CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-262

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 21-262 **DATE REVIEWED:** March 14, 2001

REVIEW #: 4 **REVIEWER:** Libaniel Rodriguez

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	06/29/00	06/30/00	07/05/00
Amendment, NC	07/21/00	07/24/00	08/11/00
Amendment, BZ	08/08/00	08/08/00	08/11/00
Amendment, BC	08/16/00	08/17/00	08/29/00
Amendment, BC	10/02/00	10/03/00	10/13/00
Amendment, BC	10/06/00	10/10/00	10/19/00
Amendment, BC	10/09/00	10/10/00	10/19/00
Amendment, BC	10/17/00	10/18/00	10/25/00
Amendment, BC	11/09/00	11/13/00	11/16/00
Amendment, BC	11/21/00	11/24/00	11/24/00
Amendment, BC	11/27/00	11/28/00	12/05/00
Amendment, BC	12/08/00	12/11/00	12/11/00
Amendment, BL	12/12/00	12/13/00	12/19/00
Amendment, BL	12/13/00	12/14/00	12/19/00
The following amendments are the subject of this review.			
Amendment, BC	12/20/00	12/21/00	12/21/00
Amendment, BC	03/09/01	03/12/01	
Amendment, (fax)	03/13/01		

NAME & ADDRESS OF APPLICANT: Allergan Inc.
2525Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
Lewis Gryziewicz
Director of Regulatory Affairs
Telephone # 714-246-6088

DRUG PRODUCT NAME

Proprietary: Alphagan P
Established: Brimonidine-purite™ Ophthalmic Solution 0.15%
Code Name/#: AGN 19034-LF, Formulation 9174X

Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Selective alpha-2 adrenergic agonist. Indicated for lowering intraocular pressure in patients with open angle glaucoma and/or ocular hypertension.

DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.15% w/v
ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops

PROPOSED USUAL DOSE: One drop instilled into each affected eye, three times per day at intervals of 8 hours.
Dispensed: By prescription only. _X_ Rx __ OTC

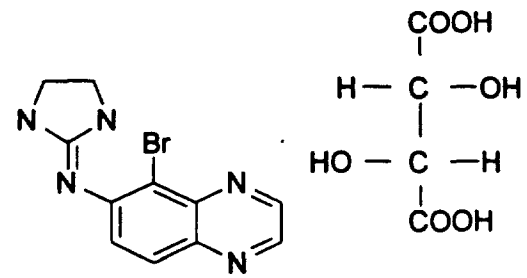
SPOT: None Needed.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See pages 5 and 6, vol. 1.2 of original NDA.

Brimonidine tartrate, (1) 6-Quinoxaline, 5-bromo-*N*-(4,5-dihydro-1 *H*-imidazol-2-yl)-, [*S*-(R*R*)]-2-3-dihydroxybutanedioate (1:1)

(2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate (1: 1)
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

MOLECULAR STRUCTURE:



Brimonidine Tartrate
(AGN 190342-LF)

SUPPORTING DOCUMENTS:

Referenced NDA 20-613 and subsequent supplements for all the information on the approved drug substance Brimonidine tartrate. (The agency agreed to cross-reference NDA 20-613 on the pre-NDA meeting held with the applicant on January 24, 2000)

DMF	Type	Holder	Item/Component	Review Date	Status	LOA Date

[redacted]

* This type I DMF was not reviewed as per current CDER review practice

CONSULTS:

CONSULT	DATE FORWARDED	STATUS
Microbiology, HFD 160	June 30, 2000	Approval recommended
EER (5 manufacturing facilities)	July 6 and 7, 2000, August 22, 2000	5 facilities acceptable to OC, See attached overall recommendation
Environmental Assessment	June 30, 2000 Categorical Exclusion Claimed	Acceptable
Labeling (Alphagan P)	December 22, 2000	Proposed name Acceptable
Methods Validation	January 2, 2001	In progress at Agency
Pharmacology (impurities) (polyethylene glycol)	June 30, 2000 October 24, 2000	Approval Recommended Approval Recommended

CONCLUSIONS & RECOMMENDATIONS: The applicant has responded adequately to CMC questions and recommendations. The methods validation packages were submitted to the [redacted] on January 2, 2001. From the point of view of CMC, this application is recommended for **approval.**

cc:
Orig. NDA 21-262
HFD-550/Division File
HFD-550/Chemist/L. Rodriguez
HFD-550/Chem. TL/L. Ng
HFD-830/DD/C-W. Chen
HFD-550/CSO/L. Gorski
HFD-550/MO/J. Harris
HFD-550/DDD/W. Chambers

/S/ 3-14-01

Libaniel Rodriguez, Ph.D.
Review Chemist, HFD-550

/S/ 3/14/01

Linda Ng, Ph. D.
Chemistry Team Leader, HFD-550

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 21-262 **DATE REVIEWED:** December 19, 2000

REVIEW #: 3 **REVIEWER:** Libaniel Rodriguez

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	06/29/00	06/30/00	07/05/00
Amendment, NC	07/21/00	07/24/00	08/11/00
Amendment, BZ	08/08/00	08/08/00	08/11/00
Amendment, BC	08/16/00	08/17/00	08/29/00
Amendment, BC	10/02/00	10/03/00	10/13/00
Amendment, BC	10/06/00	10/10/00	10/19/00
Amendment, BC	10/09/00	10/10/00	10/19/00
Amendment, BC	10/17/00	10/18/00	10/25/00
Amendment, BC	11/09/00	11/13/00	11/16/00
Amendment, BC	11/21/00	11/24/00	11/24/00
The following amendments are the subject of this review.			
Amendment, BC	11/27/00	11/28/00	12/05/00
Amendment, BC	12/08/00	12/11/00	12/11/00
Amendment, BL	12/12/00	12/13/00	12/19/00
Amendment, BL	12/13/00	12/14/00	12/19/00

NAME & ADDRESS OF APPLICANT: Allergan Inc.
2525Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
Lewis Gryziewicz
Director of Regulatory Affairs
Telephone # 714-246-6088

DRUG PRODUCT NAME

Proprietary: Alphagan P
Established: Brimonidine-purite™ Ophthalmic Solution 0.15%
Code Name/#: AGN 19034-LF, Formulation 9174X

Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Selective alpha-2 adrenergic agonist. Indicated for lowering intraocular pressure in patients with open angle glaucoma and/or ocular hypertension.

DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.15% w/v
ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops
PROPOSED USUAL DOSE: One drop instilled into each affected eye, three times per day at intervals of 8 hours.
Dispensed: By prescription only. **_X_ Rx __ OTC**

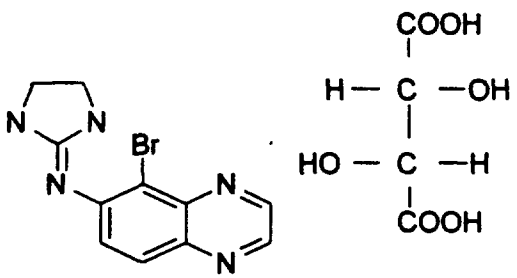
SPOT: None Needed.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See pages 5 and 6, vol. 1.2 of original NDA.

Brimonidine tartrate, (1) 6-Quinoxaline, 5-bromo-*N*-(4,5-dihydro-1 *H*-imidazol-2-yl)-, [*S*-(R*R*)]-2-3-dihydroxybutanedioate (1:1)

(2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate (1: 1)
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

MOLECULAR STRUCTURE:



Brimonidine Tartrate
(AGN 190342-LF)

SUPPORTING DOCUMENTS:

Referenced NDA 20-613 and subsequent supplements for all the information on the approved drug substance Brimonidane tartrate. (The agency agreed to cross-referencing NDA 20-613 on the pre-NDA meeting held with the applicant on January 24, 2000)

DMF	Type	Holder	Item/Component	Review Date	Status	LOA Date

[redacted]

* This type I DMF was not reviewed as per current CDER review practice

CONSULTS:

CONSULT	DATE FORWARDED	STATUS
Microbiology, HFD 160	June 30, 2000	Approval Recomended
EER (6 manufacturing facilities)	July 6 and 7, 2000, August 22, 2000	5 facilities acceptable to OC, 1 facility pending inspection
Environmental Assessment	June 30, 2000 Categorical Exclusion Claimed	Acceptable
Labeling (Alphagan P)	N/A	Proposed name Acceptable
Methods Validation	N/A	Pending
Pharmacology (impurities) (polyethylene glycol)	June 30, 2000 October 24, 2000	Approval Recommended Approval Recommended

CONCLUSIONS & RECOMMENDATIONS: The applicant has responded adequately to CMC questions and recommendations (see chemistry review notes). From the point of view of CMC, this application is recommended for **approval**, pending satisfactory inspection of the [redacted] manufacturing facility. Methods validation package will be sent to the FDA field laboratories for validation upon arrival. Mock-up with the actual size for the immediate container will be reviewed upon arrival.

cc:
Orig. NDA 21-262
HFD-550/Division File
HFD-550/Chemist/L. Rodriguez
HFD-550/Chem. TL/L. Ng
HFD-830/DD/C-W. Chen
HFD-550/CSO/L. Gorski
HFD-550/MO/J. Harris
HFD-550/DDD/W. Chambers

/S/ 12-19-00

Libaniel Rodriguez, Ph.D.
Review Chemist, HFD-550

/S/ 12/19/00

Linda Ng, Ph. D.
Chemistry Team Leader, HFD-550

DFS'd 12/4/00

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 21-262 **DATE REVIEWED:** December 4, 2000

REVIEW #: 2 **REVIEWER:** Libaniel Rodriguez

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	06/29/00	06/30/00	07/05/00
Amendment, NC	07/21/00	07/24/00	08/11/00
Amendment, BZ	08/08/00	08/08/00	08/11/00
Amendment, BC	08/16/00	08/17/00	08/29/00
Amendment, BC	10/02/00	10/03/00	10/13/00
Amendment, BC	10/06/00	10/10/00	10/19/00
Amendment, BC	10/09/00	10/10/00	10/19/00
Amendment, BC	10/17/00	10/18/00	10/25/00
The following amendments are the subject of this review:			
Amendment, BC	11/09/00	11/13/00	11/16/00
Amendment, BC	11/21/00		

NAME & ADDRESS OF APPLICANT: Allergan Inc.
2525Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
Lewis Gryziewicz
Director of Regulatory Affairs
Telephone # 714-246-6088

DRUG PRODUCT NAME
Proprietary: Alphagan P™
Established: Brimonidine-purite™ Ophthalmic Solution 0.15%
Code Name/#: AGN 19034-LF, Formulation 9174X
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Selective alpha-2 adrenergic agonist. Indicated for lowering intraocular pressure in patients with open angle glaucoma and/or ocular hypertension.

DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.15% w/v
ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops
PROPOSED USUAL DOSE: One drop instilled into each affected eye, three times per day at intervals of 8 hours.
Dispensed: By prescription only. **_X_ Rx __ OTC**

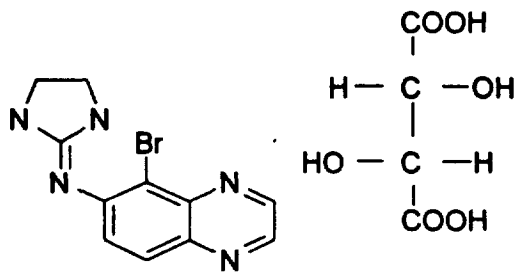
SPOT: None Needed.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See pages 5 and 6, vol. 1.2 of original NDA.

Brimonidine tartrate, (1) 6-Quinoxaline, 5-bromo-*N*-(4,5-dihydro-1 *H*-imidazol-2-yl)-, [*S*-(R*R*)]-2-3-dihydroxybutanedioate (1:1)

(2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate (1: 1)
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

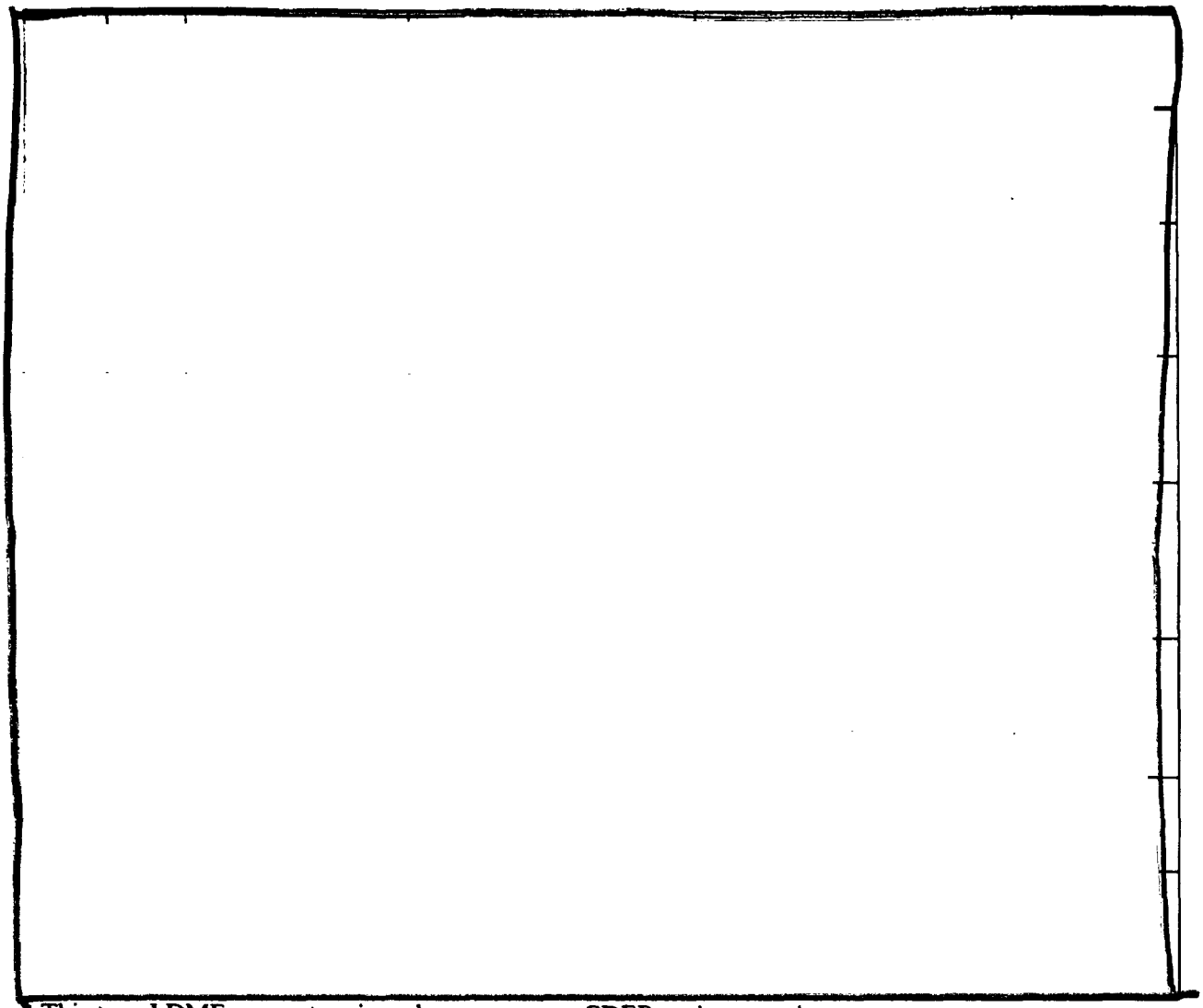
MOLECULAR STRUCTURE:



Brimonidine Tartrate
(AGN 190342-LF)

SUPPORTING DOCUMENTS:

Referenced NDA 20-613 and subsequent supplements for all the information on the approved drug substance Brimonidane tartrate. (The agency agreed to cross-referencing NDA 20-613 on the pre-NDA meeting held with the applicant on January 24, 2000.



* This type I DMF was not reviewed as per current CDER review practice.

CONSULTS:

CONSULT	DATE FORWARDED	STATUS
Microbiology, HFD 160	June 30, 2000	Approved
EER (6 manufacturing facilities)	July 6 and 7, 2000, August 22, 2000	5 facilities acceptable to OC, 1 facility pending inspection
Environmental Assessment	June 30, 2000 Categorical Exclusion Claimed	Acceptable
Labeling (Alphagan P)	N/A	Proposed name Acceptable
Methods Validation	N/A	Pending
Pharmacology (impurities) (polyethylene glycol)	June 30, 2000 October 24, 2000	Approved Acceptable

CONCLUSIONS & RECOMMENDATIONS: The applicant has responded adequately to CMC questions and recommendations (see chemistry review notes). From the point of view of CMC, this application is approvable contingent upon satisfactory outcome of the [redacted] manufacturing facility inspection and review of the mock-up label of the immediate container and package.

cc:
Orig. NDA 21-262
HFD-550/Division File
HFD-550/Chemist/L. Rodriguez
HFD-550/Chem. TL/L. Ng
HFD-830/DD/C-W. Chen
HFD-550/CSO/L. Gorski
HFD-550/MO/J. Harris
HFD-550/DDD/W. Chambers

/S/

12-4-00

Libaniel Rodriguez, Ph.D.
Review Chemist, HFD-550

/S/

12/4/00

Linda Ng, Ph. D
Chemistry Team Leader, HFD-550

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 21-262 **DATE REVIEWED:** November 8, 2000

REVIEW #: 1 **REVIEWER:** Libaniel Rodriguez

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	06/29/00	06/30/00	07/05/00
Amendment, NC	07/21/00	07/24/00	08/11/00
Amendment, BZ	08/08/00	08/08/00	08/11/00
Amendment, BC	08/16/00	08/17/00	08/29/00
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Amendment, BC			

NAME & ADDRESS OF APPLICANT: Allergan Inc.
2525Dupont Drive
P.O. Box 19534
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Lewis Gryziewicz
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Telephone # 714-246-6088

DRUG PRODUCT NAME
Proprietary: Alphagan P
Established: Brimonidine-purite™ Ophthalmic Solution 0.15%
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Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Selective alpha-2 adrenergic agonist. Indicated for lowering intraocular pressure in patients with open angle glaucoma and/or ocular hypertension.

DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.15% w/v
ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops
PROPOSED USUAL DOSE: One drop instilled into each affected eye, three times per day at intervals of 8 hours.
Dispensed: By prescription only. **_X_ Rx __ OTC**

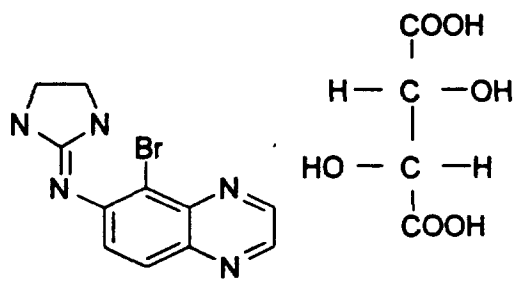
SPOT: None Needed.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See pages 5 and 6, vol. 1.2 of original NDA.

Brimonidine tartrate, (1) 6-Quinoxaline, 5-bromo-*N*-(4,5-dihydro-1 *H*-imidazol-2-yl)-, [*S*-(R*R*)]-2-3-dihydroxybutanedioate (1:1)

(2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate (1: 1)
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

MOLECULAR STRUCTURE:



Brimonidine Tartrate
(AGN 190342-LF)

SUPPORTING DOCUMENTS:

Referenced NDA 20-613 and subsequent supplements for all the information on the approved drug substance Brimonidane tartrate. (The agency agreed to cross-referencing NDA 20-613 on the pre-NDA meeting held with the applicant on January 24, 2000)

DMF	Type	Holder	Item/Component	Review Date	Status	LOA Date

[redacted]

* This type I DMF was not reviewed as per current CDER review practice.

CONSULTS:

CONSULT	DATE FORWARDED	STATUS
Microbiology, HFD 160	June 30, 2000	Pending
EER (6 manufacturing facilities)	July 6 and 7, 2000, August 22, 2000	5 facilities acceptable to OC, 1 facility pending inspection
Environmental Assessment	June 30, 2000 Categorical Exclusion Claimed	Acceptable
Labeling (Alphagan P)	N/A	Proposed name Acceptable
Methods Validation	N/A	Pending
Pharmacology (impurities) (polyethylene glycol)	June 30, 2000 October 24, 2000	Pending Information Requested.

CONCLUSIONS & RECOMMENDATIONS: The applicant has responded adequately to CMC questions and recommendations (see chemistry review notes). From the point of view of CMC, this application is approvable contingent upon satisfactory outcome of the [redacted] facility inspection and satisfactory resolution of CMC issues listed in facsimiles dated October 25, 2000 and November 8, 2000.

cc:
Orig. NDA 21-262
HFD-550/Division File
HFD-550/Chemist/L. Rodriguez
HFD-550/Chem. TL/L. Ng
HFD-830/DD/C-W. Chen
HFD-550/CSO/L. Gorski
HFD-550/MO/J. Harris
HFD-550/DDD/W. Chambers

/S/

11-8-00

Libaniel Rodriguez, Ph.D.
Review Chemist, HFD-550

/S/

11/9/00

Linda Ng, Ph. D.
Chemistry Team Leader, HFD-550