CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 050514S009

Name: Natacyn (natamycin ophthalmic suspension) Ophthalmic Suspension, 5%

Sponsor: Alcon Laboratories, Inc

Approval Date: October 30, 1978

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA050514Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA050514Orig1s009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-514/S-009

Alcon Laboratories, Inc.
c/o Alcon Research, Ltd.
Attn: Norma J. Schafer
Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Schafer:

Please refer to your supplemental new drug application dated July 16, 2001, received July 17, 2001, submitted under the Federal Food, Drug, and Cosmetic Act for Natacyn (natamycin ophthalmic suspension) Ophthalmic Suspension, 5%.

This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated April 20, 2007, April 17, and May 23, 2008. Your submission of April 20, 2007, constituted a complete response to our May 30, 2003, action letter.

This "Changes Being Effected" supplemental new drug application provides for changes to the product package insert.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format with the enclosed label.

Per our conversation on June 27, 2008, it was agreed that the following citation at the end of your May 23, 2008, package insert will be removed: *Laupen, J.O.; McLellan, W.L.; El Nakeeb, M.A.: ''Antibiotics and Fungal Physiology,'' Antimicrobial Agents and Chemotherapy, 1965: 1006, 1965.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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

7/18/2008 11:59:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA050514Orig1s009

LABELING

Natacyn®

(natamycin
ophthalmic suspension)5%
Sterile

DESCRIPTION: NATACYN® (natamycin ophthalmic suspension) 5% is a sterile, antifungal drug for topical ophthalmic administration. Each mL of the suspension contains: **Active:** natamycin 5% (50mg). **Preservative:** benzalkonium chloride 0.02%. **Inactive:** sodium hydroxide and/or hydrochloric acid (neutralized to
adjust the pH), purified water. The active ingredient is represented by the chemical structure:
Established name: Natamycin

Chemical Structure

Molecular Formula: C33H47NO13
Molecular Weight: 665.73

Chemical name: Stereoisomer of 22-[(3-amino-3,6-dideoxy- β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12- methyl-10-oxo-6,11,28-
trioxatricyclo[22.3.1.05,7] octacosa-8,14,16,18,20-pentaene-25-carboxylic acid.

Other: Pimaricin
The pH range is 5.0 – 7.5.

CLINICAL PHARMACOLOGY: Natamycin is a tetraene polyene antibiotic derived from *Streptomyces natalensis*. It possesses *in vitro* activity against a variety of yeast and filamentous fungi, including *Candida, Aspergillus, Cephalosporium, Fusarium* and *Penicillium*. The mechanism of action appears to be through binding of the molecule to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents. Although the activity against fungi is dose-related, natamycin is predominantly fungicidal.* Natamycin is not effective *in vitro* against gram-positive or gram-negative bacteria. Topical administration appears to produce effective concentrations of natamycin within the corneal stroma but not in intraocular fluid. Systemic absorption should not be expected following topical administration of NATACYN® (natamycin ophthalmic suspension) 5%. As with other polyene antibiotics, absorption from the gastrointestinal tract is very poor. Studies in rabbits receiving topical natamycin revealed no measurable compound in the aqueous humor or sera, but the sensitivity of the measurement was no greater than 2 mg/mL.

INDICATIONS AND USAGE: NATACYN® (natamycin ophthalmic suspension) 5% is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis. As in other forms of suppurative keratitis, initial and sustained therapy of fungal keratitis should be determined by the clinical diagnosis, laboratory diagnosis by smear and culture of corneal scrapings and drug response. Whenever possible the *in vitro* activity of natamycin against the responsible fungus should be determined. The effectiveness of natamycin as a single agent in fungal endophthalmitis has not been established.

CONTRAINDICATIONS: NATACYN® (natamycin ophthalmic suspension) 5% is contraindicated in individuals with a history of hypersensitivity to any of its components.

PRECAUTIONS: General. FOR TOPICAL OPHTHALMIC USE ONLY — NOT FOR INJECTION. Failure of improvement of keratitis following 7-10 days of administration of the drug suggests that the infection may be caused by a microorganism not susceptible to natamycin.

Continuation of therapy should be based on clinical re-evaluation and additional laboratory studies.

Adherence of the suspension to areas of epithelial ulceration or retention of the suspension in the fornices occurs regularly.

Use only if the container is undamaged.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the suspension. Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long term studies done using natamycin in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with natamycin. It is also not known whether natamycin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NATACYN® (natamycin ophthalmic suspension) 5% should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when natamycin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:-The following events have been identified during post-marketing use of NATACYN® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to NATACYN®, or a combination of these factors include: allergic reaction, change in vision, chest pain, corneal opacity, dyspnea, eye discomfort, eye edema, eye hyperemia, eye irritation, eye pain, foreign body sensation, paresthesia, and tearing.

DOSAGE AND ADMINISTRATION: SHAKE WELL BEFORE USING. The preferred initial dosage in fungal keratitis is one drop of NATACYN® (natamycin ophthalmic suspension) 5% instilled in the conjunctival sac at hourly or two-hourly intervals. The frequency of application can usually be reduced to one drop 6 to 8 times daily after the first 3 to 4 days. Therapy should generally be continued for 14 to 21 days or until there is resolution of active fungal keratitis. In many cases, it may be helpful to reduce the dosage gradually at 4 to 7 day intervals to assure that the replicating organism has been eliminated. Less frequent initial dosage (4 to 6 daily applications) may be sufficient in fungal blepharitis and conjunctivitis.

HOW SUPPLIED: NATACYN® (natamycin ophthalmic suspension 5%) is a 15mL fill packaged in a 15 mL amber glass bottle with a black phenolic closure. A flint glass dropper with a red plastic closure and a black rubber bulb are packaged separately in a clear plastic blister with Tyvek backing.

NDC 0065-0645-15

STORAGE: Store between 2-24ºC (36-75ºF). *Do not freeze*. Avoid exposure to light and excessive heat.

Rx Only

Revised: May 2008

9003666-0508
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 050514S009

LABELING REVIEW(S)

Medical Officer's Review NDA 50-514
Labeling Supplement

NDA 50-514	Submission Date: April 20, 2007
S-009	Reviewer Received: June 4, 2007
	Review Date: February 19, 2008

Sponsor: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099

Drug: Natacyn (natamycin ophthalmic suspension, USP) 5%

Pharmacologic Category: antibiotic

Submitted:

The applicant has submitted an amendment in response to an approvable letter sent May 30, 2003. The current amendment addresses the deficiencies communicated in the approvable letter.

Following is the labeling submitted by the applicant. Changes that have been previously agreed upon in response the to the February 20, 2002 approvable letter have been incorporated to reduce redundancy. Applicant deletions are noted by ~~strikeout~~ and additions are distinguished by single underline.

Natacyn®

(natamycin
ophthalmic suspension)5%
Sterile
DESCRIPTION: NATACYN® (natamycin ophthalmic suspension) 5% is a sterile, antifungal drug for topical ophthalmic administration. Each mL of the suspension contains: **Active:** natamycin 5% (50mg). **Preservative:** benzalkonium chloride 0.02%. **Inactive:** sodium hydroxide and/or hydrochloric acid (neutralized to adjust the pH), purified water. The active ingredient is represented by the chemical structure:
Established name: Natamycin

Chemical Structure

Molecular Formula: C33H47NO13
Molecular Weight: 665.73

Chemical name: Stereoisomer of 22-[(3-amino-3,6-dideoxy- β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12- methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.$0^{5,7}$] octacosa-8,14,16,18,20-pentaene-25-carboxylic acid.

Other: Pimaricin
The pH range is 5.0 – 7.5.

Reviewer's Comment: *The applicant has added the pH range as requested in the May 30, 2003 approvable letter. Acceptable.*

The applicant has not revised the package insert to include the osmolarity or osmolality of the product as requested in the February 26, 2002 approvable letter. It is recommended that the osmolality be included in the DESCRIPTION section.

CLINICAL PHARMACOLOGY: Natamycin is a tetraene polyene antibiotic derived from *Streptomyces natalensis*. It possesses *in vitro* activity against a variety of yeast and filamentous fungi, including *Candida, Aspergillus, Cephalosporium, Fusarium* and *Penicillium*. The mechanism of action appears to be through binding of the molecule to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents. Although the activity against fungi is dose-related, natamycin is predominantly fungicidal.* Natamycin is not effective *in vitro* against gram-positive or gram-negative bacteria. Topical administration appears to produce effective concentrations of natamycin within the corneal stroma but not in intraocular fluid. Systemic absorption should not be expected following topical administration of NATACYN® (natamycin ophthalmic suspension) 5%. As with other polyene antibiotics, absorption from the gastrointestinal tract is very poor. Studies in rabbits receiving topical natamycin revealed no measurable compound in the aqueous humor or sera, but the sensitivity of the measurement was no greater than 2 mg/mL.

INDICATIONS AND USAGE: NATACYN® (natamycin ophthalmic suspension) 5% is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis. As in other forms of suppurative keratitis, initial and sustained therapy of fungal keratitis should be determined by the clinical diagnosis, laboratory diagnosis by smear and culture of corneal scrapings and drug response. Whenever possible the *in vitro* activity of natamycin against the responsible fungus should be determined.
The effectiveness of natamycin as a single agent in fungal endophthalmitis has not been established.

CONTRAINDICATIONS: NATACYN® (natamycin ophthalmic suspension) 5% is contraindicated in individuals with a history of hypersensitivity to any of its components.

PRECAUTIONS: General. FOR TOPICAL OPHTHALMIC USE ONLY — NOT FOR INJECTION. Failure of improvement of keratitis following 7-10 days of administration of the drug suggests that the infection may be caused by a microorganism not susceptible to natamycin.

Continuation of therapy should be based on clinical re-evaluation and additional laboratory studies.

Adherence of the suspension to areas of epithelial ulceration or retention of the suspension in the fornices occurs regularly. - (b) (4)

(b) (4)

Reviewer's Comments: *The applicant has deleted the above wording as suggested in the February 26, 2002 approvable letter. Acceptable.*

Use only if the container is undamaged.

Reviewer's Comment: *The applicant has added the additional precaution statement "Use only if the container is undamaged". Acceptable.*

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the suspension. Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis.

Reviewer's Comment: *The applicant has added the following contact lens statement to the Information for Patients section: "Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis." Acceptable.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long term studies done using natamycin in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with natamycin. It is also not known whether natamycin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NATACYN® (natamycin ophthalmic suspension) 5% should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when natamycin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:- (b) (4) (b) (4)

Reviewer's Comment: *The above statement has been deleted from the Adverse Reactions sections as requested in the February 26, 2002 approvable letter. Acceptable.*

The following events have been identified during post-marketing use of NATACYN® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to NATACYN®, or a combination of these factors include: allergic reaction, change in vision, chest pain, corneal opacity, dyspnea, eye discomfort, eye edema, eye hyperemia, eye irritation, eye pain, foreign body sensation, paresthesia, and tearing.

Reviewer's Comments: *The adverse events listed have been revised to reflect the changes requested in the May 30, 2003 approvable letter. Acceptable.*

DOSAGE AND ADMINISTRATION: SHAKE WELL BEFORE USING. The preferred initial dosage in fungal keratitis is one drop of NATACYN® (natamycin ophthalmic suspension) 5% instilled in the conjunctival sac at hourly or two-hourly intervals. The frequency of application can usually be reduced to one drop 6 to 8 times daily after the first 3 to 4 days. Therapy should generally be continued for 14 to 21 days or until there is resolution of active fungal keratitis. In many cases, it may be helpful to reduce the dosage gradually at 4 to 7 day intervals to assure that the replicating organism has been eliminated. Less frequent initial dosage (4 to 6 daily applications) may be sufficient in fungal blepharitis and conjunctivitis.

HOW SUPPLIED: NATACYN® (natamycin ophthalmic suspension 5%) is a 15mL fill packaged in a 15 mL amber glass bottle with a black phenolic closure. A flint glass dropper with a red plastic closure and a black rubber bulb are packaged separately in a clear plastic blister with Tyvek backing.

Reviewer's Comments: *The description has been expanded to include the fill size as requested in the May 30, 2003 approvable letter. Acceptable.*

NDC 0065-0645-15

STORAGE: Store between 2-24ºC (36-75ºF). *Do not freeze*. Avoid exposure to light and excessive heat.

Rx Only

*Laupen, J.O.; McLellan, W.L.; El Nakeeb, M.A.: ‘‘Antibiotics and Fungal Physiology,’’ Antimicrobial Agents and Chemotherapy, 1965: 1006, 1965.

Revised: March 2007

AAA1062-0307
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Recommendations:

The proposed labeling incorporates all of the requested changes from the May 30, 2003 approvable letter. An approval letter should be drafted for this supplement.

Jennifer D. Harris, MD
Medical Officer

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

/s/

Jennifer Harris
4/9/2008 12:05:53 PM
MEDICAL OFFICER

William Boyd
4/10/2008 07:06:59 AM
MEDICAL OFFICER

NDA 50-514/S-009

Clinical Review of NDA 50-514
Labeling Supplement

Submission Dates: 09/16/02
Receipt Date: 09/17/02
Review Date: 12/10/02, revised 12/16/02, revised 3/3/03

Applicant:
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099

Representative:
Norma J. Schafer
Regulatory Affairs Analyst
Phone: 817-551-8568
Fax: 817-551-4630

Drug: Natacyn® (natamycin ophthalmic suspension, USP) 5%

Category: Antibiotic

Submitted: **Amendment to Special Supplement-Changes Being Effected**
The applicant submits final printed labeling mounted on heavyweight paper. No carton or container labels are included with the supplement or amendment.

This amendment has been submitted in response to an approvable letter sent on February 26, 2002. The original supplement included proposed changes to the **ADVERSE EVENTS** section. The current submission responds to deficiencies related to the **DESCRIPTION**, **PRECAUTIONS**, **ADVERSE REACTIONS**, **HOW SUPPLIED**, and **REFERENCES** sections of the package insert.

Following is the labeling submitted by the company in the amendment. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by double underline within the review. Applicant additions are distinguished by single underline.

NDA 50-514/S-009

NATACYN®
(natamycin ophthalmic suspension)
5%
Sterile

DESCRIPTION
NATACYN® (natamycin ophthalmic suspension)5% is a sterile, antifungal drug for topical ophthalmic administration. Each mL of the suspension contains: **Active:** Natamycin 5% (50 mg). **Preservative:** benzalkonium chloride 0.02%. **Inactive:** sodium hydroxide and/or Hydrochloric Acid (neutralized to adjust the pH to 5.0 to 7.5), purified Water.

Reviewer's comment: *The applicant has moved the ingredient listing into the DESCRIPTION section of the package insert. The applicant was advised in the February 26, 2002 approvable letter to include all inactive ingredients. No changes have been made to the list. The changes are acceptable as written pending chemistry concurrence on the action letter for this supplement.*

The active ingredient is represented by the chemical structure:

Established name: Natamycin

[Structure]

Molecular Formula: $C_{33}H_{47}NO_{13}$
Molecular Weight: 665.73

Reviewer's comment: *The applicant has included the molecular formula and molecular weight of the product as requested. Acceptable.*

Chemical name: Stereoisomer of 22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.$0^{5,7}$] octacosa-8,14,16,18,20-pentaene-25-carboxylic acid.

Other: Pimaricin
The product has an osmolality of ???

Reviewer's comments: *The applicant has not revised the package insert in order to include the osmolarity or osmolality of the product as requested in the February 26, 2002 approvable letter. It is recommended that the osmolality be included in the* **DESCRIPTION** *section of the package insert.*

CLINICAL PHARMACOLOGY:

Natamycin is a tetraene polyene antibiotic derived from *Streptomyces natalensis*. It possesses *in vitro* activity against a variety of yeast and filamentous fungi, including *Candida, Aspergillus, Cephalosporium, Fusarium* and *Penicillium*. The mechanism of action appears to be through binding of the molecule to the sterol moiety of the membrane to produce depletion of essential cellular constituents. Although the activity against fungi is dose-related, natamycin is predominantly fungicidal. Natamycin is not effective *in* vitro against gram-positive or gram-negative bacteria. Topical administration appears to produce effective concentrations of natamycin within the corneal stroma but not in intraocular fluid. Systemic absorption should not be expected following topical administration of NATACYN (natamycin ophthalmic suspension) 5%. As with other polyene antibiotics, absorption from the gastrointestinal tract is very poor. Studies in rabbits receiving topical natamycin revealed no measurable compound in the aqueous humor or sera, but the sensitivity of the measurement was no greater than 2mg/mL.

INDICATIONS AND USAGE: NATACYN (natamycin ophthalmic suspension) 5% is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis. As in other forms of suppurative keratitis, initial and sustained therapy of fungal keratitis should be determined by the clinical diagnosis, laboratory diagnosis by smear and culture of corneal scrapings and drug response. Whenever possible the *in vitro* activity of natamycin against the responsible fungus should be determined. The effectiveness of natamycin as a single agent in fungal endophthalmitis has not been established.

CONTRAINDICATIONS: NATACYN (natamycin ophthalmic suspension) 5% is contraindicated in individuals with a history of hypersensitivity to any of its components.

PRECAUTIONS: General. (b) (4) FOR TOPICAL OPHTHALMIC USE ONLY- NOT FOR INJECTION. Failure of improvement of keratitis following 7 to 10 days of administration of the drug suggests that the infection may be caused by a microorganism not susceptible to natamycin.

Reviewer's comment: *The applicant has capitalized the phrase "FOR TOPICAL USE ONLY" and included the word "OPHTHALMIC." Acceptable.*

Continuation of therapy should be based on clinical re-evaluation and additional laboratory studies.
Adherence of the suspension to areas of epithelial ulceration or retention of the suspension in the fornices occurs regularly. (b) (4)
(b) (4)

Reviewer's comment: *The February 26, 2002 approvable letter suggests eliminating the underlined language above. The applicant has elected to retain the precaution regarding monitoring. Not Acceptable.*

Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis.

Reviewer's comment: *The applicant has revised the* **PRECAUTIONS** *section to include the statement "Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis." as requested in the approvable letter. Acceptable. The phrase, "There have only been a limited number of cases in which natamycin has been used; therefore," has been removed as requested. Acceptable.*

Information for Patients: Do not touch dropper tip to any surface as this may contaminate the suspension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long term studies done using natamycin in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproductive studies have not been conducted using natamycin. Also it is not known whether natamycin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NATACYN® (natamycin ophthalmic suspension) 5% should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when natamycin is administered to a nursing mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Reviewer's comments: *The applicant has included a Geriatric Use subsection in the* **PRECAUTIONS** *section of the product labeling as directed in 21 CFR 201.57 (a)(10)(ii). Acceptable.*

ADVERSE REACTIONS: (b) (4)

(b) (4)

Reviewer's comment: *The approvable letter of February 26, 2002 proposed deletion of the underlined phrase above. The applicant has elected to retain the phrase. Not Acceptable.*

The following events have been identified during post-marketing use of NATACYN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to NATACYN, or a combination of these factors include:

Reviewer's comment: *The approvable letter of February 26, 2002 proposed deletion of the underlined phrase above. The applicant has elected to retain the phrase. Acceptable.*

(b) (4)

Reviewer's comment: *The approvable letter of February 26, 2002 proposed that all* **ADVERSE REACTIONS** *be included in the package insert listed in alphabetical order, (including those listed in the previously approved label. Alternatively, the applicant was instructed to provide justification for exclusion of "eye hyperemia". The applicant has revised the package insert to include the phrase "eye hyperemia. However, several adverse reactions have been excluded.* ***Not acceptable****. The package insert must be revised to read as follows:*

"allergic reaction, change in vision, chest pain, corneal opacity, dyspnea, eye discomfort, eye edema, eye hyperemia, eye irritation, eye pain, foreign body sensation, paresthesia, and tearing."

The original submission provided an Adverse Event Reporting history. Between 1985 and June 2001, the applicant has received 25 non-serious reports of adverse events. The applicant's statement indicates that inclusion is based on seriousness, frequency, causal relationship or a combination. However, the frequency of the events are eye discomfort (6), eye hyperemia (4), eye pain (3), allergic reaction (2), eye irritation (2), foreign body sensation, eye edema, corneal opacity, chest pain, dyspnea, paresthesia, tearing, and change in vision. The applicant has again chosen to include some events while excluding other events without justification. It is recommended that all events therefore be included listed in alphabetical order, (including those listed in the previously approved label). The applicant has also chosen to replace the term "allergic reaction" with "ocular allergy" and to replace the term "eye irritation" with "ocular irritation". The applicant should use the terms reported.

DOSAGE AND ADMINISTRATION: SHAKE WELL BEFORE USING**.** The preferred initial dosage in fungal keratitis is one drop of NATACYN (natamycin ophthalmic suspension) 5% instilled in the conjunctival sac at hourly or two-hourly intervals. The frequency of application can usually be reduced to one drop 6 to 8 times daily after the first 3 to 4 days. Therapy should generally be continued for 14 to 21 days or until there is resolution of active fungal keratitis. In many cases it may be helpful to reduce the dosage gradually at 4 to 7 day intervals to assure that the replicating organism has been eliminated. Less frequent initial dosage

(4 to 6 daily applications) may be sufficient in fungal blepharitis and conjunctivitis.

HOW SUPPLIED: (b) (4)

Reviewer's comment: *The applicant has deleted the wording above from the package insert. Acceptable.*

NATACYN (natamycin ophthalmic suspension5%) is packaged in a 15mL amber glass bottle with a black phenolic closure. A flint glass dropper with a red plastic closure and a black rubber bulb are packaged separately in a clear plastic blister with Tyvek backing.

Reviewer's comment: *The February 26, 2002 approvable letter recommended that the* **HOW SUPPLIED** *section be revised to include the target fill volume for the container size, color and type of container material for the bottles and dropper assembly as applicable. The applicant has complied with the request. However, the label should clarify whether the fill volume is 15 ml.*

NDC 0065-0645-15

Storage: Store between 2-24°C (36-75°F). *Do not freeze.* Avoid exposure to light and excessive heat.

Reviewer's comments: *As requested, the* **HOW SUPPLIED** *section be revised in order to simplify the description of Storage conditions as described above. Acceptable.*

Rx Only

Reviewer's comments: *As requested, the applicant has eliminated the* **REFERENCE** *section. Acceptable.*

(b) (4)

Reviewer's comment: *The applicant should delete the reference listed above or provide justification for including the dated reference in the label.*

(b) (4)

Reviewer's comment: *The copyright date is not included on the current proposed label. Acceptable.*

Alcon® (b) (4)

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Reviewer's comment: *The word "PHARMACEUTICALS" has been removed from the company name. Acceptable.*

NDA 50-514/S-009

Revised: March 2002
Reviewer's comment: *The applicant has included a revised date. Acceptable.*

35382-0302

Reviewer's comment: *The applicant has revised the internal tracking numbers. Acceptable.*

Recommendations: *The proposed package insert is approvable. An approvable letter should be drafted. In order for the application to be approved, the applicant must:*

1. *Revise the* **ADVERSE REACTIONS** *section of the package insert, to include all reported events in alphabetical order or provide justification for exclusion of events that have not been listed in the package insert. The event reported should be used unless rationale for using alternative language is provided. Specifically, the following sentence should replace the fourth sentence in the* **ADVERSE REACTIONS** *section of the package insert, "The events, which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to NATACYN, or a combination of these factors include: allergic reaction, change in vision, chest pain, corneal opacity, dyspnea, eye discomfort, eye edema, eye hyperemia, eye irritation, eye pain, foreign body sensation, parethesia, and tearing."*
2. *Eliminate the following sentences from the* **General** *subsection of the P***RECAUTIONS** *section, "It is possible that adverse reactions of which we have no knowledge at present may occur. For this reason, patients on this drug should be monitored at least twice weekly. Should suspicion of drug toxicity occur, the drug should be discontinued."*
3. *Eliminate the following sentence from the* **ADVERSE REACTIONS** *section of the package insert, "One case of conjunctival chemosis and hyperemia, thought to be allergic in nature has been reported."*

In addition, we have the following recommendation:

The **DESCRIPTION** *section should be revised to include the pH and osmolarity or osmolality.*

Lisa M. Hubbard, R.Ph.

Jennifer Harris, M.D.

cc:
NDA 50-514

NDA 50-514/S-009
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/s/

Lisa Hubbard
4/14/03 08:44:39 AM
MEDICAL OFFICER

Jennifer Harris
4/14/03 08:50:57 AM
MEDICAL OFFICER

Wiley Chambers
4/17/03 02:32:53 PM
MEDICAL OFFICER

NDA 50-514/S-009

Clinical Review of NDA 50-514
Labeling Supplement

Submission Dates: 07/16/01
Receipt Date: 07/17/01
Review Date: 12/08/02

Applicant:

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099

Representative:

Sarah J. Cantrell
Manager, Regulatory Affairs
Phone: 817-551-4517
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Drug:

Natacyn® (natamycin ophthalmic suspension) Ophthalmic Suspension, 5%

Category:

Antibiotic

Submitted:

Special Supplement-Changes Being Effected with final printed insert mounted on heavyweight paper **ADVERSE REACTIONS** section. The Adverse Reaction history is included in the submission. No carton or container labels were included with the supplement.

Following is the labeling submitted by the company. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by double underline within the review.

NDA 50-514/S-009

NATACYN®
(natamycin ophthalmic suspension)
5%
Sterile

DESCRIPTION
NATACYN® (natamycin ophthalmic suspension)5% is a sterile, antifungal drug for topical ophthalmic administration. The active ingredient is represented by the chemical structure:

[Structure]

Chemical name: Stereoisomer of 22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.$0^{5,7}$] octacosa-8,14,16,18,20-pentaene-25-carboxylic acid.

Other: Pimaricin

Each mL of the suspension contains: **Active:** Natamycin 5% (50 mg). **Preservative:** Benzalkonium Chloride 0.02%. **Inactive:** Sodium Hydroxide and/or Hydrochloric Acid (neutralized to adjust the pH to 5.0 to 7.5), Purified Water.

The product has an osmolality of ???

Molecular Formula
???

Molecular Weight
???

DM-00

Reviewer's comments: *It is recommended that the osmolarity or osmolality as appropriate and the pH be added to the* **DESCRIPTION** *section. Please also note, this section should include the product molecular formula, molecular weight, and a complete listing of inactive ingredients.*

CLINICAL PHARMACOLOGY:
Natamycin is a tetraene polyene antibiotic derived from *Streptomyces natalensis.* It possesses *in vitro* activity against a variety of yeast and filamentous fungi, including *Candida, Aspergillus, Cephalosporium, Fusarium* and *Penicillium.* The mechanism of action appears to be through binding of the molecule to the sterol moiety of the membrane to produce depletion of essential cellular constituents. Although the activity against fungi is dose-related, natamycin is predominantly fungicidal. Natamycin is not effective *in* vitro against gram-positive or gram-

negative bacteria. Topical administration appears to produce effective concentrations of natamycin within the corneal stroma but not in intraocular fluid. Systemic absorption should not be expected following topical administration of NATACYN (natamycin ophthalmic suspension)5%. As with other polyene antibiotics, absorption from the gastrointestinal tract is very poor. Studies in rabbits receiving topical natamycin revealed no measurable compound in the aqueous humor or sera, but the sensitivity of the measurement was no greater than 2mg/mL.

INDICATIONS AND USAGE: NATACYN (natamycin ophthalmic suspension) 5% is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis. As in other forms of suppurative keratitis, initial and sustained therapy of fungal keratitis should be determined by the clinical diagnosis, laboratory diagnosis by smear and culture of corneal scrapings and drug response. Whenever possible the *in vitro* activity of natamycin against the responsible fungus should be determined. The effectiveness of natamycin as a single agent in fungal endophthalmitis has not been established.

CONTRAINDICATIONS: NATACYN (natamycin ophthalmic suspension) 5% is contraindicated in individuals with a history of hypersensitivity to any of its components.

PRECAUTIONS: General. For topical eye use only- NOT FOR INJECTION. Failure of improvement of keratitis following 7 to 10 days of administration of the drug suggests that the infection may be caused by a microorganism not susceptible to natamycin.
Continuation of therapy should be based on clinical re-evaluation and additional laboratory studies.
Adherence of the suspension to areas of epithelial ulceration or retention of the suspension in the fornices occurs regularly. ~~There have only been limited number of cases in which natamycin has been used; therefore, it is possible that adverse reactions of which we have no knowledge at present may occur. For this reason, patients on this drug should be monitored at least twice weekly. Should suspicion of drug toxicity occur, the drug should be discontinued.~~

Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis.

Reviewer's comment: *The* **PRECAUTIONS** *section should include the statement "Patients should be advised not to wear contact lenses if they have signs and symptoms of fungal blepharitis, conjunctivitis, and keratitis." Such wording is more consistent with recently approved anti-infective therapies such as NDA 21-199 QUIXIN(levofloxacin ophthalmic solution) 0.5%. The statement regarding the "limited number of cases" and use of the drug product should be eliminated since the product has been in commercial distribution since1978.*

Information for Patients: Do not touch dropper tip to any surface as this may contaminate the suspension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long term studies done using natamycin in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproductive studies have not been conducted using natamycin. Also it is not known whether natamycin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NATACYN® (natamycin ophthalmic suspension) 5% should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when natamycin is administered to a nursing mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Reviewer's comments: *The package insert should include a Geriatric Use* subsection *in the* **PRECAUTIONS** *section of the product labeling as directed in 21 CFR 201.57 (a)(10)(ii). The wording provided above would be acceptable.*

ADVERSE REACTIONS: (b) (4)
~~allergic in nature, has been reported.~~

The following events have been identified during post-marketing use of NATACYN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, (b) (4) (b) (4) (b) (4) (b) (4) allergic reaction, change in vision, chest pain, corneal opacity, , dyspnea, eye discomfort, eye edema, eye hyperemia, eye irritation, eye pain, foreign body sensation, paresthesia, and tearing.

Reviewer's comments: *The applicant provides an Adverse Event Reporting history in support of the proposed paragraph above. Between 1985 and June 2001, the applicant has received 25 non-serious reports of adverse events. The applicant's statement indicates that inclusion is based on seriousness, frequency, causal relationship or a combination. However, the frequency of the events are eye discomfort (6), eye hyperemia (4), eye pain (3), allergic reaction (2), eye irritation*

(2), foreign body sensation, eye edema, corneal opacity, chest pain, dyspnea, paresthesia, tearing, and change in vision. The applicant has therefore, chosen to include some infrequent, less serious events such as "tearing", while excluding other more frequent, possibly more serious events such as "eye hyperemia." It is recommended that all events therefore be included listed in alphabetical order , (including those listed in the previously approved label). Alternatively, justification for exclusion of "eye hyperemia" should be submitted.

DOSAGE AND ADMINISTRATION: SHAKE WELL BEFORE USING**.** The preferred initial dosage in fungal keratitis is one drop of NATACYN (natamycin ophthalmic suspension)5% instilled in the conjunctival sac at hourly or two-hourly intervals. The frequency of application can usually be reduced to one drop 6 to 8 times daily after the first 3 to 4 days. Therapy should generally be continued for 14 to 21 days or until there is resolution of active fungal keratitis. In many cases it may be helpful to reduce the dosage gradually at 4 to 7 day intervals to assure that the replicating organism has been eliminated. Less frequent initial dosage (4 to 6 daily applications) may be sufficient in fungal blepharitis and conjunctivitis.

HOW SUPPLIED: 15 mL in glass bottles with sterile dropper assembly.

Reviewer's comments: *It is recommended that the* **HOW SUPPLIED** *section be revised to include the target fill volume for the container size, color and type of container material for the bottles and dropper assembly as applicable.*

NDC 0065-0645-15

Storage: (b) (4) (b) (4) - Store between 2-24°C (36-75°F). *Do not freeze.* Avoid exposure to light and excessive heat.

Reviewer's comments: *It is recommended that the* **HOW SUPPLIED** *section be revised in order to simplify the description of Storage conditions as described above.*

Rx Only

(b) (4)

(b) (4)

Reviewer's comments: *The applicant should eliminate the references described above. The product has been in commercial distribution since 1978. Relevant clinical information is widely available through textbooks.*

Alcon® PHARMACEUTICALS
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Revised: May 2001

Recommendations: *The proposed package insert is approvable. The applicant must include the reported events in alphabetical order or provide justification for exclusion of eye hyperemia. An approvable letter should be drafted and the new proposed wording should be provided for the applicant. Additionally, the applicant should be informed of the recommendations as described throughout the review above.*

Lisa M. Hubbard, R.Ph.

Jennifer Harris, M.D.

cc:

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Jennifer Harris
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Wiley Chambers
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