbers 5 and 10) are distracting especially since the strength is prominently displayed below.

Pfizer response 5a:

Standard Pfizer trade dress for solid oral dosage forms uses this graphic on packaging to help readily recognize the tablet shape and color (purple). This trade dress graphic has been used on all solid dosage forms packaged by Pfizer since approximately 1993.

FDA comment 5b:

Revise the Individual Folding Carton (5mg and 10mg) 3 x 10 count as follows:
Revise the net quantity to read "30 chewable tablets – 3 X 10 tabs/card".

Pfizer response 5b:

We prefer the designation of "30 chewable tablets" because the intended unit of sale is 30 tablets (the full contents of the Individual Folding Carton) and do not want to encourage dispensing of individual blister cards.

FDA comment 5c:

Revise the Individual Folding Carton (5mg and 10mg) 3 x 10 count as follows:
Increase the prominence of the statement "Tablet not recommended for children under the age of 2 years old."

Pfizer response 5c:

The above-referenced statement was increased in both size and boldness to increase prominence.

FDA comment 6:

Additional Pfizer responses to FDA package labeling comments:

In addition to the above listed changes, the following items were also modified to incorporate FDA's labeling comments throughout Zyrtec (cetirizine HCl) Chewable Tablet package labeling as noted above:

- a.
- b. Increased prominence of 'Tablet not recommended for children under the age of 2 years old' on professional components:
- Professional Sample Blister One Count (10mg)
 - Professional Sample Carton (10mg) 30 cards X 1 tablet
 - Professional Sample Individual Folding Carton (10 mg) Early Experience Kit
 - Professional Sample Shipping Carton (10mg) Early Experience Kit
- c. Changed presentation of the words 'chewable tablet' to be consistent with trade components:
- Re-designed Zyrtec (cetirizine HCl) CHEWABLE TABLET logo such that the chewable tablet letters are all in capital letters and increased the size of 'cetirizine HCl'
 - Changed 'chewable tablet' to CHEWABLE TABLET' on the side panels of the Professional Sample Individual Folding Carton (10 mg) Early Experience Kit
- d. Added the name of the product to the center of the blister labels (10mg trade and professional sample, and 5mg trade)

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FDA comment 7:

Revise the proposed label with the recommended changes as marked in the attached label.

Pfizer response 7:

| Page (as numbered in 3Mar04 fax) | FDA Proposal | Pfizer Position |
|--|--|---|
| 3 | Add betacyclodextrin to list of inactive ingredients for tablet formulation. | Please note betacyclodextrin is not an inactive ingredient of the tablet formulation. Betacyclodextrin is an inactive ingredient in the chewable tablet formulation as indicated by 'betadex' under the list of inactive ingredients for the chewable tablet. We are agreeable to changing betadex to betacyclodextrin. |
| 9 | Change Pregnancy Category B wording | Agree |
| 13 | Adverse Reactions- remove _____ | Agree |
| 13 | Γ L | Pfizer requests more clarification to FDA's rationale for proposing the adverse events listed. |
| 14 | Dosage and Administration – reword to add clarity of 2.5mg dosing for syrup only and 5mg dosing for either syrup or chewable tablet | Agree |
| 15 | Dosage and Administration – add subsection "Dose Adjustment for geriatric patients 77 years of age and older: In patients 77 years of age and older, a dose of 5mg once daily is recommended." | Pfizer requests discussion regarding the proposed. |
| 16 | Unclear | Add UCB logo. |

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2004

| | |
|-----------------------------------|--|
| To: Samantha Wolfe | From: Colette Jackson |
| Company: Pfizer | Division of Pulmonary and Allergy Drug Products |
| Fax number: 212-857-3558 | Fax number: 301-827-1271 |
| Phone number: 212-573-2241 | Phone number: 301-827-9388 |
| Subject: NDA 21-621 | |

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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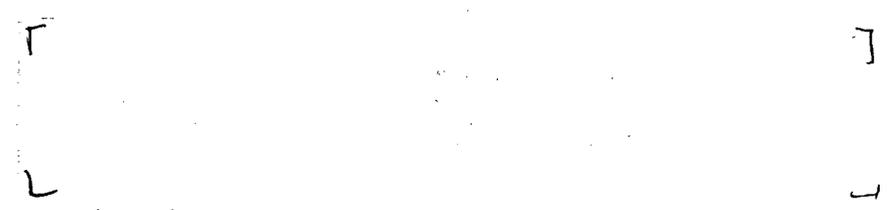
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NDA 21-621
Zyrtec Chewable Tablets

Please refer to your May 15, 2003, new drug application (NDA) for Zyrtec (cetirizine HCl) Chewable Tablets, 5 mg and 10 mg, and we have the following preliminary labeling comments and/or recommendations.

1. Revise the Professional Sample Blister (5 mg and 10 mg) One Count as follows:
 - a. Front panel:

Relocate the strength so that it appears in conjunction with the established name and increase its prominence.
 - b. Back panel:

The product name and website obscure the readability of the stamped lot number and expiration date. Revise accordingly.
2. Revise the Professional Sample Carton (5 mg and 10 mg) 30 cards X 1 tablet and the Individual Folding Carton Professional Sample (10 mg) Ten Count. Refer to comment 1.a
3. Revise the Professional Sample Shipping Carton (Early Experience Kit 10 mg) (10 x 10) as follows:
 - a. 
 - b. This carton contains 10 professional sample cartons of 10 tablets each and is referred to as the 'Early Experience Kit'. Explain what is meant by this terminology.
 - c. Revise as referenced in 1.a.
4. Revise the Blister Label (5 mg and 10 mg) 10 count to differentiate between the 5 mg and 10 mg blister label with the use of contrasting color, boxing, or some other means.

5. Revise the Individual Folding Carton (5 mg and 10 mg) 3 x 10 count as follows:
 - a. The numbers 5 and 10 inside the blue circle have no designation. Delete the blue circle. The blue circle (containing the numbers 5 and 10) are distracting especially since the strength is prominently displayed below.
 - b. Revise the net quantity to read "30 chewable tablets – 3 X 10 tabs/card".
 - c. Increase the prominence of the statement "Tablet not recommended for children under the age of 2 years old".
6.

7. Revise the proposed label with the recommended changes as marked in the attached label.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

Enclosure: Recommendations to the Proposed Label

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WITHHOLD 14 PAGE(S)

DRAFT
LABELING

cc:

HFD-570/Bosken
HFD-570/Gilbert-McClain
HFD-570/Fadiran
HFD-570/Shah
HFD-570/McGovern
HFD-570/Jao
HFD-570/Lostritto

Drafted: February 22, 2004

Initialed:

Barnes/February 27, 2004
Bosken/ February 27, 2004
Gilbert-McClain/March 1, 2004
Fadiran/ March 1, 2004
Shah/ March 1, 2004
McGovern/ March 1, 2004
Lostritto for Jao/ March 1, 2004
Lostritto/ March 1, 2004
Chowdhury/ March 2, 2004

Finalized: CCJ/March 3, 2004

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Colette Jackson
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Clinical Team Leader Review Memorandum

Memorandum to: NDA 21-621 file
Product: Cetirizine (Zyrtec®) chewable tablet
Applicant: Pfizer Inc.
Memo Date: February 23, 2004
Memo From: Lydia I. Gilbert-McClain, MD, Clinical Team Leader

Background

NDA 21-621 for cetirizine (Zyrtec®) chewable tablets was submitted under Section 505 (b)(2) of the FD&C Act which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product. The regulation allows for a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The sponsor (Pfizer) used the currently marketed 10-mg Zyrtec® tablets as the reference product.

Zyrtec® (5mg and 10 mg) tablets and Zyrtec® syrup (1 mg/ml) are approved for the treatment of seasonal and perennial allergic rhinitis in subjects 2 years of age and older and chronic idiopathic urticaria in subjects 6 months of age and older. The Applicant proposes the same dosing administration for the chewable tablet and no new indications are proposed. The tablets are bilayer immediate release tablets formulated as purple round tablets containing an active layer with the drug and other inactive ingredients including betacyclodextran (Betadex), and an inactive layer containing mannitol, dyes and other sweeteners.

The development program was a bioequivalence program comparing the 10 mg reference product (commercial Zyrtec), to the 10 mg chewable tablet. Bioequivalence studies with the 5 mg product were not conducted and the sponsor requested a waiver for this in view of similar dissolution profiles between the 5 mg and the 10 mg products. Establishment of efficacy was not required and safety information was obtained from the clinical pharmacology studies, post-marketing experience with Zyrtec® and a search of the AERS database.

A brief overview of the pertinent findings is presented below. For further details, please refer to the excellent reviews by the primary review disciplines (Dr. Carol Bosken-Medical Officer review, Dr Sandra Suarez-Sharp – Biopharmaceutics/Clinical pharmacology, and Dr. Edward Jao - CMC).

Summary of Clinical Pharmacology/Biopharmaceutics and Clinical safety

Of the 7 clinical pharmacology studies conducted, 3 were considered to be relevant to the NDA. These studies used the Zyrtec® 10-mg commercial tablet as the reference product, and the pharmacokinetic parameters of the 10-mg CT tablet was compared to that of the 10-mg commercial tablet taken with and without water, and in the fed and