CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-784

Chemistry Review(s)

CHEMISTRY REVIEW

NDA 50-784

Zithromax® film-coated tablet

Pfizer Inc.,

Andrew Yu
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS,
HFD-520

Chemistry Review Data Sheet

1. NDA 50-784

2. REVIEW #:1

3. REVIEW DATE: 4/29/02

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-50-711(approved 7/18/96)	2/15/94
NDA 50-670 (approved 11/1/91)	4/11/90
NDA-50-710 (approved 10/19/95)	10/29/93

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 50-784	27-JUL-01
NDA 50-784 BC (EA)	09-OCT-01
NDA 50-784 BC (dissolution data)	20-NOV-01
NDA 50-784 BC (Response to IR)	05-MAR-02
NDA 50-784 BC (Response to deficiency)	29-MAR-02
NDA 50-784 BC (Response to IR)	26-APR-02

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Inc

CHEMISTRY REVIEW

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Address:	50 Pequot Ave. New London CT 06320
Representative:	Ronald I Trust
Telephone:	860-732-6991

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zithromax® film-coated tablet
b) Non-Proprietary Name (USAN): Azithromycin
c) Code Name/# (ONDC only): CP-62993
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
- Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: 21CFR 314.50

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Oral tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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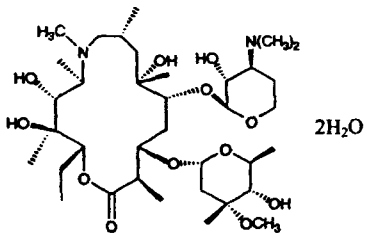
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Azithromycin Dihydrate $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$ MW: 785.03
(2S,5R,6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid dihydrate



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	IV	—		1		4/26/02	Previously approved in 250 mg tablet
—	III	—		3		8/8/01	For stability only, no change since the last review
—	III	—		3		8/3/01	No change since the last review
—	III	—		3		6/6/00	No change since the last review
—	III	—		3		8/24/97	No change since the last review
—	III	—		3		3/24/00	No change since the last review

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	III			3		12/17/99	No change since the last review
	III			3		8/31/00 8/31/00 8/31/00	No change since the last review
	III			4		4/26/02	Closure used in lower strength tablet also.

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Azithromycin 250 film-coated tablets	NDA 50-711	250 mg film coated tablet that shares a common blend
Azithromycin Powder for Oral Suspension	NDA 50-710	100 mg/5 ml and 200mg/5ml suspension dosage form
Azithromycin Capsule	NDA 50-670.	250 mg capsule dosage form

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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Thamban Valappil
EES	completed	4/26/02	Andrew Yu
Pharm/Tox	Pending		Kenneth Seethaler
Biopharm	Pending		Charles Bonapace
LNC	NA		
Methods Validation	NA	4/26/02	Andrew Yu
OPDRA	Pending		D. Diwa, D. Toyer
EA	Completed	4/26/02	Andrew Yu
Microbiology	Pending		Harold Silver

The Chemistry Review for NDA 50-784

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from CMC view point, the label is pending final revision; all other CMC deficiencies are resolved and all facility inspections are acceptable. Please see CMC comment to Sponsor at the end of this review.

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

None at this point.

II. Summary of Chemistry Assessments

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

Azithromycin is derived from erythromycin, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38} H_{72} N_2 O_{12}$. Azithromycin drug substance is available as the dihydrate, and is a white crystalline powder with a molecular weight of 785.0.

the dihydrate is relatively stable. No polymorphic crystal transformation occurs during processing that would affect its solubility/dissolution or solid state compression characteristic of the drug. ZITHROMAX is supplied for oral administration as film-coated, capsular shaped tablets containing azithromycin dihydrate equivalent to 500 mg azithromycin. The following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin and D&C Red #30 aluminum lake are compatible with the drug. The was previously employed in the manufacturing of the 250 mg tablet (NDA 50-711). The 500 mg tablets proposed in this NDA are packaged in TRI-PAK of 3, unit dose blister of 50 and bottle of 30.

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

The drug product in the present NDA is intended for oral administration. The recommended dose regimen for one of several proposed indication involves loading dose of 500 mg on day one followed by 250 mg q.d. on days two through five. The 500 mg tablet was previously not available and is proposed in this NDA. The new dose strength is stable under the proposed storage condition of 15 to 30° C.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance, azithromycin dihydrate met identity, purity, and stability requirements; it also met acceptance criteria for formulating as an immediate release oral product. Specifications and test methods are well documented, and the process impurity as well as residual solvents during synthesis of the drug are adequately controlled. A similar product was approved in a previous NDA review which used the same drug source. The excipients used in Zithromax 500 mg tablet meet compendial requirements. There are no known incompatibility problem between the excipients and the active ingredient. Since [redacted] were used in the 250 mg tablet, the dissolution data of the new tablet were compared with the approved 250 mg tablet. There were some differences observed during the early phase of the dissolution cycle in some test batches, indicating that the 500 mg tablet might dissolve slightly faster than the 250 mg, however, a repeat analysis and a review of the dissolution method employed indicates that the differences were limited and reversed in later time period. The transient difference reflects inherent dissolution method variability rather than true difference. When dissolution was performed for long period, the difference was not significant and the tablet met USP based specification established for this product. The conclusion was supported by Biopharmaceutics.

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block /S/

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

Redacted 37

pages of trade secret and/or confidential commercial information

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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/

Andy Yu
5/3/02 12:54:51 PM
CHEMIST

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David Katague
5/3/02 01:08:24 PM
CHEMIST