CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-809

CHEMISTRY REVIEW(S)

NDA 50-809

Azithromycin For Injection

Sicor Pharmaceuticals

Andrew Yu
HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-809

2. REVIEW#: 1

3. REVIEW DATE: 1/31/06

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Pre-IND 67,798	11-June-2004

6. Submission being review: Original

Submission(s) Reviewed	Document Date
NDA 50-809	29-July-2005
Amendment (Stability update)	31-Janurary 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Sicor Pharmaceuticals

Address: 19 Hughes, Irvine CA 92618

Representative: Sonia Hernandez

Telephone: 949-455-4779

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Azithromcyin for injection
c) Code Name/# (ONDC only): FIJ
d) Chem. Type/Submission Priority (ONDC only): New Dosage form

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(2)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 500 mg and 2.5 g per vial

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: X___Rx ___OTC

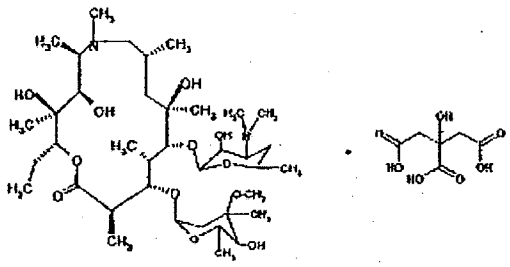
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)-oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one hydrogencitrate,

Molecular weight 941.13
Formula $C_{44}H_{80}N_2O_{19}S_3$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II		Azithromcyin hydrogencitrate	1	Inadequate	5/10/06	Some deficiencies pending

[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
Pre-IND	PIND 67,798	Pre-IND dated 6/11/04 to discuss the 505(b)(2) for Azithromycin

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	4/20/06	S. Fergusion
Pharm/Tox	N/A		
Biopharm	N/A		
LNC			
Methods Validation	Not a new drug		Package not sent to District Laboratory
OPDRA (DMETS)	Pending (——— sent by C. Debellas)	3/3/06	DMETS staff
EA	Categorical exclusion claimed-Adequate		N/A
Microbiology	Deficiencies pending		Steven Langille

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes _____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 50-809

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approvable (AE) to this application NDA 50-809 from CMC view point.

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

II. Summary of Chemistry Assessments

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

The drug substance was provided by the DMF holder

This NDA application is recommended approvable (AE) from CMC view point due to a

The drug substance manufacturing site was found acceptable by the Office of Compliance based on profile. The product manufacturing site was inspected and found acceptable. Sicor did not claim EA exemption or a full EA package in the NDA. Instead, Sicor presented EA information on 50-733 (Azithromycin Intravenous injection from Pfizer) apparently obtained through FOI. The sponsor did not respond to this deficiency/IR comment.
A consolidated list of all deficiencies and comments sent is included in page 68 of this review.

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

The drug product is a lyophilized powder for injection containing 500 mg of azithromycin. The initial solution of azithromycin is reconstituted with 4.8 mL of Sterile water for injection to the 500 mg vial. A pharmacy bulk of 2.5 gm azithromycin per vial is also proposed. The pharmacy bulk is reconstituted with 23 mL of Sterile water for injection. The reconstituted solution is stable for 24 hours when stored below 30°C or 86 °F. This solution should be inspected visually for particulate matters prior to administration. This solution is diluted in several media prior to administration. The dilution to a concentration ranged of 1.0-2.0 mg/mL are described for Normal saline, 5% Dextrose in water, Lactated Ringer's Solution and several other media are described in detail in the Package insert.

C. Basis for Approvability or Not-Approval Recommendation

NDA 50-809 is recommended as approvable from CMC view point. The applicant has not

The sponsor has not responded to important deficiency questions dated 3/2/06 and 3/16/06 on this issue.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Andrew Yu Chemist/Date: 10/10/06
Norman Schmuff DPA4 Branch Chief/
Carman Debellas, PM/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

65 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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
5/26/2006 10:19:32 AM
CHEMIST

Elaine Morefield
5/26/2006 10:35:35 AM
CHEMIST

NDA 50-809

Azithromycin For Injection

Sicor Pharmaceuticals

Andrew Yu
HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-809

2. REVIEW#: 2

3. REVIEW DATE: 11/30/06

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
NDA 50-809	29-July-2005
Amendment (Stability update)	31-Janurary 2006

6. Submission being review: Original

Submission(s) Reviewed	Document Date
50-809BC (response to Def.)	5/24/06
50-809AC (re-submission)	**6/16/06**
50-809BC (Amended method)	8/8/06
50-809US (response to Def.)	7/26/06
50-809US (response to Def.)	8/14/06
50-809US (Update stability & CMC commitment)	12/8/06
50-809BC (Specification change)	12/12/06

7. NAME & ADDRESS OF APPLICANT:

Name: Sicor Pharmaceuticals

Address: 19 Hughes, Irvine CA 92618

Chemistry Review Data Sheet

Representative: Sonia Hernandez

Telephone: 949-455-4779

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b) Non-Proprietary Name (USAN): Azithromcyin for injection
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- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(2)

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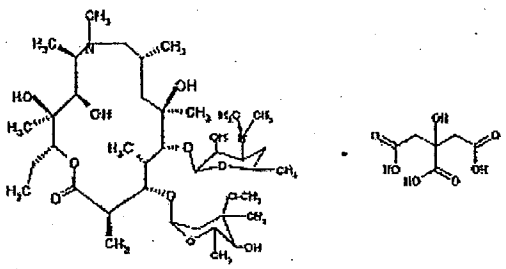
Molecular weight 941.13
Formula $C_{44}H_{80}N_2O_{19}S_3$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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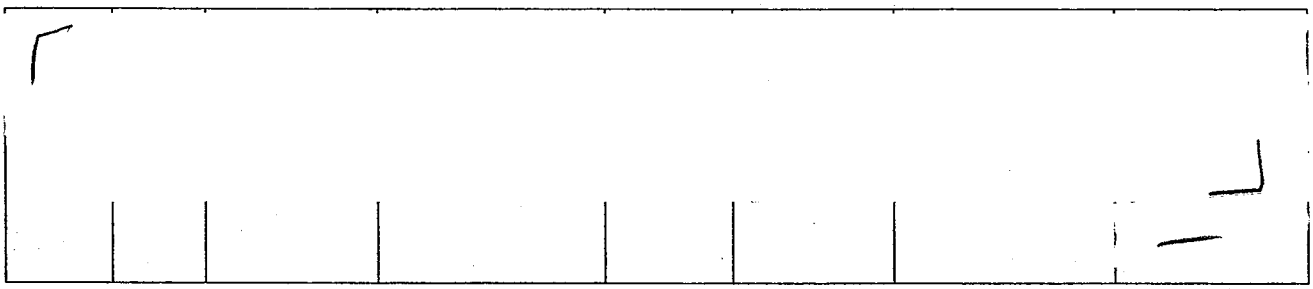
—	II	—	Azithromcyin hydrogencitrate	1	Adequate	10/10/06	Major deficiencies resolved.



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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre-IND	PIND 67,798	Pre-IND dated 6/11/04 to discuss the 505(b)(2) for Azithromycin

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	8/1/06	J. D'Ambrogio
Pharm/Tox		11/7/06	Wendy Schmidt (email)
Biopharm	N/A		
LNC			
Methods Validation	Acceptable with	10/10/06	Performed by St Louis

	modification	And 11/21/06	FDA Laboratory
OPDRA (DMETS)	Pending (___ sent by C. Debellas)	3/3/06	DMETS staff
EA	Categorical exclusion claimed-Adequate		N/A
Microbiology	Recommends approval	5/23/06	Steven Langille

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 50-809

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval (AP) to this application NDA 50-809 from CMC consideration. Approvable deficiencies cited in review # 1 were mostly resolved in the re-submission (Page 45-75). The remaining "analytical method" deficiency will be addressed by post approval commitment as agreed upon with the sponsor. The manufacturing facilities are all acceptable.

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

II. Summary of Chemistry Assessments

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

The drug product is a lyophilized powder for injection containing 500 mg of azithromycin and 2.5 g respectively in two different configuration. The drug substance, azithromycin hydrogen citrate is made by the DMF holder, This product was "approvable" in review #1 and re-submitted in this review cycle. The initial proposed brand name was withdrawn by the sponsor. The sponsor has committed to improve the method for the analysis of

used during manufacturing. This issue was the key CMC issue for "approvable" action in

review#1 during the first submission of this NDA.

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

The drug product is a lyophilized powder for injection containing 500 mg of azithromycin. The initial solution of azithromycin is reconstituted with 4.8 mL of Sterile water for injection to the 500 mg vial. A pharmacy bulk of 2.5 gm azithromycin per vial is also proposed. The pharmacy bulk is reconstituted with 23 mL of Sterile water for injection. The reconstituted solution is stable for 24 hours when stored below 30°C or 86 °F. This solution should be inspected visually for particulate matters prior to administration. This solution is diluted in several media prior to administration. The dilution to a concentration ranged of 1.0-2.0 mg/mL are described for Normal saline, 5% Dextrose in water, Lactated Ringer's Solution and several other media are described in detail in the Package insert.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submissions and the Drug Master File provide adequate information on the chemistry and manufacturing controls for the production of this lyophilized product for injection. A list of CMC deficiencies and questions previously communicated to the sponsor were adequately responded in the re-submission. The primary deficiency was the finding of

The applicant has satisfactorily demonstrated with long term stability for three lots that the product is stable for 24 months. Both Azithromycin content and several degradation products/impurities are within specification. The The manufacturing sites have been found acceptable with the Office of Compliance. The proposed product specifications are adequate. The proposed shelf life of the drug product of two years was granted after an additional six months of stability was submitted just before the PDULFA due date.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

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

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

72 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Andy Yu
12/18/2006 08:45:02 AM
CHEMIST

Norman Schmuff
12/18/2006 09:08:21 AM
CHEMIST