

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-132

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-427
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: September 30, 2008
PRODUCT: Acuvail™ (ketorolac tromethamine ophthalmic solution) 0.45%
INTENDED CLINICAL POPULATION: For the treatment of postoperative pain and inflammation in patients who have undergone cataract extraction
SPONSOR: Allergan
DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Anti-Infective and Ophthalmology Products
PHARM/TOX REVIEWER: Conrad H. Chen, Ph.D.
PHARM/TOX SUPERVISOR: Wendelyn Schmidt, Ph.D.
DIVISION DIRECTOR: Wiley Chambers, M.D.
PROJECT MANAGER: Raphael Rodriguez
Date of review submission to Division File System (DFS):

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW.....	4
2.6.1 INTRODUCTION AND DRUG HISTORY.....	4
2.6.2 PHARMACOLOGY.....	5
2.6.2.1 Brief summary	5
2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....	6
2.6.4.1 Brief summary	6
2.6.4.3 Absorption	6
2.6.4.4 Distribution.....	11
2.6.4.5 Metabolism.....	11
2.6.4.6 Excretion.....	11
2.6.4.7 Pharmacokinetic drug interactions.....	11
Studies have not been conducted following ophthalmic administration of ketorolac.....	11
2.6.4.8 Other Pharmacokinetic Studies.....	11
2.6.4.9 Discussion and Conclusions	11
2.6.4.10 Tables and figures to include comparative TK summary	11
2.6.6 TOXICOLOGY.....	12
2.6.6.1 Overall toxicology summary	12
2.6.6.2 Single-day toxicity.....	12
2.6.6.3 Repeat-dose toxicity	13
2.6.6.4 Genetic toxicology.....	14
2.6.6.5 Carcinogenicity.....	14
2.6.6.6 Reproductive and developmental toxicology.....	14
2.6.6.7 Local tolerance	15
2.6.6.8 Special toxicology studies	15
2.6.6.9 Discussion and Conclusions	16
2.6.7 TOXICOLOGY TABULATED SUMMARY	17
OVERALL CONCLUSIONS AND RECOMMENDATIONS.....	18

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability
The approval is recommended.
- B. Recommendation for nonclinical studies
None
- C. Recommendations on labeling
The Section 8.1 Pregnancy and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility is similar to that for approved products Acular LS and Toradol. The proposed labeling is acceptable.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings
Ketorolac tromethamine is an NSAID with analgesic, anti-inflammatory, and anti-pyretic activity. The non-clinical safety studies for ocular use of ketorolac tromethamine have been evaluated during the approval of Acular® (0.5% ketorolac tromethamine ophthalmic solution), Acular® PF (0.5% ketorolac tromethamine ophthalmic solution preservative free), and Acular LS® (0.4% ketorolac tromethamine ophthalmic solution).
The reformulated 0.45% ketorolac tromethamine pH 6.8 (Acuvail™) contained CMC and eliminated the preservative BAK. Acuvail™ delivers ketorolac more efficiently in rabbit ocular tissues as compared to the aqueous-based vehicle used in Acular® and Acular LS®. Therefore, the dosing frequency of the Acuvail™ can be reduced to two times a day as compared to four times a day for Acular® and Acular LS®.
In the newly conducted 28-day GLP ocular toxicity studies in NZW rabbits, Acuvail™ administered 5x/day was well-tolerated. The ocular irregularities (epithelial thinning) observed in the early toxicity studies with BAK-containing KT formulation were not observed in the current study.
- B. Pharmacologic activity
Ketorolac tromethamine is an NSAID with analgesic, anti-inflammatory, and anti-pyretic activity. When given topically, ketorolac demonstrated potent anti-inflammatory activity in several models of ocular inflammation in rats and rabbits.
- C. Nonclinical safety issues relevant to clinical use
There are no non-clinical safety issues related to clinical use of this product.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-427

Review number: No. 1

Sequence number/date/type of submission: SN000/September 29, 2008/Original application

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Allergan, Inc.

Manufacturer for drug substance: (b) (4)

Reviewer name: Conrad H. Chen, Ph.D.

Division name: Division of Anti-Infective and Ophthalmology Products

Review completion date: March 31, 2009

Drug:

Trade name: Acuvail™

Generic name: Ketorolac tromethamine ophthalmic solution 0.45%

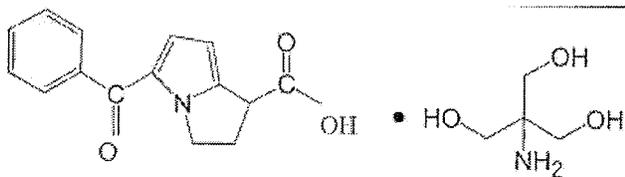
Code name: Not indicated

Chemical name: (±)-5-benzoyl-2,3-dihydro-1Hpyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

CAS registry number: 74103-07-4

Molecular formula/molecular weight: Its molecular formula is C₁₉H₂₄N₂O₆. Its molecular weight is 376.41.

Structure:



Relevant INDs/NDAs/DMFs:

NDA 19-700, Acular® (ketorolac tromethamine ophthalmic solution) 0.5%

NDA 20-811, Acular® PF (ketorolac tromethamine ophthalmic solution) 0.5%

Preservative-Free

NDA 21-528, Acular LS® (ketorolac tromethamine ophthalmic solution) 0.4%

IND 21,132, Ketorolac tromethamine ophthalmic solution 0.45%

Drug class: NSAID

Intended clinical population: For the treatment of pain and inflammation following cataract surgery

Clinical formulation:

Table 3.2.P.1-1 Composition of Ketorolac Tromethamine Ophthalmic Solution, 0.45%

Ingredient	Grade	Function	Concentration (% w/v)
Ketorolac Tromethamine	Test to USP/Ph Eur	Active	0.45%
Carboxymethylcellulose (b) (4)	USP/Ph Eur	(b) (4)	(b) (4)
(b) (4)			
Carboxymethylcellulose (b) (4)	USP/Ph Eur	(b) (4)	(b) (4)
(b) (4)			
Sodium Chloride	USP/Ph Eur	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	USP/Ph Eur	(b) (4)	(b) (4)
Sodium Hydroxide (1N)	NF/Ph Eur	pH adjustment	Adjust to pH 6.8
Hydrochloric Acid (1N)	NF/Ph Eur	pH adjustment	Adjust to pH 6.8
Purified Water	USP/Ph Eur	(b) (4)	(b) (4)

Route of administration: Topical ocular

Recommended Dosing:

Patient Dosing

One drop of ACUVAIL™ should be applied 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.

Dosing on the Day of Surgery by Medical Personnel

Approximately 2 hours prior to surgery, 1 drop is administered approximately every 20 minutes by medical personnel for a total of 3 drops. Prior to discharge instill 1 additional drop.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The sponsor cross-referenced to IND 21,132, NDA 19-700, NDA 20-811, and NDA 21-528 for the pharmacology information.

When given systemically to rodents, ketorolac demonstrated potent analgesic and anti-inflammatory activity, which was mediated primarily *via* inhibition of arachidonic acid cyclooxygenase. When given topically, ketorolac demonstrated potent anti-inflammatory activity in several models of ocular inflammation in rats and rabbits.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Acular® (0.5% ketorolac tromethamine ophthalmic solution) has been marketed in the US as a nonsteroidal anti-inflammatory ophthalmic agent since 1997 and in Europe since 1989. The absorption, distribution, metabolism, and excretion (ADME) of ketorolac have been extensively studied during the development of Acular® (0.5% ketorolac tromethamine ophthalmic solution), Acular® PF (0.5% ketorolac tromethamine preservative free ophthalmic solution), and Acular LS® (0.4% ketorolac tromethamine ophthalmic solution).

Ketorolac concentrations in plasma, aqueous humor, and iris ciliary body were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The ocular pharmacokinetic study results demonstrate that 0.45% ketorolac tromethamine formulated with CMC at pH 6.8 delivers ketorolac more efficiently in rabbit ocular tissues as compared to the aqueous-based vehicle used in Acular® and Acular LS®. A comparison of ketorolac exposure in rabbit aqueous humor following a single drop (35 to 50 µL) ophthalmic administration of these formulations is presented in the following table.

Table 2.6.4.1-1 Comparison of ketorolac exposure in rabbit aqueous humor

PK Parameter	ACULAR® (0.5% KT) ^a	0.45% KT CMC-based pH 6.8 ^b	ACULAR LS® (0.4% KT) ^b
C _{max} (ng/mL or ng-eq/mL)	217 (109)	389 (258)	211 (106)
AUC ₀₋₄ (ng·hr/mL or ng-eq·hr/mL)	583 (51)	939 (163)	465 (65)

a: Data from Report DM 579, see module Module 1.4.1, Table 4.2, 50 µL drop

b: Report PK-07-096, 35 µL drop

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

KT: Ketorolac Tromethamine

CMC: Carboxymethylcellulose

Ketorolac levels achieved with the new formulation (0.45%) are less than the ocular and systemic drug levels previously demonstrated to be well tolerated in long term toxicology studies in which rabbits received up to 4% ketorolac tromethamine formulated in the Acular® and Acular LS® aqueous-based formulation (NDA 19-700, submitted May 27, 1987 and NDA 21-528, submitted August 7, 2002).

2.6.4.3 Absorption

Aqueous humor:

1. Effect of pH (from Allergan Report PK-07-096)

Following a single bilateral topical ocular instillation of one of four 0.45% ketorolac tromethamine formulations with varying pH from 7.4 to 6.8, formulated with CMC to an approximately equal level of viscosity (21-22 centipoise or cps), ketorolac was absorbed into the aqueous humor in rabbits to varying degrees as follows.

Table 2.6.4.3-1 Aqueous humor ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of ketorolac tromethamine formulations with varying pH

Species n/timepoint	Formulation	Dose (%w/v)	Relative %F	AUC ₀₋₄ (ng-hr/mL)	C _{max} (ng/mL)	T _{max} (hr)	Allergan Report
3F (6 eyes)	CMC, pH 7.4, 22 cps	0.45	135	627 (51)	265 (71)	2.00	PK-07-020
	CMC, pH 7.2, 22 cps	0.45	133	619 (50)	240 (84)	1.00	
	CMC, pH 7.0, 21 cps	0.45	142	658 (73)	268 (125)	1.00	
	CMC, pH 6.8, 22 cps	0.45	202	939 (163)	389 (258)	2.00	
	ACULAR LS®	0.4	100	465 (65)	211 (106)	1.00	

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

% F: Relative bioavailability expressed as a percent of the AUC₀₋₄ value following a single ocular instillation of a 35 µL drop of ACULAR LS®

CMC: Carboxymethylcellulose

F: Female

cps: centipoise

Among these formulations, the greatest C_{max} value of 389±258 ng/mL and greatest AUC₀₋₄ value of 939±163 ng-hr/mL were measured for the formulation with a pH value of 6.8.

- Effect of carboxymethylcellulose (CMC) (from Allergan Report PK-07-020)
The absorption of ketorolac from Acular LS® and from formulations containing CMC and HPMC (hydroxypropylmethylcellulose) into the aqueous humor of rabbits was compared following a single bilateral ocular instillation in rabbits. The results showed that the CMC-based formulation achieved the greatest ketorolac exposure in aqueous humor. The C_{max} and AUC_{0-t} was 480±160 ng/mL and 2420±250 ng-hr/mL, respectively, for the KT formulation containing CMC.

Table 2.6.4.3-2 Aqueous humor ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of various ketorolac tromethamine formulations

Species n/timepoint	Formulation	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng-hr/mL)	Allergan Report
2F (4 eyes)	CMC, 20.2 cps	0.4	480 (160)	2.00	2420 (250)	PK-07-020
	HPMC, 19.9 cps	0.4	346 (125)	2.00	1660 (190)	
	ACULAR LS®	0.4	334 (74)	2.00	1570 (100)	

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

CMC: Carboxymethylcellulose

F: Female

cps: centipoise

3. Effect of viscosity (from Allergan Report PK-07-0096 and PK-08-002)
Following a single bilateral topical instillation of 0.45 % ketorolac tromethamine CMC-based formulations with same pH value but different levels of viscosity, the aqueous humor ketorolac absorptions were compared. The results showed that as viscosity increased, ketorolac exposure in the aqueous humor appeared to decrease as shown in the following table.

Table 2.6.4.3-3 Aqueous humor ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of ketorolac tromethamine formulations with varying levels of viscosity

Species n/timepoint	Formulation	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng-hr/mL)	Allergan Report
3F (6 eyes)	CMC, pH 7.0, 21 cps	0.45	268 (128)	1.00	658 (73)	PK-07-096
	CMC, pH 7.0, 11 cps	0.45	347 (218)	1.00	649 (74)	
	ACULAR LS®	0.4	211 (106)	1.00	465 (65)	
3F (6 eyes)	CMC, pH 7.4, 11 cps	0.45	218 (58)	ND	ND	PK-08-002
	CMC, pH 7.4, 15 cps	0.45	187 (27)	ND	ND	
	CMC, pH 7.5, 22 cps	0.45	154 (28)	ND	ND	

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

CMC: Carboxymethylcellulose

F: Female

cps: centipoise

ND = not determined

4. Combined effect of CMC and pH (from Allergan Report PK-08-033)
Following a single bilateral topical ocular instillation of one of two 0.2% ketorolac tromethamine formulations (pH 6.8), the CMC-based formulation achieved 2-fold greater ketorolac exposure in aqueous humor as compared to a second formulation without CMC. C_{max} was 178 and 84.6 ng/mL and AUC_{0-t} was 1220 and 554 ng-hr/mL, respectively.
The 0.45% ketorolac tromethamine CMC-based formulation (pH 6.8) achieves greater ketorolac levels (about 50% increase) than Acular LS® (0.4% ketorolac tromethamine ophthalmic solution). The C_{max} was 456 and 310 ng/mL, respectively.

Table 2.6.4.3-4 Aqueous humor ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of ketorolac tromethamine formulations with and without CMC

Species n/timepoint	Formulation	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng·hr/mL)	Allergan Report
2F (4 eyes)	CMC, pH 6.8, 9-11 cps	0.2	178 (76)	2.00	1220 (90)	PK-08-033
	No CMC, pH 6.8, 1 cps	0.2	84.6 (21.2)	1.00	554 (42)	
	CMC, pH 6.8, 9-11 cps	0.45	456 (100)	2.00	ND	
	ACULAR LS®	0.4	310 (77)	2.00	2350 (130)	

C_{max}: Mean (±SD)
 AUC: Composite AUC (±SE)
 CMC: Carboxymethylcellulose
 F: Female
 cps: centipoise
 ND = not determined

Iris-Ciliary Body (from Allergan Report PK-08-033)

Following a single bilateral topical ocular instillation of one of two 0.2% ketorolac tromethamine formulations (pH 6.8), the CMC-based formulation achieved 2-fold greater ketorolac exposure in iris-ciliary body as compared to a second formulation without CMC. The C_{max} was 193 and 145 ng/mL and AUC_{0-t} was 2010 and 1160 ng·hr/mL, respectively.

The 0.45% ketorolac tromethamine CMC-based formulation (pH 6.8) achieves greater ketorolac iris-ciliary body levels as compared to Acular LS® (0.4% ketorolac tromethamine ophthalmic solution). The C_{max} was 403 and 216 ng/mL, respectively.

Table 2.6.4.3-5 Iris-ciliary body ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of various ketorolac tromethamine formulations

Species n/timepoint	Formulation	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng·hr/mL)	Allergan Report
2F (4 eyes)	CMC, pH 6.8, 9-11 cps	0.2	193 (53)	0.500	2010 (180)	PK-08-033
	No CMC, pH 6.8, 1 cps	0.2	145 (47)	1.00	1160 (100)	
	CMC, pH 6.8, 9-11 cps	0.45	403 (172)	2.00	ND	
	ACULAR LS®	0.4	216 (43)	1.00	1390 (130)	

C_{max}: Mean (±SD)
 AUC: Composite AUC (±SE)
 CMC: Carboxymethylcellulose
 F: Female
 cps: centipoise
 ND = not determined

Vitreous Humor (from Allergan Report PK-08-033)

Following a single bilateral topical ocular instillation of one of two 0.2% ketorolac tromethamine formulation (pH 6.8), the CMC-based formulation achieved 3-fold greater exposure in vitreous humor as compared to a second formulation that was identical with the exception that CMC was absent. The 0.2% ketorolac tromethamine CMC-based formulation at pH 6.8 achieved comparable exposure in vitreous humor as compared to Acular LS® (0.4% ketorolac tromethamine ophthalmic solution), despite being formulated at half the drug strength.

Table 2.6.4.3-6 Vitreous humor ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of various ketorolac tromethamine formulations

Species n/timepoint	Formulation	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng-hr/mL)	Allergan Report
2F (4 eyes)	CMC, pH 6.8, 9-11 cps	0.2	10.6 (5.2)	1.00	46.3 (4.6)	PK-08-033
	No CMC, pH 6.8, 1 cps	0.2	4.77 (2.26)	0.500	13.8 (2.2)	
	ACULAR LS®	0.4	12.1 (3.3)	0.500	37.1 (4.8)	

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

CMC: Carboxymethylcellulose

F: Female

cps: centipoise

Systemic Absorption (from Allergan Report PK-07-090)

The toxicokinetics of ketorolac were characterized in study TX07042 (Acular Reformulation: 1-Month Ocular Toxicity Study in Rabbits).

The left eye of female rabbits received one drop (~40 µL) of placebo or 0.45% ketorolac tromethamine in a CMC-based formulation, at least 5 times daily for 28 consecutive days. The right eye remained as the untreated control. On Days 1 and 28, blood samples were collected from the same 4 rabbits/group at 0 (predose), 0.5, 1, 2, 6, and 20 hours after the 5th instillation.

Systemic exposure of ketorolac on Day 1 was similar to that on Day 28 in the 0.45% group. The C_{max} was 99.0 and 111 ng/mL and AUC_{0-t} was 260 and 372 ng-hr/mL, respectively. The results are shown in the following table.

Table 2.6.4.3-7 Plasma ketorolac (AGN-191578) pharmacokinetics in NZW rabbits after topical ocular administration of 0.45% ketorolac tromethamine

Species n/timepoint	Study Day	Dose (%w/v)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng-hr/mL)	Allergan Report
4F	1	0.45	99.0 (15.0)	0.500	260 (46)	PK-07-0901
	28	0.45	111 (41)	0.500	372 (125)	

C_{max}: Mean (±SD)

AUC: Composite AUC (±SE)

F: Female

It was found that the systemic ketorolac exposure achieved in the 28-day rabbit ocular toxicity study did not exceed levels achieved following a single dose of Acular® (0.5% ketorolac tromethamine ophthalmic solution). Following a single bilateral ocular instillation of 0.5% ¹⁴C-ketorolac tromethamine in rabbits, the plasma C_{max} was 139 ng-eq/mL and AUC_{0-t} was 701 ng-eq-hr/mL (data from NDA 19-700, submitted May 27, 1987).

2.6.4.4 Distribution

Reviewed under NDA 19-700, submitted on May 27, 1987.

2.6.4.5 Metabolism

Reviewed under NDA 19-700, submitted on May 27, 1987.

2.6.4.6 Excretion

Reviewed under NDA 19-700, submitted on May 27, 1987.

2.6.4.7 Pharmacokinetic drug interactions

Studies have not been conducted following ocular administration of ketorolac.

2.6.4.8 Other Pharmacokinetic Studies

Studies have not been conducted following ocular administration of ketorolac.

2.6.4.9 Discussion and Conclusions

In summary, 0.45% ketorolac tromethamine formulated with CMC to pH 6.8 is expected to improve ketorolac delivery to ocular tissues which allows for a reduction in drug strength and dosing frequency from currently marketed products (Acular® and Acular LS®).

The 0.45% ketorolac tromethamine formulated with CMC to pH 6.8 administered twice per day is anticipated to deliver drug levels to ocular tissues that are efficacious but less than ocular and systemic drug levels previously demonstrated to be safe in long term toxicology studies (NDA 19-700).

2.6.4.10 Tables and figures to include comparative TK summary

See Table 2.6.4.1-1 in Section 2.6.4.1 Brief Summary.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The non-clinical and clinical safety profile of several KT ocular formulations has been established with the marketed products Acular® (0.5%), Acular® PF (0.5%), and Acular LS® (0.4%). To support the safety of Acuvail™ (reformulated KT 0.45%, BAK preservative free CMC-based and pH 6.8), 1-day ocular tolerability, 1-month ocular toxicity, and 6-day ocular wound healing studies were conducted. No drug- or vehicle-related effects were found during the course of the studies.

2.6.6.2 Single-day toxicity

Study title: 1-Day Ocular Tolerability Study in Rabbits

Key study findings: NZW female rabbits were administered 0.45% KT new formulation or Acular LS®, 6 drops for one day to the left eye. No drug-related effects were noted for KT new formulation while Acular LS® caused minimal ocular discomfort and mild transient conjunctival congestion.

Study no.: TX06091

Volume #, and page #: Electronic submission

Conducting laboratory and location: Allergan, Inc., Irvine, California 92612

Date of study initiation: March 12, 2007

GLP compliance: No

QA report: yes () no (x)

Drug, lot #, and % purity: Ketorolac Tromethamine (KT) batch number CC05050003; 0.45% ketorolac tromethamine formulation number 9852X

Methods

Doses: Placebo, 0.45% KT in new formulation, or Acular LS® (0.4% KT) 6 drops for one day was administered to left eye at 1 hour intervals; the right eye was untreated

Species/strain: NZW rabbits

Number/sex/group or time point (main study): 3 females/group

Route, formulation, volume, and infusion rate: Topical ocular administration

Satellite groups used for toxicokinetics or recovery: None

Age: Approximately 6 months of age

Weight: Between 3.83 and 4.23 kg

Unique study design or methodology (if any): None

Observations and times:

The following parameters were evaluated: Viability, clinical observations, ocular discomfort, gross ocular observations, and ophthalmic examinations (papillary reflex and slit lamp examinations with fluorescein staining). Ophthalmic examinations will be performed once prior to Day 1 and once within two hours following the sixth dose on Day 1. Additional slit lamp examinations may be performed at the discretion of the Study Director on Day 1 and/or Day 2.

Results:

No mortality or 0.45% KT new formulation-related effects were observed during the course of this study. In contrast, the Acular LS® formulation caused minimal ocular discomfort and mild transient conjunctival congestion.

2.6.6.3 Repeat-dose toxicity

Study title: 1-Month Ocular Toxicity Study in Rabbits

Key study findings: Eight female NZW rabbits were treated with a topical ocular drop of 0.45% ketorolac tromethamine in new formulation at least 5 times daily for 28 days, followed by a 14-day recovery period. No drug-related effects were observed. The systemic exposure (AUC) of ketorolac on Day 1 was similar to that of on Day 28.

Study no.: TX07042

Volume #, and page #: Electronic submission

Conducting laboratory and location: Allergan, Inc., Irvine, CA 92612

Date of study initiation: April 26, 2007

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, and % purity: KT Lot Number CC05050002, Purity ~100%; Formulation Number 9852X, Lot No.12863A1

Methods

Doses: A drop (~40 µL) of Placebo or 0.45% KT new formulation was administered to left eyes at least 5 times per day for 28 days; the right eyes were untreated.

Species/strain: NZW rabbits

Number/sex/group or time point (main study): 8 females/group

Route, formulation, volume, and infusion rate: Topical ocular administration

Satellite groups used for toxicokinetics or recovery: 6 females/group were sacrificed on Day 29; 2 females/group served as recovery group and were sacrificed on Day 43.

Age: Almost 5 months old

Weight: 3.45 to 3.80 kg

Sampling times: On Days 1 and 28, blood samples were collected from 8 females/group at 0, 0.5, 1, 2, 6, and 20 hour after 5th instillation for the toxicokinetics study.

Unique study design or methodology (if any): 14 days-recovery study was conducted on 2 females/group after 28-days drug administration.

Observations and times:

The following parameters were evaluated: Viability, clinical observations gross ocular observations, ophthalmic examinations (slit lamp biomicroscopy, papillary reflex, and ophthalmoscopy), intraocular pressure (IOP)/tonometry, body weight, food consumption,

toxicokinetics (TK), macroscopic observations and microscopic pathology of ocular tissues. Ophthalmic examinations were performed prior to Day 1, on Day 23 and on Day 29. The examinations at the end of the recovery period were omitted as no significant drug-related findings were noted on Days 23 and 29.

Results:

No mortality or drug-related effects on clinical observations, gross ocular observations, ophthalmic examinations, IOP, body weight, food consumption, macroscopic observations, and microscopic pathology were noted during the course of this study.

The plasma TK parameters of ketorolac (AGN-191578) are summarized as follows:

Day 1		
Treatment Group	C _{max} (ng/mL)	AUC _{0-t} (ng·hr/mL); SD
2	99.0	260; 46
Day 28		
Treatment Group	C _{max} (ng/mL)	AUC _{0-t} (ng·hr/mL); SD
2	111	372; 125

Group 2: 0.45% ketorolac tromethamine (AGN-191578-J; ~40 µL), ≥5X/day.
N = 4/sex/group/timepoint.

Ketorolac was absorbed into the systemic circulation of the rabbits following ocular administration. The systemic exposure (AUC) of ketorolac on Day 1 was similar to that of on Day 28.

2.6.6.4 Genetic toxicology

Reviewed under NDA 19-700, submitted on May 27, 1987.

2.6.6.5 Carcinogenicity

Reviewed under NDA 19-700, submitted on May 27, 1987.

Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are respectively 926 times and 370 times higher than the typical human topical ophthalmic daily dose of 0.324 mg given as BID to an affected eye on a mg/kg basis.

Reviewer's comment:

The clinical pharmacology study was not conducted in human clinical trials.

The typical human topical ophthalmic daily dose is 0.324 mg/person (4.5 mg/mL x 0.036 mL/drop, BID).

0.324 mg divided by 60 kg=0.0054 mg/kg/day

5 mg divided by 0.0054 mg=926

2 mg divided by 0.0054 mg=370

2.6.6.6 Reproductive and developmental toxicology

Reviewed under NDA 19-700, submitted on May 27, 1987.

Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits and rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively. These

doses are respectively 667 times and 1852 times higher than the typical human topical ophthalmic daily doses of 0.324 mg. Additionally, when administered to rats after Day 17 of gestation at oral doses up to 1.5 mg/kg/day (278 times the typical human topical ophthalmic daily dose on a mg/kg basis), ketorolac tromethamine resulted in dystocia and increased pup mortality.

Reviewer's comment:

3.6 mg divided by 0.0054 mg=667

10 divided by 0.0054 mg=1852

1.5 mg divided by 0.0054 mg=278

2.6.6.7 Local tolerance

Local (ocular) tolerability was reviewed under 2.6.6.2. and 2.6.6.3.

2.6.6.8 Special toxicology studies

Study title: 6-Day Ocular Wound Healing Study in Rabbits

Key study findings: After anterior keratectomy, NZW female rabbits (5/group) were given Acular LS® or KT at 0.35% or 0.45% in the new formulation *via* topical ocular administration, up to 4 times per day for 6 days. Both Acular LS® and 0.45% KT in the new formulation resulted in statistically significant delay in corneal wound healing in comparison with the blank control. However, at any tested time point after anterior keratectomy, no statistically significant differences in the rate of corneal wound healing were observed between the two placebos (Acular LS® and new formulation) or between Acular LS® and KT at 0.35% or 0.45% in the new formulation.

Study no.: TX07062

Volume #, and page #: Electronic submission

Conducting laboratory and location: Allergan, Inc., Irvine, CA 92612

Date of study initiation: April 13, 2007

GLP compliance: No

QA reports: yes () no (x)

Drug, lot #, and % purity: KT, Lot No. R16795; Reformulated KT 0.35%, Lot No.12864A1; Reformulated KT 0.45%, Lot.No.12863A1

Formulation/vehicle: 0.325% CMC (medium viscosity), 0.175% CMC (high viscosity), 0.2% sodium citrate, 0.7% sodium chloride, and purified water

Methods

Doses: Four, 3, or 2 daily drops of Acular LS®, 0.35% KE, or 0.45% KE, respectively, from the first day of treatment (Day 1) to Day 5, and one drop of each on Day 6.

Study design: The objective of this study was to evaluate the effects of reformulated KT, in comparison with Acular LS®, on the rate of corneal wound healing when given topically to the eyes of NZW rabbits for 6 days following anterior keratectomy.

Thirty rabbits weighing 2.0-2.5 kg were used. The day of anterior keratectomy was also

Group	No. of Animals and Sex	Group Identification	Dosing Frequency/Day^a (OU)
1	5F	Blank Control	N/A
2	5F	9439X: ACULAR LS® Placebo	4X
3	5F	9437X: ACULAR LS®	4X
4	5F	9854X: New Formulation Placebo	3X
5	5F	9853X: 0.35% Ketorolac Tromethamine in New Formulation	3X
6	5F	9852X: 0.45% Ketorolac Tromethamine in New Formulation	2X

OU = both eyes ^aOn Day 6, all rabbits in Groups 2 to 6 were dosed only once in the morning prior to the first daily slit lamp

the first day of dosing (Day 1).
The study group arrangement was as follows.

Results: In comparison with the blank control at approximately 120 hours post anterior keratectomy (Day 6), both Acular LS® and 0.45% KT in the new formulation resulted in statistically significant delay in corneal wound healing. Specifically on Day 6, the mean corneal wound area measured for the blank control was approximately 2% of its baseline mean (measured post surgery on Day 1), while the mean area measured for Acular LS® or 0.45% KT in the new formulation was approximately 9% or 11% of its baseline mean, respectively. However, when the placebos of Acular LS® and the new formulations were compared, no statistically significant differences in the rate of corneal wound healing were observed at any tested time point post anterior keratectomy (p>0.1). Furthermore, when Acular LS® was compared with KT at 0.35% or 0.45% in the new formulation, no statistically significant differences in the rate of corneal wound healing were observed at any tested time point post anterior keratectomy (p>0.1).

2.6.6.9 Discussion and Conclusions

The non-clinical and clinical safety of the following marketed products is well-established:

Acular® (ketorolac tromethamine ophthalmic solution) 0.5%

Acular® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free

Acular LS® (ketorolac tromethamine ophthalmic solution) 0.4%

In the previously conducted ocular toxicity studies, KT formulations at up to 4% administered 3x/day for 28 days in NZW rabbits, Dutch Belted rabbits and cynomolgus monkeys were well tolerated. KT at 0.5% administered 9x/day for 6-month in cynomolgus monkeys was also safe (NDA 19-700).

In the newly formulated KT 0.45%, the preservative BAK (benzalkonium chloride) is removed. By addition of CMC and the reduction of pH to 6.8 in the new formulation, the bioavailability of KT in the ocular tissues was enhanced. Therefore, the dosing frequency of the KT new formulation can be reduced to two times a day with a reduction in the toxicity.

In the newly conducted 28-day GLP ocular toxicity studies in NZW rabbits, the newly formulated 0.45% KT administered 5x/day was well-tolerated. The ocular irregularities (epithelial thinning) observed in the early toxicity studies with BAK-containing KT formulation were not observed in the current study.

Both Acular LS® and KT 0.45% new formulation produced the delay in corneal wound healing 120 hours post anterior keratectomy in rabbits.

2.6.7 TOXICOLOGY TABULATED SUMMARY

To support the clinical use of reformulated KT (based on unpreserved CMC), the following 1-day ocular tolerability, 1-month ocular toxicity, and 6-day ocular wound healing studies were conducted.

2.6.7.1. Toxicology: Overview

Overview Tromethamine				Test Article: Ketorolac			
Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (% w/v)	GLP Compliance	Testing Facility	Study Number
Acute Toxicity	Rabbit, New Zealand White	Topical Ocular	1 Day	Placebo (0%, new formulation) 0.4% (ACULAR LS®) 0.45% (new formulation) Each at 1 drop (~40 µL) 6 times per day, OS	No	Allergan, Inc., Irvine, California U.S.A.	TX06091
Repeat-Dose Toxicity	Rabbit, New Zealand White	Topical Ocular	28 Days	Placebo (0%, new formulation) 0.45% (new formulation) Each at 1 drop (~40 µL) ≥5 times per day, OS	Yes	Allergan, Inc., Irvine, California U.S.A.	TX07042
Other Toxicity	Rabbit, New Zealand White	Topical Ocular	6 Days	Placebo (0%, new formulation) Placebo (0%, ACULAR LS®) 0.35% (new formulation) 0.4% (ACULAR LS®) 0.45% (new formulation) Each at 1 drop (~40 µL) ≤4 times per day, OS and OD	No	Allergan, Inc. Irvine, California U.S.A.	TX07062

OS - Left eye; OD - Right eye

The following ocular toxicity studies from NDA 19-700 (submitted on May 27, 1987) were cross-referenced in the current NDA.

Table 2.6.6.9-1 Previously Conducted Nonclinical Ocular Toxicity Studies in Support of ACULAR®, ACULAR® PF, and ACULAR LS®

Report Number ^a	Species/Strain	Dosing Duration	Dose ^b	Drop Size	Daily Dosing Frequency ^c
69-B-82-37619-00-31-3-EY-LL	NZW Rabbits	1 Days	40 mg/mL	0.1 mL	1
10-B-83-37619-00-31-3-EY-LL	NZW Rabbits	1 Days	5 mg/mL	0.1 mL	12
81-B-82-37619-00-31-3-EY-TX	NZW Rabbits	10 Days	40 mg/mL	0.1 mL	2
110-B-83-37619-00-31-3-EY-TX	NZW and Dutch Belted Rabbits	28 Days	40 mg/mL	0.1 mL	3
163-B-82-37619-00-31-3-EY-TX	Dutch Belted Rabbits	28 Days	40 mg/mL	0.1 mL	3
84-B-82-37619-00-31-3-EY-TX	Dutch Belted Rabbits	36 Days	40 mg/mL	0.1 mL	3
16-B-83-37619-00-31-3-EY-TX	NZW Rabbits	42 Days	40 mg/mL	0.1 mL	3
21-KF-83-37619-00-31-3-EY-TX	Cynomolgus Monkeys	28 Days	40 mg/mL	0.1 mL	3
127-KF-84-37619-313-EY-TX	Cynomolgus Monkeys	29 Days	5 mg/mL	0.1 mL	9
136-KF-83-37619-00-31-3-EY-TX	Cynomolgus Monkeys	6 months	5 mg/mL	0.08 mL	9

^aSee Module 1.4.4, Tables 5.1 and 5.2.

^bHighest dose evaluated. Formulation pH: ~7.4.

^cTotal number of topical ocular drops per day.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Ketorolac tromethamine is an NSAID with analgesic, anti-inflammatory, and anti-pyretic activity. When given topically, ketorolac demonstrated potent anti-inflammatory activity in several models of ocular inflammation in rats and rabbits.

The oral form of ketorolac tromethamine (Toradol) was approved in 1991.

Acular® (0.5% ketorolac tromethamine ophthalmic solution, NDA 19-700) has been marketed in the US as a nonsteroidal anti-inflammatory ophthalmic agent since 1997 and in Europe since 1989. Acular® PF (0.5% ketorolac tromethamine ophthalmic solution Preservative-Free, NDA 20-811) was approved in 1997 and Acular LS® (0.4% ketorolac tromethamine ophthalmic solution, NDA 21-528) was approved in 2003 in the US.

The non-clinical studies of these products have been reviewed previously in the above mentioned NDAs. The sponsor has referred to these NDAs for the non-clinical information.

The subject of this NDA is Acuvail™ (0.45% ketorolac tromethamine ophthalmic solution). This reformulated KT ocular product is pH 6.8, CMC-based and preservative free. The preservative (BAK) in Acular® is removed. Therefore, the toxicity by BAK is eliminated.

Based on the results from pharmacokinetic studies with new formulations, the sponsor concluded that 0.45% ketorolac tromethamine formulated with CMC at pH 6.8 delivers ketorolac more efficiently in rabbit ocular tissues as compared to the aqueous-based vehicle used in Acular® and Acular LS®. Therefore, the dosing frequency of the KT new formulation can be reduced to two times a day as compared to four times a day for Acular® and Acular LS®.

Ketorolac levels achieved with the new formulation (0.45%) are less than the ocular and systemic drug levels previously demonstrated to be well tolerated in long term toxicology studies in which rabbits received up to 4% ketorolac tromethamine formulated in the Acular® and Acular LS® aqueous-based formulation (NDA 19-700, submitted May 27, 1987 and NDA 21-528, submitted August 7, 2002).

In the newly conducted 28-day GLP ocular toxicity studies in NZW rabbits, the newly formulated 0.45% KT administered 5x/day was well-tolerated. The ocular irregularities (epithelial thinning) observed in the early toxicity studies with BAK-containing KT formulation were not observed in the current study.

It was found that both Acular LS® and KT 0.45% new formulation produced the delay in corneal wound healing 120 hours post anterior keratectomy in rabbits. However, no statistically significant differences in the rate of corneal wound healing were observed between Acular LS® and KT new formulations at 0.45% ($p > 0.1$).

Unresolved toxicology issues (if any): None

Recommendations:

The approval of NDA 22-427 is recommended.

Suggested labeling:

The proposed labeling is acceptable.

Signatures (optional):

Reviewer Signature Conrad H. Chen, Ph.D.

Supervisor Signature Wendelyn Schmidt, Ph.D.

Concurrence Yes No

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

/s/

Conrad Chen

5/14/2009 11:51:43 AM

PHARMACOLOGIST

The approval of NDA 22-427 is recommended.

Wendelyn Schmidt

5/18/2009 03:57:09 PM

PHARMACOLOGIST