CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Ketorolac tromethamine
PRODUCT (Brand Name):	NA
DOSAGE FORM:	Ophthalmic solution
DOSAGE STRENGTHS:	Ketorolac tromethamine 0.4%
INDICATION:	Reduction in ocular pain associated with refractory surgery
NDA:	21-528
NDA TYPE:	S
SUBMISSION DATE:	8/7/02
SPONSOR:	Allergen Inc.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.
OCPB DIVISON:	DPE III, HFD 880
OND DIVISION:	ODE V, HFD 550

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EXECUTIVE SUMMARY

Background:

Ketorolac tromethamine is a NSAID with established analgesic, anti-inflammatory, and anti-pyretic activity. Ketorolac ophthalmic solution, 0.4% is indicated for the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing and photophobia following refractory surgery.

Ketorolac is currently marketed by Allergan as a 0.5% preserved formulation (ACULAR®) and 0.5% non-preserved formulation (ACULAR® PF) since 1992 for the treatment of ocular itching due to allergic conjunctivitis, an indication different from that proposed for 0.4% ketorolac ophthalmic solution.

Ketorolac is also available as tablets and injectable for IM or IV use with maximum daily dose of 120 mg, not to exceed 5 days.

Ketorolac tromethamine ophthalmic solution 0.4% contains ketorolac tromethamine 0.4% supplied as an aqueous solution in an ophthalmic vehicle containing water, edetate disodium, octoxynol, sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust the pH and the preservative benzalkonium chloride (0.006%).

As the use of ACULAR® 0.5% is associated with ocular adverse events, primarily ocular burning and stinging, this NDA evaluates a formulation of ketorolac tromethamine ophthalmic solution that contains lower levels of potential irritants including octoxynol, edetate disodium, and the preservative benzalkonium chloride. Additionally, the formulation represents a 20% reduction in concentration of the active ingredient, ketorolac tromethamine (from 0.5% in the currently marketed ACULAR ® product to 0.4%).

Dosing and Administration:

The recommended dose of 0.4% ketorolac ophthalmic solution is one drop four times a day for up to 4 days in the operated eye.

Considering a drop size of 50 µL, a total of 0.8 mg (4 x 0.2 mg) of ketorolac will be administered daily per eye up to 4 days through the ocular route. These doses are much lower than the oral or IM/IV doses.

Formulation:

Component	Concentration (% w/v)	Concentration (mg/mL)
Ketorolac tromethamine	0.4	4.0
Benzalkonium chloride (10% w/v stock solution	0.006	0.06
Edetate Disodium	0.015	0.15
Octoxynol-40 (70% w/w stock solution)	[redacted]	[redacted]
Sodium Chloride	[redacted]	[redacted]
1N Hydrochloric Acid or 1N Sodium Hydroxide	Adjust pH to 7.3 to 7.5	
Purified Water	q.s. ad to 100%	q.s. ad to 1 mL

Systemic Absorption of Ketorolac tromethamine 0.4% after Topical Ocular Dosing:

No new studies have been conducted to assess the systemic absorption of ketorolac tromethamine from the 0.4% ophthalmic solution. This product contains a lower concentration of the active ingredient as compared to the marketed 0.5% ketorolac ophthalmic solution (ACULAR- with preservative and ACULAR-PF- without preservative). A formulation comparison between 0.4% and 0.5% ketorolac ophthalmic solution is given below:

Ingredient	Ketorolac tromethamine ophthalmic solution 0.4%	ACULAR 0.5%
Ketorolac tromethamine	0.4	0.5
Benzalkonium chloride, NF	0.006	0.01
Edetate disodium, USP	0.015	0.1
Octoxynol-40	[redacted]	[redacted]
Sodium chloride, USP		
NaOH, NF	pH 7.3-7.5	pH 7.3-7.5
HCl, NF	pH 7.3-7.5	pH 7.3-7.5
Purified water, USP	qs	qs

Looking at the comparative concentrations of the active and the inactive ingredients suggests that the systemic absorption with 0.4% ketorolac ophthalmic solution is not likely to be higher than the marketed ACULAR product due to the following reasons:

- The concentration of the active ingredient is 20% lower in the 0.4% ketorolac ophthalmic formulation.
- Preservatives help in increasing drug penetration across the cornea. In the current formulation, the concentration of benzalkonium chloride is lower than the marketed 0.5% ketorolac (ACULAR) ophthalmic solution formulation. Hence, its effect on increased absorption as compared to ACULAR will be minimal.
- Disodium edetate is a disodium salt of EDTA, a chelating agent known to assist in corneal drug penetration. This is also present in concentration much lower the concentration in ACULAR.
- Octoxynol-40 is used as an emulsifier and is present in [redacted] concentrations as compared to ACULAR.

- The pH (7.4) and the osmolarity (290 mOsml/kg) of the ophthalmic solution remain the same.
- Moreover, the total duration of treatment is up to 14 days for ACULAR (indicated for the treatment of ocular itching due to allergic conjunctivitis) and up to 4 days for 0.4% ketorolac ophthalmic solution (indicated for the reduction of ocular pain after refractory surgery). Hence, the total cumulative dose of ketorolac is significantly lower in the 0.4% formulation.

Since many of the inactive ingredients are known to contribute to ocular adverse events it is likely that decreasing their concentration will reduce the frequency of local adverse events, thereby enhancing comfort. In some cases, the ocular irritation may also affect the efficacy of the drug.

The references provided by the sponsor as part of the NDA application for the Human Pharmacokinetics section includes pharmacokinetic information on ketorolac after oral, IM or IV dosing, hence carries little relevance for evaluating systemic absorption after ocular dosing, and therefore have not been reviewed for this NDA.

The following systemic and aqueous humor concentrations have been taken from the ACULAR product (submitted as part of NDA 19-700) for labeling purposes:

Systemic Concentrations:

One drop (0.05 mL) of 0.5% ketorolac tromethamine ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

Aqueous Humor Concentrations:

Two drops (0.1 mL) of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E 2 (PGE2) levels in aqueous humor. The mean concentration of PGE 2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving ketorolac tromethamine 0.5% ophthalmic solution.

RECOMMENDATION

The Clinical Pharmacology and Biopharmaceutics section of the NDA 21-528 is acceptable from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics. "CLINICAL PHARMACOLOY" section of the label containing the

pharmacokinetic information is identical to the ACULAR product. However, the following labeling comment should be conveyed to the sponsor.

LABELING RECOMMENDATION

Under the "CLINICAL PHARMACOLOGY" section of the label a subsection entitled the "Pharmacokinetics" should be inserted before the included paragraphs describing the results following dosing with the 0.5% product.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D._____

APPEARS THIS WAY
ON ORIGINAL

APPENDIX

PROPOSED PACKAGE INSERT

Number of Pages Redacted 5

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Draft Labeling
(not releasable,

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-528	Brand Name	
OCPB Division (I, II, III)	III	Generic Name	Ketorolac tromethamine
Medical Division	550	Drug Class	NSAID
OCPB Reviewer	Veneeta Tandon	Indication(s)	Reduction of ocular pain [redacted] burning/stinging and [redacted] following refractive surgery
OCPB Team Leader	Dennis Bashaw	Dosage Form	Ophthalmic solution
		Dosing Regimen	1 drop 4 times a day up to 4 days in the operated eye
Date of Submission	8/6/02	Route of Administration	topical
Estimated Due Date of OCPB Review	March 03	Sponsor	Allergan
PDUFA Due Date	6/6/03	Priority Classification	S
I. Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2.				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse.				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference.				
Bioequivalence studies -				
traditional design; single / multi dose.				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	5			
Total Number of Studies				

Filability and QBR comments		
II.	"X" if yes	Comments
III. Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
IV. Comments sent to firm ? V.	No	Comments have been sent to firm (or attachment included) FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above	0.5% ketorolac tromethamine ophthalmic solution is already approved in the US. The subject of this NDA is a lower concentration (0.4%). No new PK studies have been conducted for this NDA. Label contains information from the approved 0.5% ketorolac tromethamine ophthalmic solution. Literature reports provided.	
Primary reviewer Signature and Date	Veneeta Tandon	
Secondary reviewer Signature and Date	Dennis Bashaw	

CC: NDA 21-258, HFD-850(Electronic Entry or Lee), HFD-550(Rodriguezr), HFD-880(TL, DD, DDD)

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

/s/

Veneeta Tandon
3/21/03 11:55:22 AM
BIOPHARMACEUTICS

Dennis Bashaw
3/21/03 02:36:55 PM
BIOPHARMACEUTICS

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