CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-770

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

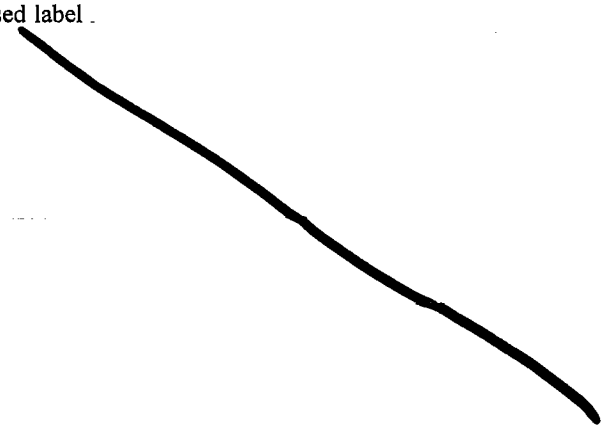
Public Health Service
Food and Drug Administration

MEMO to File

NDA: 21-770
PRODUCT (Generic Name): Brimonidine Tartrate Ophthalmic Solution, 0.1% (Brimonidine Purite)
PRODUCT (Proposed Brand Name): Alphagan

In the final Clinical Pharmacology and Biopharmaceutics review by Dr. Tapash Ghosh, labeling recommendations were not provided. This memo transmits the recommended labeling language for the Clinical Pharmacology/Pharmacokinetics section.

It is the recommendation of the Division of Pharmaceutical Evaluation-III that the statements in the sponsor's proposed label



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/s/

Dennis Bashaw
3/28/05 03:21:45 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Brimonidine Tartrate Ophthalmic Solution, 0.1% (Brimonidine Purite)
PRODUCT (Proposed Brand Name):	Alphagan [redacted]
DOSAGE FORM:	Ophthalmic Solution
DOSAGE STRENGTHS:	0.1%
NDA:	21-770
PROPOSED INDICATIONS:	Reduction of intra ocular pressure (IOP)
NDA TYPE:	505(b)(1)
SUBMISSION DATE:	May 27, 2004
SPONSOR:	Allergan, Irvine, CA
REVIEWERS:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Edward D. Bashaw, Pharm. D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 550

I. BACKGROUND

Drug Classification: 3S

Dosage Form: Ophthalmic solution, 0.10%

Indication: For the reduction of intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

Pharmacologic Class: Alpha adrenergic receptor agonist. Mechanism of action of lowering IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Clinical Endpoints: Lowering of IOP

Dosage and administration: One drop in the affected eye(s) three times daily, approximately 8 hours apart.

Formulation: The proposed product, Brimonidine Purite (Alphagan [redacted] ophthalmic solution 0.1%, is a lower strength formulation of brimonidine tartrate based on approved ALPHAGAN® P (NDA 21-262). The drug substance, brimonidine tartrate, is the same as in approved ALPHAGAN® (NDA 20-613) and ALPHAGAN® P (NDA 21-262). The proposed product contains the same ingredients as the currently approved product, ALPHAGAN® P; no other ingredients have been added. Only levels of the drug substance, borate buffer, salts and product pH have been modified. A summary of the different brimonidine tartrate ophthalmic solutions that Allergan has developed is provided in Table 1.

Table 1: Summary of Brimonidine Tartrate Ophthalmic Solutions Developed by Allergan

Allergan formula reference number	7831X	9174X	9541X
Ingredient (%w/v)	ALPHAGAN® (NDA 20-613)	ALPHAGAN® P (NDA 21-262)	Brimonidine Purite® 0.1%
Brimonidine Tartrate	0.20	0.15	0.10
Benzalkonium Chloride			
Purite®			
Polyvinyl Alcohol			
Sodium Carboxymethyl cellulose (CMC)			
Sodium Citrate			
Citric Acid			
Boric Acid			
Sodium Borate			
Sodium Chloride			
Potassium Chloride			
Calcium Chloride			
Magnesium Chloride			
Hydrochloric Acid & Sodium Hydroxide			
pH Specification			
Purified Water			

II. EFFICACY, SAFETY AND SYSTEMIC EXPOSURE

What were the Phase 3 efficacy and safety studies?

This NDA provides clinical study report (study 190342-021) with the proposed dose in the target population. According to the medical reviewer, the primary efficacy endpoint, mean intraocular pressure (IOP), is demonstrated to be equivalent when comparing brimonidine tartrate ophthalmic solution 0.1% (also referred to as Brimonidine Purite) to a previously approved drug, brimonidine tartrate ophthalmic solution 0.2% (also referred to as Alphagan). Compared with the Brimonidine Purite group, a greater percentage of patients in the Alphagan group discontinued for lack of efficacy and due to adverse events. From a clinical perspective NDA 21–770 is recommended for approval for the treatment of open angle glaucoma or ocular hypertension in subjects 2 years or older.

What is the systemic exposure of brimonidine from this 0.1% ophthalmic solution of Brimonidine-Purite™ ?

The Clinical Pharmacology and Biopharmaceutics (CPB) information of the previous NDA (21-262) from the same sponsor on brimonidine tartrate ophthalmic solution 0.15%

(also referred to as ALPHAGAN® P) was reviewed earlier. Brimonidine is systemically absorbed after topical topical application of the Brimonidine-Purite™ ophthalmic solution to the eye. The sponsor did not conduct any PK study in this NDA. However, the sponsor evaluated the systemic exposure (PK-98-130) of brimonidine from a 0.1% and 0.2% ophthalmic solution of Brimonidine-Purite™ compared it to historical data of 0.2% ALPHAGAN® during submission of NDA 21-262 for Brimonidine-Purite™ 0.15%. Based on the results of this study, the sponsor extrapolated the predicted parameters for 0.15% ophthalmic solution of Brimonidine-Purite™, and the approach was found acceptable for approval of NDA 21-262. No new CPB information has been provided in this NDA. The following summary of the study PK-98-130 has been excerpted from the NDA (21-262):

Study Population: 39 healthy volunteers 18 years of age or older (21M & 18F)

Dose: One drop of Brimonidine-Purite™, 0.1% or 0.2% solution or Brimonidine-Purite™ vehicle to each eye 3 times daily for 27 1/3 days in a parallel study design.

Blood Samples: Blood samples up to 8 hours were taken from each volunteer after the first daily dose on Day 1 and Day 7. Additional samples at 1 hour post dose on Days 8 and 28. Day 1 and day 7 mean plasma concentration-time profiles of brimonidine and the pharmacokinetic parameters during Brimonidine-Purite™ treatment are shown below.

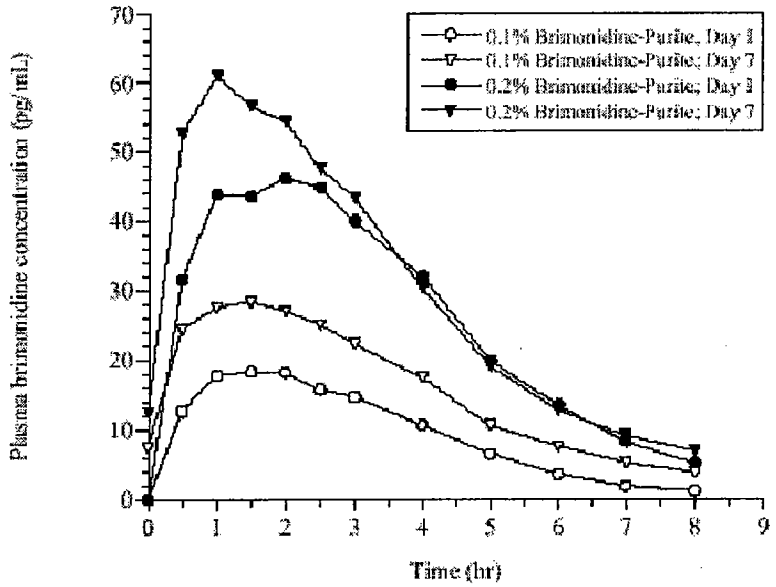

Table 2: Pharmacokinetic parameters of brimonidine in human plasma after 1 dose (day 1) or 19 doses (day 7) of Brimonidine-Purite 0.1% or 0.2% TID to each eye of healthy subjects. Parameters are expressed as mean ± SD (N).

Formulation	Day	C_{max} (pg/mL)	t_{max} (hr)	$AUC_{0-t_{last}}$ (pg•hr/mL)	AUC_{0-8} (pg•hr/mL)	$t_{1/2}$ (hr)
0.1%	1	23.3 ± 14.1 (13)	1.54 ± 0.66 (13)	79.3 ± 47.8 (12)	NC[1]	NC[1]
	7	30.0 ± 17.8 (13)	1.30 ± 0.68 (13)	127 ± 87 (13)	136 ± 85 (12)	1.88 ± 0.81 (12)
0.2%	1	48.4 ± 35.1 (13)	1.77 ± 0.60 (13)	211 ± 147 (13)	NC[1]	NC[1]
	7	64.7 ± 37.8 (13)	1.35 ± 0.94 (13)	245 ± 124 (13)	245 ± 124 (13)	1.95 ± 0.63 (13)

1 Not calculated

Since the pharmacokinetic parameters are dose proportional, the sponsor extrapolated the pharmacokinetic parameters for 0.15% Brimonidine-Purite™ from the data for 0.1% and 0.2% Brimonidine-Purite™ solutions, as shown in the following table.

Formulation	Day[2]	N	C_{max} (pg/mL)	$AUC_{last,ss}$[3] (pg•hr/mL)	AUC_{0-24}[3] (pg•hr/mL)
Brimonidine-Purite™ 0.2% TID	7	13 (7M + 6F)	64.7 ± 37.8	245 ± 124	735
ALPHAGAN® 0.2% BID	10	7 (3M + 4F)	58.5 ± 29.9	309 ± 142	618
Brimonidine-Purite™ 0.15% TID[4]	7	13 (7M + 6F)	42.4	191	572
ALPHAGAN® 0.2% TID[5]	10	7 (3M + 4F)	NE[6]	NE[6]	927

Overall, the systemic exposure of brimonidine from the Brimonidine-Purite™ formulation appears to be lower than the marketed formulation ALPHAGAN® formulation and the t_{max} appears to be faster as well. For this lower strength (0.1%) formulation of Brimonidine-Purite™ the levels would be expected to be proportionally lower.

III. RECOMMENDATION:

Based on the systemic exposure information provided in the previous NDA 21-262 (Brimonidine Tartrate Ophthalmic Solution, 0.15%), the clinical pharmacology and biopharmaceutics section of this NDA (21-770) for a lower strength product is acceptable. There are no comments for the sponsor.

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/s/

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1/11/05 04:03:09 PM
BIOPHARMACEUTICS

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