CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-490/S007

20-613/S018

21-262/S006

ADMINISTRATIVE DOCUMENTS

PATENT INFORMATION

The following patents are currently in effect Chlorine Dioxide (Purite) containing ophthalmic preparations.

Patent Numbers:	5,424,078 / 5,736,165
Expiration Dates:	June 13, 2012 / April 7, 2015
Type of Patents:	Drug (Composition / Formulation, Use)
Patent Owner:	Allergan, Inc.

PATENT CERTIFICATION

I, the undersigned, hereby declare that U.S. Patent Nos. 5,424,078 and 5,736,165 cover the formulation, composition, and/or method of use of Chlorine Dioxide (Purite). This is one of the products that are the subject of this application for which approval is being sought.

Peter A. Kresel, M.S., M.B.A.
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.

8/13/01
(Date)

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA **June 25, 1999**. Application Written Request was made to: **NDA 20-490**
Timeframe Noted in Written Request for Submission of Studies **September 1, 2001**. (per amended WR dated 4/5/01)
NDA 20-490/S-007, 20-613/S-018, 21-262/S-006 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor **Allergan Inc.**
Generic Name **brimonidine tartrate ophthalmic solution** Trade Name **Alphagan**
Strength Dosage **0.5%** Form/Route **Ophthalmic Solution**
Date of Submission of Reports of Studies **August 14, 2001.**
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) **October 14, 2001.**

Was a formal Written Request made for the pediatric studies submitted?	Y X	N
Were the studies submitted after the Written Request?	Y X	N
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y X	N
Was the timeframe noted in the Written Request for submission of studies met?	Y X	N
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y X	N
Did the studies fairly respond to the Written Request?	Y X	N

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-104.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity X **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-613, 20-490	NCE	06-Sep-2001
21-262	NP	16-May-2004
20-613, 21-262	6194415	28-Jun-2015
20-613, 21-262	6248741	28-Jun-2015
21-262	5424078	13-Jun-2012
21-262	5736165	07-Apr-2015

/S/

SIGNED _____ **DATE** 10/9/01

Revised: 6/27/2001

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

/s/

Terrie Crescenzi
10/12/01 03:47:33 PM

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021262	**Trade Name:**	ALPHAGAN P
Supplement Number:	006	**Generic Name:**	BRIMONIDINE TARTRATE
Stamp date:	8/15/01	**Action Date:**	8/15/01
Supplement Type:	SE5		
COMIS Indication:	INDICATED FOR THE LOWERING OF INTRAOCULAR PRESSURE IN PATIENTS WITH OPEN-ANGLE GLAUCOMA/OCULAR HYPERTENSION		

Indication #1: Alphagan is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. - Date Entered: 12/12/01

Status: Pediatric Ranges were specified.

Range #1 Status: Completed

Edit this Range Delete this Range

Range Values: Minimum: 2 yr Maximum: 7 yr

This page was printed on 12/12/01

/S/

Signature

12/12/01

Date

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	020490	**Trade Name:**	ALPHAGAN
Supplement Number:	007	**Generic Name:**	BRIMONIDINE TARTRATE
Stamp date:	8/15/01	**Action Date:**	8/15/01
Supplement Type:	SE5		
COMIS Indication:	TREATMENT OF POST-OPERATIVE ELEVATED INTRAOCULAR PRESSURE ASSOCIATED WITH AIT IN PATIENTS OAG AND/OR OHT		

Indication #1: Alphagan is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. - Date Entered: 12/12/01

Status: Pediatric Ranges were specified.

Range #1 Status: Completed

Edit this Range Delete this Range

Range Values: Minimum: 2 yr Maximum: 7 yr

This page was printed on 12/12/01

/S/

Signature

12/12/01

Date

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	020613	**Trade Name:**	ALPHAGAN
Supplement Number:	018	**Generic Name:**	BRIMONIDINE TARTRATE
Stamp date:	8/15/01	**Action Date:**	8/15/01
Supplement Type:	SE5		
COMIS Indication:	BRIMONIDINE IS EFFECTIVE FOR LOWERING INTRAOCULAR PRESSURE IN PATIENTS WITH CHRONIC OPEN ANGLE GLAUCOMA OR OCULAR HYPERTENSION		

Indication #1: Alphagan is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. - Date Entered: 12/12/01

Status: Pediatric Ranges were specified.

Range #1 Status: Completed

Edit this Range Delete this Range

Range Values: Minimum: 2 yr Maximum: 7 yr

This page was printed on 12/12/01

/S/

Signature

12/12/01

Date

DEBARMENT CERTIFICATION

Allergan, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Peter A. Kresel, M.S., M.B.A. (Date)
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Allergan, Inc.	August 14, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
800/347-4500	714/246-4272
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-262

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Brimonidine tartrate	ALPHAGAN® P Ophthalmic Solution

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 5-Bromo-6 (2-imidazolidinylideneamino) quinoxaline L-tartrate

CODE NAME *(If any)* N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ophthalmic solution	0.15%	Topical, ophthalmic

(PROPOSED) INDICATION(S) FOR USE: For the control of IOP in patients with chronic open-angle glaucoma or ocular hypertension.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☒ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☒ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Submission of pediatric study report - pediatric exclusivity determination requested.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

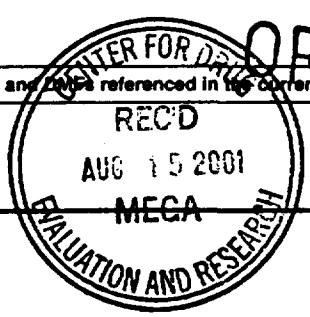
ESTABLISHMENT INFORMATION-(Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See continuation sheet

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-490
NDA 20-613

ORIGINAL



1 003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

. completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

2. TELEPHONE NUMBER *(Include Area Code)*

(800) 347-4500

3. PRODUCT NAME

ALPHAGAN® P(brimonidine tartrate ophthalmic solution) 0.15%

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021262

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☒ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Lori Gryzenia	Director, Regulatory Affairs	8/13/01

TELECONFERENCE MEETING MINUTES
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products

MEETING DATE: 10/10/01 **TIME:** 3 PM EST

NDAS & PRODUCTS:
20-490 Alphagan (brimonidine tartrate ophthalmic solution) 0.5%
20-613 Alphagan (brimonidine tartrate ophthalmic solution) 0.2%
21-262 Alphagan P (brimonidine tartrate ophthalmic solution) 0.15%

SPONSOR: Allergan, Inc.

MEETING TYPE: Notify sponsor their applications qualify for pediatric exclusivity.

BACKGROUND INFORMATION: The Pediatric study report for the Alphagan applications was submitted August 15, 2001. The Center's Pediatric Exclusivity Board met today, October 10, 2001, and granted Allergan 6 months additional exclusivity based on the data submitted to these applications.

DISCUSSION ITEMS:

In a teleconference between myself and Lewis Gryziewicz, Director of Regulatory Affairs at Allergan, I notified the sponsor that the application submitted to all three of their Alphagan applications have met the requirements as stated in the pediatric written request letter issued on June 25, 1999. As a result Alphagan will receive an additional 6 months of exclusivity.

I let him know that the FDA/CDER Pediatric Webpage would be updated with this information in the next couple days and he could expect to see the information reflected in the next printing of the Orange Book. Also, that I anticipated faxing draft labeling to Allergan on these submissions prior to December 1, 2001.

The call ended amicably.

See appended signature page

Lori Gorski
Project Manager

MEETING MINUTES

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/s/

Lori Gorski
10/10/01 03:49:58 PM
CSO

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, Allergan	**From:** Lori Gorski
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone: 714-246-6088	**Phone:** 301-827-2521
Pages: 1 (including cover page)	**Date:** October 18, 2001

Re: Alphagan pediatric supplements – request for clarification on clinical information

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

• **Comments:**

Lew,

Please provide the following clinical information for the Alphagans & Alphagan P pediatric supplements.

Clinical volume 37-2, page 137 contains Table 27 – Visual Acuity (LEA Symbols): Change in Line Number Comparison of Patient's Final Evaluation to Baseline Number and Percent of Patients (Safety Population). Visual acuity data is provided for 27 patients in the Alphagan treatment group and 22 patients in the Trusopt treatment group.

Can you explain why visual acuity data was not obtained for 11 patients in the Alphagan treatment group and 16 patients in the Trusopt treatment?

If you have any further questions, please contact me.

Thanks,
Lori Gorski

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/s/

Lori Gorski
10/22/01 11:28:05 AM
CSO

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, Allergan	**From:** Lori Gorski
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone: 714-246-6088	**Phone:** 301-827-2521
Pages: 1 (including cover page)	**Date:** November 5, 2001

Re: Alphagan pediatric supplements – request for clarification on clinical information

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

• **Comments:** Lew,

Please provide the following clinical information for the Alphagans & Alphagan P pediatric supplements.

1) The amendment dated October 19, 2001, identified the 27 patients who did not have visual acuity data. An explanation was provided for 4 of the patients (2 in each of the two treatment groups were too young to cooperate). The information contained in Attachment 4 states that visual acuity was not done at all visits for the other 23 patients (14 in the Alphagan group and 9 in the Trusopt group). No explanations were provided.

   Were the protocol deviations investigated? Please explain why visual acuity was not obtained for these patients.

If you have any further questions, please contact me.

Thanks,
Lori Gorski

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/s/

Lori Gorski
11/5/01 10:10:23 AM
CSO