CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-770

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # **21-770**

Trade Name **Alphagan P, 0.1%**

Generic Name **brimonidine tartrate ophthalmic solution**

Applicant Name **Allergan, Inc.** HFD # **520**

Approval Date If Known **August 19, 2005**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /X/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ **NO /X/**

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ **NO /X/**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **21-262** **brimonidine tartrate 0.15%**

NDA# **20-613** **brimonidine tartrate 0.2%**

NDA# 20-490 **brimonidine tartrate 0.5%**

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ **NO /X/**

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ **NO /X/**

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #190342-021

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ **NO /X/**

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug

product?

Investigation #1 YES /___/ **NO /X/**

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study #190342-021

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # **32,292** **YES /X/** ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Preparer: **Martin P. Nevitt, M.D., M.P.H.**
Title: **Medical Officer**

Concurrence by: **Wiley A. Chambers, M.D.**
Title: **Deputy Division Director**

Form OGD-011347 Revised 05/10/2004

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

/s/

Wiley Chambers
8/19/2005 04:56:52 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-770

Stamp Date: June 1, 2004 **Action Date:** August 19, 2005

HFD-520

Trade and generic names/dosage form: Alphagan P (brimonidine tartrate ophthalmic solution) 0.1%

Applicant: Allergan, Inc. **Therapeutic Class:** Alpha Agonist

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1:

Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Is there a full waiver for this indication (check one)?

☐ ✓ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ ✓ **Products in this class for this indication have been studied/labeled for pediatric population**

☐ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**

☐ **There are safety concerns**

☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**

☐ **Disease/condition does not exist in children**

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Michael Puglisi
Consumer Safety Officer

cc: NDA 21-770
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0264-1
July 12, 2005	August 28, 2005	
DATE OF DOCUMENT:	**PDUFA DATE:**	
June 27, 2005	August 28, 2005	

TO: Janice Soreth, M.D.
Director, Division of Anti-Infective and Ophthalmology Products
HFD-520

THROUGH: Mike Puglisi
Project Manager, Division of Anti-Infective and Ophthalmology Products
HFD-520

PRODUCT NAME:	**NDA SPONSOR:** Allergan, Inc.
Alphagan® P (Brimonidine Tartrate Ophthalmic Solution) 0.1% NDA#: 21-770	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Alphagan® P. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III. of this review in order to minimize potential errors with the use of this product.

3. Upon product launch DMETS recommends that the sponsor provide education for healthcare providers that there will be two strengths of Alphagan P.

4. DDMAC finds the proprietary name Alphagan P acceptable from a promotional perspective.

Denise Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 3, 2005

NDA# 21-770

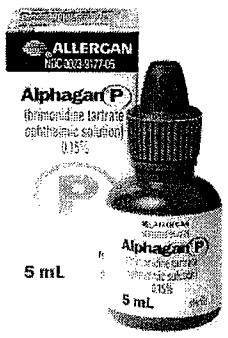
NAME OF DRUG: Alphagan® P (Brimonidine Tartrate Ophthalmic Solution) 0.1%

NDA HOLDER: Allergan, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products (HFD-520), for assessment of the proprietary name, "Alphagan P" regarding potential name confusion with other proprietary or established drug names. Draft package insert labeling was provided for review and comment.

Allergan currently markets Alphagan P (Brimonidine Tartrate Ophthalmic Solution), as a 0.15% solution. The modifier "P" denotes the presence of Purite®, Allergan's brand name for the preservative. The sponsor has now proposed to use the same proprietary name, Alphagan P, for the lower strength (0.1%) which carries the same indication, dose, dosing regimen, and the "P" also denotes the presence of Purite®. The sponsor had originally proposed the modifier [redacted] for this product to indicate [redacted] In a review dated November 17, 2004 (ODS 04-0264), DMETS did not recommend the use of the proprietary name, Alphagan [redacted] due to the potential for confusion with Alphagan P [redacted] An older formulation of Brimonidine Tartrate Ophthalmic Solution, marketed as "Alphagan", was available in a 0.2% strength but was discontinued in 2003 (see images below).



Currently Marketed Product

Product Discontinued in 2003

PRODUCT INFORMATION

Alphagan P is Brimonidine Tartrate Ophthalmic Solution, 0.1% an alpha adrenergic receptor agonist indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The recommended dosage is one drop in the affected eye(s) three times daily, approximately 8 hours apart. Alphagan P will be available in teal LDPE bottles with purple caps in 5 mL, 10 mL, and 15 mL sizes. The color purple for the cap is reserved for ophthalmic adrenergic agonists.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Alphagan P to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alphagan P. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Alphagan P acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Alphagan P. These products are listed in Table 1 (see top of page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s); Established name	Usual adult dose*	Other**
Alphagan P	Brimonidine Tartrate Ophthalmic Solution, 0.1%	Instill one drop in the affected eye(s) 3 times daily.	
Alphagan***	Brimonidine Tartrate Ophthalmic Solution, 0.2%	Instill one drop in the affected eye(s) 3 times daily.	SA/LA
Alphagan P	Brimonidine Tartrate Ophthalmic Solution, 0.15% (with Purite preservative)	Instill one drop in the affected eye(s) 3 times daily.	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Product no longer marketed. Removed from the marketplace in 2003.

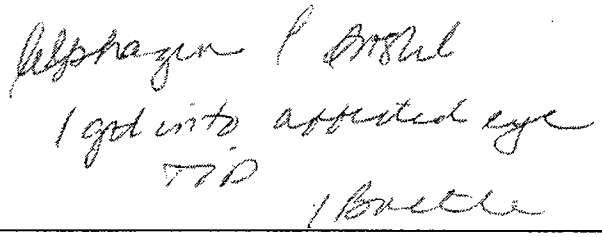
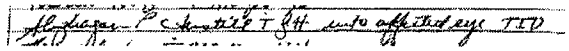
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Alphagan P were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Alphagan P with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Alphagan P (see top of page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. DMETS notes that the strength of 0.1% was inadvertently omitted from the prescription studies.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Alphagan P One drop into affected eye 3 times daily. 1 bottle
Inpatient RX: 	

2. Results:

Several respondents from the written inpatient and outpatient prescriptions omitted the modifier "P", submitting the interpretations similar to Alphagan. Alphagan is no longer marketed but generic versions are still available. Additionaly, the modifier "P" was misinterpreted as "T", "D", "NP, and "MP" in the verbal prescription studies. Other interpretations from the outpatient written study included "Celphazen" and "Celphagen P"; these are similar to the marketed product Cefazolin. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. AERS SEARCHES

A search of the FDA Adverse Event Reporting System (AERS) database was conducted in order to determine any post-marketing safety reports of medication errors associated with Alphagan® and/or Alphagan®P. The MedDRA Preferred Terms (PTs), "Medication Error", "Accidental Overdose", "Overdose", "Pharmaceutical Product Complaint", and "Treatment Non-Compliance", and the drug names, "ALPHAGAN%" and "BRIMONIDINE%" were used to perform the search. No new additional reports of confusion were identified in the current AERS search. At the time of last review, dated November 17, 2004 (ODS 04-0264), a similar search of AERS uncovered one report of name confusion between Alphagan® and Alphagan® P. It was not reported whether the incorrect medication was actually administered. There were also two reports of the inadvertent oral administration of Alphagan®. One of the reports of oral administration describes caregiver confusion of the ophthalmic solution with the infant's antispasmodic medication resulting in hospitalizations with temporary patient harm (lethargic, pale). The other report also described hospitalization of an infant who after inadvertent administration of Alphagan 0.2% experienced respiratory depression and hyperglycemia. The root cause of this error was not provided.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Alphagan P (0.1%), the primary concerns related to look-alike and sound-alike confusion with Alphagan and Alphagan P (0.15%).

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Alphagan P could be confused with Alphagan. One participant of the inpatient study responded "Alphagan", leaving the modifier "P" off the Alphagan name. Although "Alphagan (0.2%)" has been discontinued, generic versions are available for dispensing. DMETS also believes that there is a possibility that when this new strength of Alphagan P is introduced in the marketplace, healthcare providers will write for "Alphagan P" (without a strength), not realizing that this product is no longer a single strength product. Postmarketing experience has shown that the addition of a new strength to a product line has resulted in practitioner confusion and we expect that similar confusion may also occur with addition of the 0.1% strength of Alphagan P. For this reason, DMETS contacted the Medical Review Officer regarding the clinical implications from inadvertent administration of the incorrect strength of Alphagan P, e.g., application of 0.1% rather than 0.15% or vice versa. The Medical Review Officer responded that the products would be equally efficacious and that there would not be a safety risk for patients inadvertently administering the higher strength. Although the Division states that there is no safety or efficacy consequence of administration of the incorrect strength of Alphagan P or generic versions of Alphagan, DMETS recommends that the sponsor provide educational material about the availability of the new strength upon product launch. Additionally, DMETS refers the sponsor to labeling recommendations in Section III of this review for to clearly differentiate the product strengths.

Several misinterpretations of the modifier were provided in the prescription study (T, D, NP, MP). Since the Alphagan P 0.15% is currently marketed and no errors have been reported with the modifier, DMETS does not believe that these misinterpretations pose a safety concern. Similarly, the misinterpretations "Celphazen" and "Celphagen P" which are similar to the currently marketed product Cefazolin do not pose a safety concern as post-marketing reports of confusion have not been submitted to the Agency at this time and does not warrant further review.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft package insert labeling provided with this submission, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error. We note that revised container labels and carton labeling were not submitted for review and comment. Therefore we have repeated our comments from the November 17, 2004, review of the container labels, carton and package insert labeling.

A. GENERAL COMMENTS

1. We note that the preservative for this product bears the tradename "Purite®". We ask that you define Purite® in terms of its ingredients where it appears throughout your labels and labeling.

3. DMETS is aware of postmarketing reports of inadvertent oral administration of Alphagan resulting in hospitalization of pediatric patients. DMETS recommends the addition of a prominent statement on container labels and carton labeling of "Alphagan" products that these product are for use only in the eye. Alternatively (or additionally), DMETS recommends that an eye pictorial appear on those labels and labeling.

4. DMETS recommends that the statement, "New Product Strength" appears on product labels and labeling for a period of time not to exceed six months.

5. When preparing product labeling, please ensure that the expression of strength is well differentiated from the expression of strength of the existing Alphagan P product. DMETS recommends the use of contrasting colors, boxing, or some other means to differentiate the product strengths.

6. According to the Division's Project Manager, the sponsor has proposed a separate package insert for the lower strength product. DMETS does not recommend two separate package inserts for the two different strengths as this may cause confusion and error. For example, practitioners may not be aware of the two different strengths if only one strength is listed and/or they may think that the products are not indicated or dosed similarly. Traditionally, a combined package insert is used for different strengths of the same active ingredient.

B. CONTAINER LABELS [[redacted] 5 mL, 10 mL, and 15 mL]

1. See comments A2 through A5.

2. Please ensure that your statement of product strength appears with prominence.

C. CARTON LABELING [[redacted], 5 mL, 10 mL, and 15 mL]

See GENERAL COMMENTS and B2.

D. INSERT LABELING

1. DESCRIPTION

See comment A1.

2. HOW SUPPLIED

a. Include the established name of this drug product in this section.

b. Make a statement that the bottles are individually contained.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Alphagan® P. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III. of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. Upon product launch DMETS recommends that the sponsor provide education for healthcare providers that there will be two strengths of Alphagan P.

D. DDMAC finds the proprietary name Alphagan® P acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-827-1998.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Prescription Studies for Alphagan® P

Verbal	Inpatient	Outpatient
Alphagan P	Alphagan P	Alphagam
Alphaghan P	Alphagan P	LePhagen P
Effergan T	Alphagan P	Olphagn
Alphagan T	Aliphagan P	Alphagan P
Alphocant D	Alphagan	Lelphazin P
Alfergen-P	Alphagar	Celphazen P
Alphagan P	Alphagan P	Alphagin
Alfagan NP	Alphagar-P	Celphagen P
Alphagan P	Alphagan P	Alphagan
Alphagerin P	Alghagn P	Alphagan P
Aprican P	Alphagan P	Alphagan P
Alfragan P	Alydragar P	Alphagan P
Alfracan T	Alphan P	Alphagan P
Alfurgan MP	Alphagan P	Alphagan P
Alphagan-P	Alphagan P	Alphazin P
Alphagan P	Alphagan P	
Alphagan T	Alphagan P	
	Alphagan P	
	Alphagan P	

cc: NDA 21-770
HFD-520: Division Files/ Mike Puglisi, Project Manager
HFD-520: Janice Soreth, Division Director
HFD-520: Martin Nevitt, Medical Review Officer
HFD-040: Catherine Gray, Regulatory Review Officer, DDMAC
HFD-040: Debi Tran, Regulatory Review Officer, DDMAC
HFD-420: Diane Smith, Project Manager, DMETS
HFD-420: Charlie Hoppes, Safety Evaluator, DMETS
HFD-420: Alina Mahmud, Team Leader, DMETS
HFD-420: Denise Toyer, Deputy Division Director, DMETS

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/s/

Alina Mahmud
8/11/05 12:00:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/12/05 09:05:52 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/12/05 09:14:17 AM
DRUG SAFETY OFFICE REVIEWER

14 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-770

Allergan, Inc.
Attention: Lewis Gryziewicz, R.Ph.
Director, Pharmaceutical Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Gryziewicz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Brimonidine Tartrate Ophthalmic Solution, 0.1%

Review Priority Classification: Standard (S)

Date of Application: May 27, 2004

Date of Receipt: June 1, 2004

Our Reference Number: NDA 21-770

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 31, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 1, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Michael Puglisi
6/17/04 03:50:04 PM
for Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-770

Allergan, Inc.
Attention: Lewis Gryziewicz, R.Ph.
Director, Pharmaceutical Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Gryziewicz:

Please refer to your May 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Ophthalmic Solution, 0.1%.

We also refer to your submissions dated July 15 and 27, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 31, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Michael Puglisi
8/13/04 11:22:10 AM
for Carmen DeBellas

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Lew Gryziewicz	**From:** Mike Puglisi, Project Manager
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (including cover page)	**Date:** August 24, 2004

Re: Micro Comments/Deficiencies for NDA 21-770

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Lew,

Here are some comments/deficiencies from the Micro reviewer concerning NDA 21-770, for brimonidine tartrate ophthalmic solution, 0.1%. Please respond in an amendment to your NDA. Please let me know if you have any questions about these comments. Thanks.

-Mike

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Michael Puglisi
8/24/04 02:21:24 PM

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Lew Gryziewicz	**From:** Mike Puglisi, Project Manager
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (including cover page)	**Date:** March 4, 2005

Re: Microbiology Comments/Deficiencies re: NDA 21-770

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Lew,

The second microbiology review for NDA 21-770 has just been completed. Attached are several comments/deficiencies. Please respond in an amendment to the NDA. Please let me know if you have any questions about these comments. Thanks.

-Mike

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative 3

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/s/

Michael Puglisi
3/4/05 11:52:59 AM

TELECONFERENCE MEETING MINUTES

MEETING DATE: 10/20/03 TIME: 11:30 am LOCATION: CORP. S400

IND # 32,292 Meeting Request Submission Date – 9/3/03
Date Scheduled – 9/9/03
Meeting Packages Submitted – 9/26/03

DRUG: Brimonidine Tartrate Ophthalmic Solution

SPONSOR: Allergan, Inc.

TYPE OF MEETING: Pre-NDA

FDA PARTICIPANTS:
Wiley A. Chambers/ Deputy Division Director
Brian Harvey/ Deputy Office Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Matthew Feinsod/ Staff Fellow
Linda Ng/ Chemistry Team Leader
Libaniel Rodriguez/ Chemistry Reviewer
Stan Lin/ Biostatistics Team Leader
Mike Puglisi/ Project Manager
Raphael Rodriguez/ Project Manager
Lori Gorski/ Project Manager

INDUSTRY PARTICIPANTS:
Andrew Acheampong/ Pharmacokinetic Research
Lewis Gryziewicz/ Director, Regulatory Affairs
Carlos Felix/ Biostatistician
Tina Ariaee/ Pharmaceutical Regulatory Affairs
Amy Batoosingh/ Director, Clinical Research
Linda Cleary/ Project Manager
Bora Han/ Toxicologist
Richard Graham/ Pharmaceutical Development
Robert Keaney/ Manager, Clinical Research

QUESTIONS TO THE AGENCY:

OVERALL

1. Allergan plans to submit an electronic NDA in CTD format in compliance with the FDA Guidance for Industry "Submitting Marketing Applications According to the ICH-CTD Format". Does FDA want a paper copy of any or all parts of the NDA?

FDA Response: *Allergan would not be required to submit a paper version of the NDA if an electronic version were submitted.*

However, paper desk copies of selected sections, particularly CMC and Clinical, would speed the review process.

2. In Module 2, Overview and Summaries, we will summarize data from ALPHAGAN® and ALPHAGAN® P NDAs and will incorporate new studies that were conducted for Brimonidine Purite® 0.1% (pH 7.7). Appendix 3 contains an outline of our application. Is the NDA outline acceptable?

FDA Response: *The outline presented for Module 2 in Appendix A appears acceptable.*

3. Allergan will not include study reports that have already been submitted to previous ALPHAGAN® and ALPHAGAN® P NDAs, they will be cross referenced. Does FDA agree?

FDA Response: *Acceptable, provided the previously submitted study reports are complete and are referenced by application, submission date, and page number.*

CHEMISTRY

1. The NDA will contain stability data on three registration stability batches manufactured at either [redacted] as compared to the commercial scale of either [redacted] These registration stability batches were stored at 40C/20% RH and 25C/40% RH for [redacted] Three month data from three commercial scale process validation batches will also be included from the site of manufacture. These data will be included in the submission and the studies are ongoing and data will be submitted from later time points when available. Does FDA agree that these studies represent sufficient stability for submission?

FDA Response: *Yes the proposed stability data is sufficient for NDA submission.*

2. Brimonidine Purite® 0.1% (pH 7.7) will be manufactured using Active Pharmaceutical Ingredient from the approved suppliers in NDA 20-613 ALPHAGAN® 0.2%. We propose to cross reference this application for the API and that no such information is required for the upcoming Brimonidine Purite® 0.1% (pH 7.7) NDA submission. Does FDA agree?

FDA Response: *Yes the proposed cross-reference is acceptable.*

Additional CMC Comment:
Please provide a comparison of the composition of the two formulations, Brimonidine purite 0.1% (pH 7.7) and Brimonidine purite 0.1% (pH 7.2).

NONCLINICAL

1. Over the course of development of Brimonidine tartrate ophthalmic solution for use as an IOP-lowering agent, several nonclinical ADME studies have been conducted to elucidate the ocular and systemic pharmacokinetics of brimonidine. Some of these studies have been submitted in previous NDAs (20-613 and 21-262). For this submission, the Pharmacokinetics section will include two ocular bioavailability studies:

- One study performed in rabbits with Brimonidine Purite® 0.1% (pH 7.7) versus the marketed formulation ALPHAGAN P® 0.15% (pH 7.2).
- One study in rabbits comparing ALPHAGAN® 0.2% versus ALPHAGAN® P 0.15%.

Based on these studies, ocular bioavailability of brimonidine was similar among ALPHAGAN® 0.2%, ALPHAGAN P® 0.15% and Brimonidine Purite® 0.1% (pH 7.7). These two studies are sufficient to conclude that ocular absorption of brimonidine is enhanced in the Brimonidine Purite® 0.1% (pH 7.7) formulation. Does FDA agree?

FDA Response: *The sponsor can submit data of the proposed studies in support of the NDA. However, acceptability of the study is a review issue.*

2. A clinical PK study was performed with Brimonidine Purite® 0.1% (pH 7.2) (report PK-98-130, NDA 21-262). Allergan proposes to evaluate the exposure multiples for Brimonidine Purite® 0.1% (pH 7.7) based on the Brimonidine Purite® 0.1% (pH 7.2) solution. Does FDA agree?

FDA Response: *Acceptable for review, however, the study results will have to be reviewed before a determination can be made concerning approval.*

HUMAN PHARMACOKINETICS

1. The human pharmacokinetics of brimonidine and its systemic exposure after topical ocular applications have previously been well established using concentrations ranging from [redacted] brimonidine (ALPHAGAN® , NDA 20-613) and 0.1% to 0.2% Brimonidine Purite® (pH 7.2) formulations (ALPHAGAN® P, NDA 21-262).

   For this submission, Allergan did not conduct a human PK study with Brimonidine Purite® 0.1% (pH 7.7). Instead, we will use previously conducted PK studies (Report PK-98-130 in NDA 21-262; PK-95-042 in NDA 20-613) to establish the systemic exposure in humans of this new formulation. Does FDA agree?

FDA Response: *Acceptable for review, however, the study results will have to be reviewed before a determination can be made concerning approval.*

CLINICAL and STATISTICAL

1. Allergan proposes not to include Individual Patient Data Listings or Case Report Tabulations in Module 5. Instead, Allergan will provide FDA with electronic SAS Transport Files for all datasets. Does FDA agree?

FDA Response: *Agree. Allergan should also submit the Case Report Forms for all discontinued subjects, regardless of cause.*

2. The phase 3 program consists of a single clinical study comparing Brimonidine Purite® 0.1% (pH 7.7) with Brimonidine tartrate 0.2% Ophthalmic Solution (ALPHAGAN®), as discussed at the December 11, 2002 meeting (see Appendix 4 for meeting minutes) with representatives of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. Does FDA agree that the NDA can be based on a single clinical study?

FDA Response: *The single phase 3 study (190342-021) comparing brimonidine purite 0.1% with brimonidine tartrate 0.2% ophthalmic solution (Alphagan) is acceptable if it demonstrates equivalence to Alphagan.*

Replicated superiority studies would be required for Allergan to make additional labeling claims.

3. Allergan has submitted a draft Statistical Analysis Plan for the phase 3 study (Appendix 5), in which unadjusted IOP is identified as the primary efficacy variable. This approach differs from the statistical section of the current protocol. Does FDA agree with the approach described in the statistical analysis plan?

FDA Response: *Per the Sponsor, study 190342-021 has not been unmasked. To be used as a single equivalence study to support an NDA, the analysis plan should be focused on equivalence.*

Prepared by: Michael Puglisi
Project Manager
HFD-550

Concurrence by: William Boyd, M.D.
Clinical Team Leader
HFD-550

Wiley A. Chambers, M.D.
Deputy Division Director
HFD-550

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/s/

Wiley Chambers
10/27/03 11:13:55 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 11/18/04

TO: Michael Puglisi, Project Manager
Martin Nevitt, M.D., Clinical Reviewer
Division of Anti-inflammatory, Analgesic, and Ophthamolgical Drugs HFD-550

THROUGH: Leslie K. Ball, M.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Dianne Tesch, CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-770

APPLICANT: Allergan

DRUG: Brimonidine tartrate ophthalmic solution 1%

CHEMICAL CLASSIFICATION: 3S

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: lowering of intraocular pressure in patients with open angle glaucoma or ocular hypertension

CONSULTATION REQUEST DATE: July 6, 2004

ACTION GOAL DATE: March 1, 2005

I. BACKGROUND:

The goal of the inspection was to verify data integrity. This investigator was chosen because of

high enrollment, and because he was also a high enroller for another NDA (21-764) for which an inspection was requested. Dr. Wirta was last inspected February, 2002. The inspection was classified VAI for three instances of inadequate informed consent. The deficiency was corrected, and there was no evidence of a similar problem at the current inspection.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
David Wirta	Newport Beach	CA	7/6/04	10/12/04	NAI

A. Protocol #190342-021 compared the efficacy and safety of Brimonidine Purite ™ 0.1% with brimonidine tartrate 0.2% dosed three times daily.

1. Site #1 David Wirta, M.D., Newport Beach, California: No deficiencies were found. The data were acceptable.

   a. What was inspected: Twenty-five subjects were enrolled, 16 subjects experienced adverse events, and 3 subjects were discontinued due to adverse events. The study was conducted for 12 months. For the inspection, one third of the records of the 25 subjects who started the study were reviewed.

   b. There were no limitations to the inspection.

   c. In general the records were complete and well organized. One hundred per cent of the records were reviewed for informed consent. There were no deficiencies. There was no evidence of under reporting of adverse events or serious adverse events All study medication was accounted for.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No significant problems were identified at this inspection. No further action is indicated at this time. Only routine surveillance of Dr. Wirta's practice is recommended..

Dianne Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 1 OR 2
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-770
HFD-45/Division File / Reading File 10571
HFD-550 Puglisi Program Management Staff (electronic copy)
HFD-47// Tesch
HFD-47/Patague GCPB Files # 10571

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/s/

Dianne Tesch
1/11/05 02:14:47 PM
CSO

Leslie Ball
1/11/05 03:17:44 PM
MEDICAL OFFICER