

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-132

CHEMISTRY REVIEW(S)



NDA 22-427

**ACUVAIL (ketorolac tromethamine ophthalmic solution)
0.45% Preservative-Free**

Allergan, Inc.

**Lin Qi
Division of Anti-Infective and Ophthalmology Product**



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Chemistry Review Data Sheet

1. NDA 22-427
2. REVIEW #: 2
3. REVIEW DATE: 7/14/09
4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	9/29/2008
Amendment	11/21/2008
Amendment	3/10/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	5/1/2009
Amendment	6/17/2009
Amendment	7/8/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc.
Address: 2525 Dupont Drive
Irvine, CA 92612
Representative: Elizabeth Bancroft



Chemistry Review Data Sheet

Telephone: 714-246-4391

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ACUVAIL
- b) Non-Proprietary Name (USAN): Ketotolac tromethamine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: For the treatment of pain and inflammation following cataract surgery

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.45%

13. ROUTE OF ADMINISTRATION: Topical, ophthalmic

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:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)	II	(b)	Drug substance	1	Adequate	11/13/2008	

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

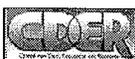
6 – DMF not available

7 – Other (explain under "Comments")

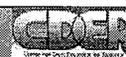
² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND 21,132	Same drug substance used
	NDA 19-700	Same drug substance used
	NDA 21-528	Same drug substance used
	NDA 20-811	Same drug substance used



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	12/19/2008	Shawnte L Adams
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable	4/30/2009	Lin Qi
OPDRA			
EA			
Microbiology	Acceptable	7/8/2009	Bryan S. Riley

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval based on product quality assessment.

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

None.

II. Summary of Chemistry Assessments

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

The drug substance ketorolac tromethamine is a white to off-white crystalline powder with a pKa of 3.49. It is a tromethamine $[\text{HOCH}_2\text{CNH}_2(\text{CH}_2\text{OH})_2]$ salt of ketorolac in a 1 to 1 molar ratio. The drug substance is freely soluble in water (>100 mg/mL) at room temperature and pH 6.8. Ketorolac tromethamine is manufactured at (b) (4) and is utilized for the current marketed product ACULAR, NDA 21-528.

The proposed drug product, ketorolac tromethamine ophthalmic solution 0.45%, is a sterile, non-preserved, clear, and colorless to pale yellow isotonic ophthalmic solution. This formulation contains 0.45% (w/v) ketorolac tromethamine. The inactive ingredients include carboxymethylcellulose (b) (4), sodium chloride (b) (4) (b) (4) and sodium citrate (b) (4).

The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid to a target pH of 6.8 for the final product. The drug product is packaged in clear, LDPE, unit dose vials in a 0.4 mL nominal fill volume/0.9 mL fill capacity. The drug product will be manufactured at Allergan America, Waco, Tx.

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

The proposed indication is for the treatment of pain and inflammation following cataract surgery. One drop of the drug product should be applied by the patient to the affected eye twice daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. A total of 4 drops should be administered the day of cataract surgery by medical personnel. The 30 vials supply can be used for the whole treatment period according the proposed dosing regimen.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The remaining issues from CMC review #1 dated April 30, 2009 relate to microbiological product quality and the GMP status of the additional endotoxin testing sites.

Dr. Bryan recommended approval in his product quality microbiological review dated July 2, 2009.

The applicant stated that the additional endotoxin testing facility, Allergan, Inc., Pharmaceutical Analysis (PAM) does not perform endotoxin testing on the finished product. The only test conducted by this facility is an endotoxin test for one of the excipients (b) (4). Therefore, this facility does not need to be inspected. The overall recommendation on GMP status of facilities recommended by the Office of Compliance is "Acceptable".

III. Administrative

A. Reviewer's Signature

{Signed and dated electronically in DFS}

B. Endorsement Block

{Signed and dated electronically in DFS}

C. CC Block

Pharmaceutical Assessment Lead
Project Manager

7 Pages Withheld as b(4) Trade Secret/Confidential

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

/s/

Lin Qi
7/15/2009 10:56:15 AM
CHEMIST

Norman Schmuff
7/15/2009 01:01:02 PM
CHEMIST



NDA 22-427

**ACUVAIL (ketorolac tromethamine ophthalmic solution)
0.45% Preservative-Free**

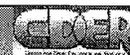
Allergan, Inc.

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Chemistry Review Data Sheet

1. NDA 22-427
2. REVIEW #: 1
3. REVIEW DATE: 4/30/2009
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

9/29/2008

Amendment

11/21/2008

Amendment

3/10/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc.

Address: 2525 Dupont Drive
Irvine, CA 92612

Representative: Elizabeth Bancroft

Telephone: 714-246-4391



Chemistry Review Data Sheet

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

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

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ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable		Lin Qi
OPDRA			
EA			
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval as there are pending issues related to adequate acceptance criteria for drug product endotoxin testing. All other drug product quality (CMC) issues are satisfactory, including the GMP status of facilities which the Office of Compliance recommends as "Acceptable".

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

None.

II. Summary of Chemistry Assessments

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

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Executive Summary Section

and through the first 2 weeks of the postoperative period. A total of 4 drops should be administered the day of cataract surgery by medical personnel.

C. Basis for Approvability or Not-Approval Recommendation

The active drug substance ketorolac tromethamine is utilized in an approved drug product under NDA 21-528 (Acular). The purpose of current application is to develop a non-preserved ophthalmic formulation of ketorolac which offers an effective treatment without the possibility of preservative toxicity.

Appropriate information are provided regarding manufacturing process, process controls, and product controls. Based on the statistical evaluation on 12 months of long term stability potency data and 18 months of long term stability data from the supportive lot, the projected expiration date is greater than 36 months for both the primary stability batches and the supportive stability batch. The proposed expiration dating for the ketorolac tromethamine ophthalmic solution 0.45% is 24 months for market configuration and the physician sample configuration when stored at 15° - 30°C (59° - 86°F) protect from light. This expiry period is acceptable.

In the amendment dated November 21, 2009, the applicant committed to establishing a drug product endotoxin specification by April 30, 2009. This application is recommended for approval pending adequate acceptance criteria for drug product endotoxin testing and a satisfactory quality microbiological review.

III. Administrative

A. Reviewer's Signature

{Signed and dated electronically in DFS}

B. Endorsement Block

{Signed and dated electronically in DFS}

C. CC Block

Pharmaceutical Assessment Lead
Project Manager

53 Pages Withheld as b(4) Trade Secret/Confidential

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

/s/

Lin Qi
4/30/2009 04:36:18 PM
CHEMIST

Norman Schmuff
4/30/2009 04:39:33 PM
CHEMIST