APPLICATION NUMBER:
21-132

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-427
Submission Date(s): 29SEP2008
Brand Name Acuvail™
Generic Name Ketorolac tromethamine ophthalmic solution 0.45%
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OCP Division DCP4
OND Division DAIOP
Applicant Allergan
Relevant IND(s) IND 021132
Submission Type; Code Original NDA
Formulation; Strength(s) Ketorolac tromethamine ophthalmic solution 0.45%
Indication Treatment of pain and inflammation following cataract surgery

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1. EXECUTIVE SUMMARY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Acuvail™, ketorolac tromethamine ophthalmic solution 0.45%, is proposed for treatment of pain and inflammation following cataract surgery. The proposed dosage and route of administration for Acuvail™ is as follows: one drop 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 two weeks of the post-operative period. Dosing on the day of surgery by medical personnel is as follows: approximately two hours prior to surgery, one drop should be administered approximately every 20 minutes by medical personnel for a total of 3 drops. Prior to discharge instill 1 additional drop.

The active component of Acuvail™, ketorolac tromethamine, has been previously approved for both ophthalmic and systemic administration. Ketorolac tromethamine is available in the currently marketed ophthalmic products ACULAR® (ketorolac tromethamine ophthalmic solution 0.5% with preservatives), ACULAR® PF (ketorolac tromethamine ophthalmic solution 0.5% preservative-free), and ACULAR LS® (ketorolac tromethamine ophthalmic solution 0.4%). ACULAR® is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of postoperative inflammation following cataract extraction. ACULAR® PF is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery. ACULAR LS® is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery, but is not approved for postoperative inflammation following cataract extraction. The recommended dosage regimen for these products is four times daily. Ketorolac tromethamine has been previously approved by the Food and Drug Administration for intravenous and intramuscular use of doses up to 120 mg/day and oral use of doses up to 40 mg/day.

The proposed Acuvail™ drug product is an unpreserved formulation of ketorolac tromethamine ophthalmic solution 0.45% developed to improve comfort, increase bioavailability, and increase patient compliance by reducing the dosing frequency from four times daily to two times daily while maintaining efficacy. Differences in the product's formulation versus the approved ACULAR® products include a lower pH, removal of benzalkonium chloride (BAK), edetate disodium, and octoxynol-40, and the addition of carboxymethylcellulose (CMC). To support product approval, a Phase 1 study was conducted to assess the safety and tolerability of the new product formulation, and two identical Phase 3 placebo-controlled efficacy studies in post-cataract surgery patients were conducted to demonstrate that the new formulation and twice daily regimen provide statistically significant improvement in reducing inflammation and pain compared to vehicle in patients with cataract surgery. No clinical pharmacology studies were submitted in this application. A waiver of the requirement for submission of evidence of in vivo bioavailability is granted since the systemic exposure of ketorolac following ophthalmic administration of Acuvail™ is not expected to exceed that of ACULAR® and is expected to be low in comparison to exposures observed following systemically administered ketorolac tromethamine, as evidenced by pharmacokinetic information available for currently marketed ketorolac-containing ophthalmic products.

1.1. Recommendation

Per 21 CFR 320.22 (e), a waiver of the requirement for submission of evidence of in vivo bioavailability is granted for the proposed drug product Acuvail™, ketorolac tromethamine ophthalmic solution 0.45%. Information on previously approved and marketed ketorolac formulations supports this recommendation.
1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The active component of Acuvail™, ketorolac tromethamine, has been previously approved for both ophthalmic and systemic administration. Ktorolac tromethamine is available in the currently marketed ophthalmic products ACULAR® (ketorolac tromethamine ophthalmic solution 0.5% with preservatives), ACULAR® PF (ketorolac tromethamine ophthalmic solution 0.5% preservative-free), and ACULAR LS® (ketorolac tromethamine ophthalmic solution 0.4%). To support the current NDA for Acuvail™, ketorolac tromethamine ophthalmic solution 0.45%, the applicant conducted a Phase 1 study to assess the safety and tolerability of the new product formulation and two identical Phase 3 placebo-controlled studies in post-cataract surgery patients. The Applicant did not perform any human pharmacokinetic assessments of ketorolac tromethamine ophthalmic solution 0.45%. The systemic bioavailability of ophthalmically applied ketorolac tromethamine has previously been evaluated with ACULAR® solution. After a single drop of ACULAR® solution administered three times daily in both eyes for 10 days, ketorolac concentrations in plasma were detectable in only 5 of 26 subjects (range: 10.7 to 22.5 ng/mL). These concentrations are approximately 3.7 to 7.8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac in humans. A comparison of total daily doses between ACULAR® and the proposed ketorolac 0.45% formulation suggests systemic exposure after twice daily ocular dosing with ketorolac 0.45% formulation is not expected to exceed that of ACULAR®. Following QID ocular dosing of ACULAR®, the maximum total daily dose is approximately 1 mg, compared to a maximum total daily dose of approximately 0.45 mg following twice daily ocular dosing of the proposed ketorolac 0.45% formulation.
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cc:
Division File: NDA 22-427
HFD-520 (CSO/Rodriguez)
HFD-520 (MO/Boyd)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)
2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic product with an active ingredient previously approved in other topical and systemic formulations, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Ketorolac tromethamine ophthalmic solution 0.45% is a sterile, non-preserved, clear, and colorless to pale yellow, isotonic solution. The formulation contains the active ingredient, ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), at a 0.45% w/v concentration. The inactive ingredients include carboxymethylcellulose (b) (4), sodium chloride (b) (4), and sodium citrate (b) (4). The pH of the bulk solution is adjusted using either 1 N sodium hydroxide or 1 N hydrochloric acid resulting in a target pH of 6.8 for the final product. All ingredients are tested to USP/NF and Ph Eur criteria.

The chemical structure and physical-chemical properties of ketorolac tromethamine are as follows:

Structural Formula: \( \text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_6 \)

Chemical Structure:

![Chemical Structure](image)

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

Compendial Name: Ketorolac tromethamine (USP)

USAN/INN: Ketorolac tromethamine

Company Laboratory Code: AGN-191578-J

Chemical Abstract Service (CAS) Registry Number: 74103-06-3

Molecular Weight: 376.41

The quantitative composition of the proposed ketorolac tromethamine ophthalmic solution drug product is shown in Table 2.2-1.
Table 2.2-1  Composition of Ketorolac Tromethamine Ophthalmic Solution, 0.45%

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

Source: Section 3.2.P.1

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Acuvail™, ketorolac tromethamine ophthalmic solution 0.45%, is proposed for treatment of pain and inflammation following cataract surgery.

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for Acuvail™ is as follows: one drop 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 two weeks of the post-operative period. Dosing on the day of surgery by medical personnel is as follows: approximately two hours prior to surgery, one drop should be administered approximately every 20 minutes by medical personnel for a total of 3 drops. Prior to discharge instill 1 additional drop.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

No clinical pharmacology studies were submitted in this NDA. To support product approval, a Phase 1 study was conducted to assess the safety and tolerability of the new product formulation (Study 191578-004), and two identical Phase 3 placebo-controlled studies in post-cataract surgery patients, specifically patients with planned unilateral, single procedure, uncomplicated phacoemulsification extracapsular cataract extraction with posterior chamber intraocular lens implant under topical or intracameral anesthesia at the start of the procedure with no capsular staining during phacoemulsification, were conducted to assess the safety and efficacy (Studies 191578-005 and 191578-006). The Phase 1 study evaluated the safety and tolerability of ketorolac tromethamine ophthalmic solution (0.35% and 0.45%) compared with ACULAR LS® 0.4% in healthy adult volunteers. The Phase 3 studies were conducted to demonstrate that the
new formulation and twice daily regimen provide statistically significant improvement in reducing inflammation and pain compared to vehicle in patients with cataract surgery. There were no assessments of systemic exposure in any of the studies conducted to support approval of ketorolac tromethamine 0.45% ophthalmic solution.

2.2.2. What are the PK characteristics of the drug?

The systemic exposure of ketorolac tromethamine 0.45% ophthalmic solution has not been assessed. The systemic bioavailability of ophthalmically applied ketorolac tromethamine has previously been evaluated with ACULAR® solution. After a single drop of ACULAR® solution administered three times daily in both eyes for 10 days, ketorolac concentrations in plasma were detectable in only 5 of 26 subjects (range: 10.7 to 22.5 ng/mL). These concentrations are approximately 3.7 to 7.8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac in humans (0.29 ± 0.07 µg/mL). A comparison of total daily doses between ACULAR® and the proposed ketorolac 0.45% formulation suggests systemic exposure after twice daily ocular dosing with ketorolac 0.45% formulation is not expected to exceed that of ACULAR®. Following QID ocular dosing of ACULAR®, the maximum total daily dose is approximately 1 mg, compared to a maximum total daily dose of approximately 0.45 mg following twice daily ocular dosing of the proposed ketorolac 0.45% formulation. In addition, systemic exposure following administration of the approved and proposed ocular formulations of ketorolac tromethamine are much lower than exposures seen following systemic administration; the maximum total daily doses following ophthalmic administration of ACULAR® and the ketorolac 0.45% formulation are 1/40th and 1/89th of the total daily dose following 10 mg oral dosing when given four times daily. Thus, the systemic exposure of ketorolac following ophthalmic administration of Acuvail™ is not expected to exceed that of ACULAR® and is expected to be low in comparison to exposures observed following systemically administered ketorolac tromethamine, as evidenced by pharmacokinetic information available for currently marketed ketorolac-containing ophthalmic products.

2.3. Intrinsic Factors
Not applicable.

2.4. Extrinsic Factors
Not applicable.

2.5. General Biopharmaceutics
Not applicable.

2.6. Analytical Section
Not applicable.
3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in bold italicized underlined type).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics
4. APPENDICES
Not applicable.
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/s/

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