CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

CHEMISTRY REVIEW(S)

NDA 21-528

Ketorolac Tromethamine Ophthalmic Solution, 0.4%

Allergan Inc.

Su C. Tso, Ph. D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-528

2. REVIEW # 1

3. REVIEW DATE: 1/24/03, revised on 3/10/03 & 4/14/03

4. REVIEWER: SU C. TSO

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL	8/6/02
Amendment	11/4/02
Amendment	12/23/02
Amendment	2/24/03
Amendment	2/28/02
Amendment	4/2/03

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan Inc.

Address: Dupont Drive, P. O. Box 19534, Irvine, CA 92623

Representative: Elizabeth Bancroft

Telephone: 714-246-4391

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: **Pending**
b) Non-Proprietary Name (USAN): Ketorolac Tromethamine
c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION:

In compliance with the FDA guidance "providing Regulatory Submissions in Electronic Format—NDAs"

10. PHARMACOL. CATEGORY: Nonsteroidal Anti-inflammatory

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.4%

13. ROUTE OF ADMINISTRATION: Topical/ocular

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

____x__Not a SPOTS product

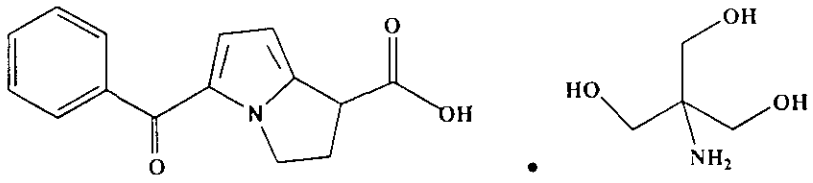
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN name:	Ketorolac tromethamine
Molecular formulas:	C_{19} H_{24} N_2 O6
Molecular weight:	376.41
CAS #	74103-07-4
Allergan code name:	AGN 191578-J

Chemical Name:

1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (+/-)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanidiol (1:1)

Chemical Structural:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	11/13/02 by S. Tso	LOA 4/19/02
	III			3	Adequate	10/5/00 by L Rodriguez	LOA: 1/17/00
	III			3	Adequate	8/8/00 by L. Rodriguez	LOA. 1/17/00
	III			1	Adequate	10/30/02 by S. Tso	LOA: 4/26/02

[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

[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
Acular	NDA 19-700 Updated	Ketorolac tromethamine, 0.5% ophthalmic solution, approved 11/9/92
Acular PF	NDA 20-811 Updated	Ketorolac tromethamine, Approved 11//3/97

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	**Pending inspection**	4/2/03	Su Tso
DMETS	**Pending**	4/2/03	
Methods Validation	Adequate. None to be validated	2/26/03	Su Tso
EA	Category Exemption	2/26/03	Su Tso
Microbiology	Approval	2/27/03	Vinayak Pawar

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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-528

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a chemistry, manufacturing, and control standpoint, pending for a satisfactory trade name review, and GPM inspection.

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, it has a pK_a of 3.46, and water solubility of 200 mg/mL Ketorolac tromethamine is manufactured at Roche Ireland Limited, Clarecastle, Co. Clare, Ireland, and supplied by Syntex USA. Ketorolac tromethamine is an approved drug substance utilized for the current marketed product ACULAR, NDA 19-700.

The proposed drug product is a 0.4% solution. It is a clear, colorless to lightly yellow sterile isotonic aqueous solution. It is preserved with 0.006% benzakonium chloride, other inactive ingredients include edetate disodium (chelating agent), octoxynol-40 (solubilizing agent) and sodium chloride (tonicity agent). The formulation is adjusted to a pH of 7.3-7.5. The formulation of the proposed drug product contains exactly the same ingredients as that of the approved ACULAR (ketorolac tromethamine ophthalmic solution) 0.5%. The drug product is packaged in a white LDPE bottle with gray color cap made of high impact polystyrene resin (5 mL in 10 mL bottle and [redacted]. The drug product will be manufactured at Allergan America, Waco, Tx.

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

The drug product is indicated for the reduction of ocular pain and ocular symptoms of foreign body sensation, photophobia, burning/stinging, and tearing following refractive surgery. The recommended dose is one drop four times a day for up to 4 days in the operated eye. The product may be approved with an expiration date of 18 months when stored at 15-25 °C.

C. Basis for Approvability or Not-Approval Recommendation

The active drug substance Ketorolac tromethamine is an approved drug under NDA 19-700 (ACULAR). The components of dosage form is the same as NDA 19-700, except the composition is different (0.4% instead of 0.5% for ACULAR).

Judging from the12 months long term stability data provided, and from the history of the approved drug ACULAR, NDA 19-700 (expiration date of 24 months), this drug product will be stable for 18 months when stored at 15 to 25 °C. However the container/closure integrity is in question since there were ——— found at the base of the tip during stability studies regardless of the container orientation. The applicant was informed to provide explanation of the formation of the ——— and provide stability data of the three validation batches to support the application (appendix IV and Appendix VII). Satisfactory explanation and correction of the ——— observed in the stability samples were provided in amendments dated 2/24/03, 2/28/03, and 4/2/03.

The application is recommended for approval pending for a satisfactory trade name review and GMP inspection at drug product manufacturing facility at Waco, Tx.

III. Administrative

A. Reviewer's Signature

Su C Tso, Ph.D.

B. Endorsement Block

Linda Ng, Ph.D., Chemistry Team Leader

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/

Su Tso
4/17/03 09:29:05 AM
CHEMIST

chemist's review # 1

Linda Ng
4/17/03 01:06:45 PM
CHEMIST
CMC recommends AP pending trade name and inspection

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

47 pages