

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-797**

**CHEMISTRY REVIEW(S)**



**CHEMISTRY REVIEW**



**NDA 50-797**

**Zmax  
Azithromycin Extended Release for Oral Suspension  
Review #1**

**Pfizer Inc.**

**Anti-Infective Drug Products**

**Shrikant N. Pagay**



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Appears This Way  
On Original



# Chemistry Review Data Sheet

1. NDA 50-797
2. REVIEW #: 1
3. REVIEW DATE: 9/8/04
4. REVIEWER: Shrikant N. Pagay
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original	8/12/04
Amendment (Facility for M & C addresses)	9/22/04
Amendment (Stability Update)	12/14/04
Correspondance (Trade name)	1/13/05
Amendment (Dissolution profiles of bio batches)	2/4/05
Amendment (Revised limits for total impurities)	2/9/05
Amendment (Response to deficiencies)	3/14/05
Amendment (Response to deficiencies)	5/25/05
Amendment (Response to Deficiencies)	6/6/8/05
Correspondance (Phase IV for Drug Substance)	6/10/05



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 50 Pequot Avenue  
New London, CT 06320

Representative: Donald R. Jaffe

Telephone: 860- 732- 8325

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Pending
- c) Code Name/# (ONDC only): NA
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: for Extended Release Oral Suspension

12. STRENGTH/POTENCY: 2.0 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

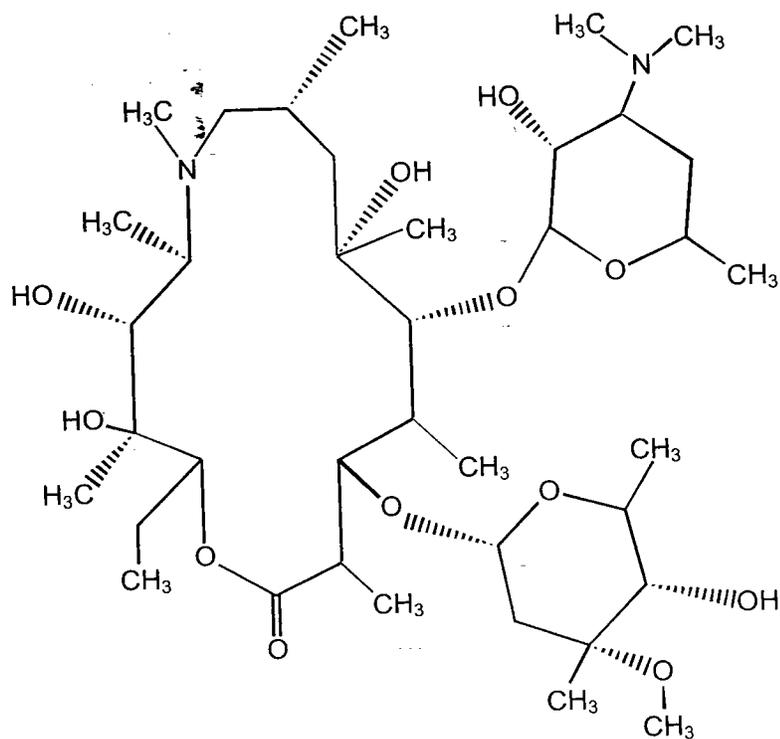
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A - (USAN 3)





# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	IV	[REDACTED]		1	Adequate	6/4/05	
	IV			1	Adequate	6/4/05	
	III			4	Adequate	6/4/05	Specific in the DMF not listed
	III			1	Adequate	6/4/05	
	III			1	Adequate	3/11/03	J. Salemme
	III			1	Adequate	6/9/03	D.Klein
	III			7			Secondary package

<sup>1</sup> 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")

<sup>2</sup> 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
NDA	50-670	Drug substance
IND	24,999	EOPII submissions
IND	66,194	Pre-NDA submissions



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	6/6/05	See Appendix for EER
Pharm/Tox	NA		
Biopharm	NA		
LNC	Establish name negotiated		Pfizer agreed, concurrence from LNC
Methods Validation	Pending	3/21/05(submitted)	
OPDRA	Trade name negotiated	5/26/05	J. Soreth (informed Pfizer on 5/26/05)
EA	Categorical Exemption accepted	5/28/05	S.Pagay
Microbiology	NA		

#### 19. COMMENTS:

Please note that all italicized portion of Chemistry Assessment Section are reviewer's comments. The remaining information (data, figures and some responses to deficiencies) is directly incorporated from the submission. This does not apply to the Chemistry Review Data Sheet and the Executive Summary Sections.

Regarding the proprietary name, Zmax [redacted] was not acceptable to DDMAC/DMET. Zmax was acceptable from promotional point but the recommendation was to use the previously approved name Zithromax. The project team allowed using Zmax as the proprietary name.

With regard to establish name, the proposed name was azithromycin [redacted]. The Label and Nomenclature Committee (LNC) recommended the name should be "azithromycin for extended release oral suspension" which will also be a recommendation for a USP Monograph for the dosage form. The firm accepted to remove the word [redacted] however, wanted to consider the establish name in ( ) as "(azithromycin extended release)" and outside ( ) "for oral suspension". The reviewer did concur with the LNC's recommendation since it will comply with a future USP Monograph. The sponsor's rationale was that the name is too long and suspension as a dosage form may not be acceptable to an adult population. Therefore, project team accepted Pfizer's second proposal. So the establish name is "(azithromycin extended release) for oral suspension".



# The Chemistry Review for NDA 050-797

## The Executive Summary

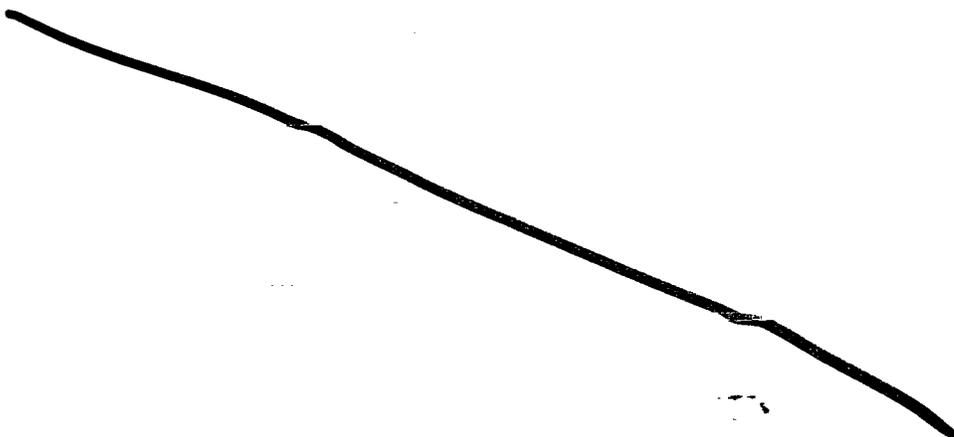
### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend to approve this application NDA 50-797 from CMC consideration.

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

#### Phase IV Commitments



### II. Summary of Chemistry Assessments

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

##### Drug Substance

Azithromycin is in a class of macrolide antibiotics. It is derived from erythromycin but it differs chemically from erythromycin in that a methyl substituted nitrogen atom is incorporated into the lactone ring. Azithromycin is further grouped in a sub-class



Executive Summary Section

designated as azalide. Azithromycin was initially approved under NDA 50-670. The previously approved drug products were capsule, powder for oral suspension and injection. Azithromycin in the proposed drug product is a microsphere combined with flavors and sugar which constituted with water to form an oral suspension. The drug substance is a dihydrate, white crystalline material and gives a very bitter taste upon ingestion. [REDACTED]

[REDACTED] USP Monograph also includes a monohydrate prepared by a different synthetic route. The commercial process in the proposed NDA for azithromycin produces only the dihydrate form (Type A). Solubility pH profile for the drug substance show that it is very soluble below pH [REDACTED] at pH [REDACTED] at pH [REDACTED] the solubility decreases to only [REDACTED] and at [REDACTED]. This information was used in developing the suspension. The drug taste was masked by formulating the suspension so that the pH is from [REDACTED]. The drug tends to decompose rapidly in the acidic pH range where the solubility is high. The pH solubility profile and pH- profile kinetics was considered in selecting the dissolution test medium. Phosphate pH 6.0 buffer was selected taking into account solubility and stability considerations.

Drug product:

The drug product is a single dose of 2 grams azithromycin. The formulation is composed of three different blends (azithromycin microspheres, vehicle blend and sucrose). [REDACTED]

[REDACTED] The selection of dosage form as a suspension allowed a convenient method to deliver a large single dose (2 grams of active moiety). [REDACTED]

[REDACTED] Glyceryl behenate and poloxamer were selected to prepare azithromycin microspheres. Glyceryl behenate is a mixture of glycerides of fatty acids, mainly saturated behenic acid.

This has been shown to improve taste and gastro-intestinal tolerance especially



**Executive Summary Section**

with the intake of such a large single dose. Other components are typically used in suspension formulation such as flavors, sweeteners, suspending agents, and viscosity enhancers. A uniform mixture is achieved upon the addition of water to prepare the suspension.

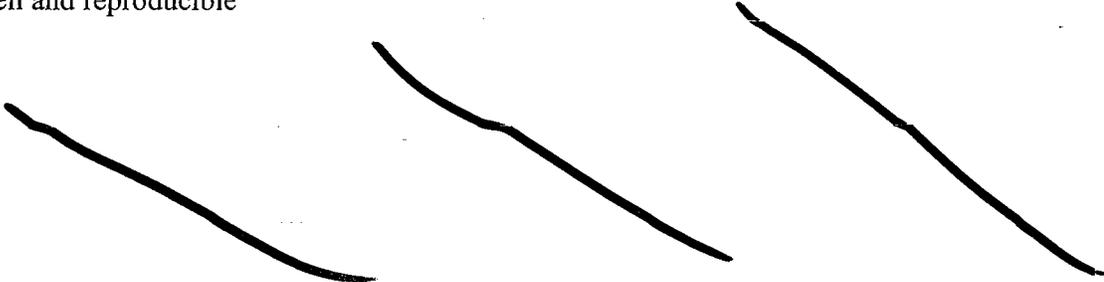
**B. Description of How the Drug Product is Intended to be Used**

The drug product is a single dose, constituted as a 60 mL suspension and administered the entire dose by mouth. The taste is very bitter, however, the suspension was formulated to mask the taste and need to tolerate only once for the entire therapy. I

**C. Basis for Approvability or Not-Approval Recommendation**

Critical CMC considerations for approval of this NDA

The dosing regimen for antibiotics and anti-infective agents is a critical issue for optimum therapy. Since antibiotics are given in large doses, developing an extended release formulation is difficult which has been achieved. The formulation is designed to achieved desired objectives, i.e., to release the drug slowly. The manufacturing process is controlled well and reproducible



The drug product is robust.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist Name/Date: Shrikant N. Pagay  
ChemistryTeamLeader Name/Date: James Vidra  
Project Manager Name/Date: Judit Milstein

**C. CC Block**

68 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-1