CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

ENVIRONMENTAL ASSESSMENT and/or FONSI

The request for a categorical exemption from the environmental assessment has been granted. See p 4 of the Chemistry Review # 2.

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21150/000
Stamp: 19-JAN-2000
Regulatory Due: 12-AUG-2001
Applicant: PFIZER
235 EAST 42ND ST
NEW YORK, NY 10017
Priority: 3S
Org Code: 570

Action Goal:
District Goal: 20-SEP-2000
Brand Name: ZYRTEC-D 12 HOUR(CETIRIZINE HCL 5MG/PSEU
Estab. Name:
Generic Name: CETIRIZINE HCL 5MG/PSEUDOEPHEDRINE 120MG

Dosage Form: (EXTENDED-RELEASE TABLET)
Strength: 5/120 MG

Application Comment: THE APPLICATION SAYS UCB SA, HOWEVER THE ONLY CFN # I FOUND IS FOR UCB BIOPHARMA, SA. THE STREET ADDRESS IS CHEMIN DU FORIEST, 1420 BRAINE-L'ALLEUD, BELGIUM.
THEIR RESPONSIBILITIES ARE DRUG SUBSTANCE MANUFACTURING, PACKAGING AND STABILITY. TESTING. ALSO DRUG PRODUCT MANUFACTURING, PACKAGING AND STABILITY TESTING. DATE OF INSPECTION READINESS IS 2/1/00. THEY HAVE THEIR OWN REGISTRATION NUMBER WHICH IS 36998. I DON'T KNOW WHAT THIS REG # MEANS. OTHER REG [redacted] PFIZER HAS 2 REG NUMBERS TOO.
EASTERN POINT: 1211022, BROOKLYN: 2410925-NYK. (I FOUND THEM TO BE CFN NUMBERS LATER). THE BROOKLYN FACILITY OF PFIZER HAS MENTIONED THEY DO APPROVAL TESTING. I INFERED THIS AS RELEASE TESTING.
(on 09-MAR-2000 by P. PERI (HFD-810) 301-827-1054)

FDA Contacts: P. PERI (HFD-810) 301-827-1054 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment [redacted]

[redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAR-2000				PERIP
OC RECOMMENDATION	10-MAR-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 1211022
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAR-2000				PERIP
OC RECOMMENDATION	10-MAR-2000			ACCEPTABLE	FERGUSONS

BASED ON PROFILE

Establishment: 2410924
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206
DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAR-2000				PERIP
SUBMITTED TO DO	10-MAR-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	10-MAR-2000	GMP			LFARINA
DO RECOMMENDATION	21-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	LFARINA
OC RECOMMENDATION	21-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: 9610703
UCB BIOPRODUCTS SA
BRAINE L'ALLEUD, , BE
DMF No: 4763 6853 AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAR-2000				PERIP
SUBMITTED TO DO	10-MAR-2000	10D			EGASM
DO RECOMMENDATION	20-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 10/1/99					
OC RECOMMENDATION	20-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAR-2000				PERIP
SUBMITTED TO DO	10-MAR-2000	GMP			EGASM
DO RECOMMENDATION	21-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 10/99, AND PER J. DIETRICK					
OC RECOMMENDATION	21-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21150/000
Stamp: 19-JAN-2000 Regulatory Due: 19-FEB-2001
Applicant: PFIZER
235 EAST 42ND ST
NEW YORK, NY 10017

Priority: S Org Code: 570
Action Goal: District Goal: 20-SEP-2000
Brand Name: ZYRTEC-D 12 HOUR(CETIRIZINE HCL 5MG/PSEU
Established Name:
Generic Name: CETIRIZINE HCL 5MG/PSEUDOEPHEDRINE 120MG
Dosage Form: EXT (EXTENDED-RELEASE TABLET
Strength: 5/120 MG

FDA Contacts: P. PERI (HFD-810) 301-827-5579 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 21-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: —

DMF No: —
AADA No

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 10-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment: 1211022
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 10-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 2410924
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206

DMF No:
AADA No:

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 21-MAR-2000

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9610703**
UCB BIOPRODUCTS SA

BRAINE L'ALLEUD, , BE

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **21-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

APPEARS THIS WAY
ON ORIGINAL

[redacted]

CLINICAL PHARMACOLOGY LABELING COMMENTS

July 2001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
Labeling Comments

NDA	NDA 21-150
Drug Substance	Cetrizine HCl / pseudoephedrine HCl
Drug Product(s)	Zyrtec-D 12 Hour extended release tablets (Cetrizine HCl 5 mg / pseudoephedrine HCl 120 mg)
Sponsor	Pfizer Inc.
Type of submission	Response to the Agency's comments in the approvable letter
Date of submission	2/12/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

1. SYNOPSIS

The present labeling comment is to provide the complete statement for "Distribution", "Metabolism", and "Elimination" under the section of Clinical Pharmacology, since the earlier review stated only the changing portion of the labeling [Refer to Dr. Young Moon Choi's review dated 6/1/2001].

In addition, the sponsor's proposal of addition of following statement to the section of Dosage and Administration is acceptable from a biopharmaceutic perspective:

> *"Zyrtec-D 12 HOUR Extended Release Tablets should be swallowed whole, and should not be broken or chewed."*

2. LABELING COMMENTS

The labeling under the following subsections should be read as follows:

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.
The apparent volume of distribution (V/F) of pseudoephedrine has been reported to be 2.6-3.3 L/kg. No plasma protein binding data in humans are available.

Metabolism: A human mass balance study of cetirizine in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

One to seven per cent of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.

Elimination: After administration of the ZYRTEC-D 12 HOUR Extended Release Tablet, the mean elimination half-life of cetirizine was 7.9 hours and the mean elimination half-life of pseudoephedrine was 6.0 hours.

It was reported that 0.4-0.7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2 to 3 fold higher than those in plasma.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

cc NDA 21-150: Division File
HFD-870: Young Moon Choi, Emmanuel Fadiran, Henry Malinowski
HFD-570: Craig Ostroff

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Young-Moon Choi
7/16/01 12:32:34 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
7/16/01 03:09:20 PM
BIOPHARMACEUTICS
I concur

APPEARS THIS WAY
ON ORIGINAL