

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	21-398
Submission Date(s):	03MAY2007
Brand Name	Combigan™
Generic Name	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
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OCP Division	DCP4
OND Division	DAIOP
Applicant	Allergan
Relevant IND(s)	IND 58,460
Submission Type; Code	505(b)(2) resubmission of NDA ; N000 (AZ)
Formulation; Strength(s)	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
Indication	Reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

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1. EXECUTIVE SUMMARY

Combigan™ ophthalmic solution is a combination product containing brimonidine 0.2%/timolol 0.5% proposed for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

Brimonidine tartrate is a selective alpha-2 adrenergic agonist. Timolol is a non-selective beta-adrenergic receptor blocking agent. The individual components of the combination product are approved and marketed in the US as brimonidine, 0.2% (ALPHAGAN®) and timolol, 0.5% (TIMOPTIC®) and are used individually for the treatment of glaucoma. The treatment regimen for Combigan™ is one drop to the effected eye(s) twice daily. As monotherapy, brimonidine, 0.2% is administered three times daily and timolol, 0.5% is administered twice daily.

The Applicant submitted the original 505(b)(2) NDA 21-398 for Combigan™ (brimonidine 0.2%/timolol 0.5%) ophthalmic solution on 17SEP2001. An approvable letter was issued on 05JUN2002 based on the determination that the submitted studies failed to demonstrate the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component in combination was

smaller than expected, and the magnitude of the observed effect was not sufficient to outweigh the risks. A complete response to the approvable letter was received on 13SEP2004, and a second approvable letter was issued on 14MAR2005, based on the same review findings. A complete response was submitted on 29JUN2006, and a third approvable letter was issued on 20DEC2006, based on the same review findings. The current submission dated 03MAY2007 is a complete response to the FDA's 20DEC2006 approvable action.

In support of the original NDA, the Applicant submitted pharmacokinetic data from three studies that evaluated the systemic bioavailability of brimonidine and timolol from Combigan™ following multiple dose administration. These included a Phase 1 crossover study evaluating the safety and pharmacokinetics of 0.2% brimonidine tartrate/0.5% timolol as the combination product compared with Alphagan® (0.2% brimonidine tartrate) and Timoptic® (0.5% timolol maleate) monotherapy following twice daily administration in normal, healthy, adult subjects for seven days; and two multicenter, randomized, double-masked, parallel studies evaluating the safety and efficacy of 0.2% brimonidine tartrate/0.5% timolol as the combination product administered twice daily compared with 0.5% timolol twice daily or Alphagan® three times daily for three months (plus a 9-month, masked extension) in patients with glaucoma or ocular hypertension, in which sparse PK sampling was performed. A complete review of these studies is presented in the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 05FEB2002. Based on the original review, the Applicant has adequately evaluated the systemic exposure of brimonidine and timolol from the combination product brimonidine 0.2% /timolol 0.5% ophthalmic solution in healthy subjects as well as in patients under clinical use conditions.

Subsequent to the original approvable action, labeling recommendations made in the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 were not implemented. In response to a request from the FDA, the Applicant submitted the proposed labeling to the NDA formatted as outlined in the physician labeling rule (PLR; Federal Register Vol. 71, No. 15, January 24, 2006). This review focuses on a review of the proposed label in PLR format based on the findings from the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 05FEB2002.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the original NDA submission is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

2. QUESTION BASED REVIEW

The clinical pharmacology and biopharmaceutics information for Combigan™ has been reviewed previously for the original 505(b)(2) NDA 21-398; no additional clinical pharmacology data were submitted in this resubmission. Refer to the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 12NOV2002 for the question-based review.

3. LABELING RECOMMENDATIONS

11 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

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9/28/2007 01:56:07 PM
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