CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-565

ADMINISTRATIVE DOCUMENTS

14. PATENT CERTIFICATION (PARAGRAPH II)

I, the undersigned, hereby declare that the following patent, formerly in effect for epinastine hydrochloride, has expired on the date listed.

Patent Number	Type Patent	Patent Owner	Expiration Date
4,313,931	Compound and Method of Use	Boehringer Ingelheim International GmbH	23 Feb 2001

In the opinion and to the best knowledge of the Allergan, there are no active patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Martin A. Voet
Title: Senior Vice President
Chief Intellectual Property Counsel

Date: November 19, 2002

16. 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, MS, MBA
Sr. Vice President
Global Regulatory Affairs

NOV 25, 2002
Date

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-565 Supplement Type (e.g. SE5): _____ Supplement Number: ___

mp Date: December 19, 2002 Action Date: October 18, 2003

HFD 550 Trade and generic names/dosage form: ELESTAT (epinastine HCl ophthalmic solution 0.05%)

Applicant: Allergan, Inc. Therapeutic Class: Anti-histamines

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: Indicated for the prevention of itching associated with allergic conjunctivitis.

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

Yes: Please proceed to Section A.

XX No: Please check all that apply: ___Partial Waiver ____Deferred __X_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 range being partially waived:

Min____	kg____	mo.____	yr.__0__	Tanner Stage____
Max____	kg____	mo.____	yr.__3__	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

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.** 3	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

The agency did not issue a written request to study the pediatric population because there are already a number of ophthalmic drug products approved for this indication. Consistent with other products in this class, clinical studies included pediatric patients to the extent possible (evaluation of itching requires subjective evaluation generally limited to patients 10 years of age and older). Additional safety information was collected in pediatric patients down to 3 years of age (lower limit of the age of patients with the disease). There were no differences in safety or efficacy between pediatric and older patients.

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:

/S1

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

/S1

Raphael Rodriguez, PM

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

EXCLUSIVITY SUMMARY for NDA # 21-565 SUPPL # _____

Trade Name ELESTAT Generic Name epinastine HCl ophthalmic solution

Applicant Name Allergan, Inc. HFD- 550
Approval Date October 10, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

   If yes, what type(SE1, SE2, etc.)?**1S - New Molecular Entity**

   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.

   N/A

   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?

5 years

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

YES /__/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # **N/A** Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/ NO /_**X**_/

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

NDA # **N/A** _____

NDA # _____ _____

NDA # _____ _____

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 /_**X**_/

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

NDA # **N/A** _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /___/ 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 9:**

_____

_____

(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 /___/

(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 /___/

If yes, explain: _____

_____

(c) 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 # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /__/

Investigation #2 YES /___/ NO /__/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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 # _____
Investigation #2, Study # _____
Investigation #3, Study # _____

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 # YES /__/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # YES /__/	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 /_X_/

If yes, explain: _____

_____

_____

/S/

Raphael R. Rodriguez, PM

/S/ _____ 10/11/03

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

cc:
Archival NDA 21-565
HFD-550 /Division File
HFD-550 /RPM/ RodriguezR
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/01

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
A **21-565**	Efficacy Supplement Type SE-	Supplement Number	
Drug: **ELESTAT (epinastine HCl ophthalmic solution 0.05%)**		Applicant: **Allergan, Inc.**	
RPM: **Raphael R. Rodriguez**		**HFD- 550**	Phone # **827-2090**
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	**NME**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**10/20/03**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ Patent	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	**Completed 10/14/03**
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**N/A**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**9/10/03; 10/2/03**
• Most recent applicant-proposed labeling	**10/10/03**
• Original applicant-proposed labeling	**12/19/02**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC 8/21/03** **DMETS 8/27/03; 11/27/01; 4/13/01; 10/14/03**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	**12/19/02; 10/10/03**
• Reviews	**9/10/03; 10/2/03; 10/6/03; 10/10/03**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**None**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**N/A**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**8/29/00**
• Pre-NDA meeting (indicate date)	**7/24/02**
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**None**
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	**N/A**

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	**10/8/03; 10/14/03**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**10/14/03**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**10/6/03**
❖ Statistical review(s) *(indicate date for each review)*	**4/1/03**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**10/9/03**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**9/12/03; 10/10/03**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**5/20/03**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**5/20/03**
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**5/2/03**
Facilities inspection (provide EER report)	Date completed: **5/20/03** **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed **(X)** Requested **9/5/03** ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**10/8/03**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**10/31/01**
❖ CAC/ECAC report	**10/31/01**

14 Draft Labeling Page(s) Withheld

4 Page(s) Withheld

Office of Drug Safety

MEMO

To: Lee Simon, M.D.
Director, Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Carol A. Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Raphael Rodriguez
Project Manager, Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550

Date: October 9, 2003

Re: ODS Consult 03-0276; Elestat (Epinastine Hydrochloride Ophthalmic Solution) 0.05%, NDA 21-565.

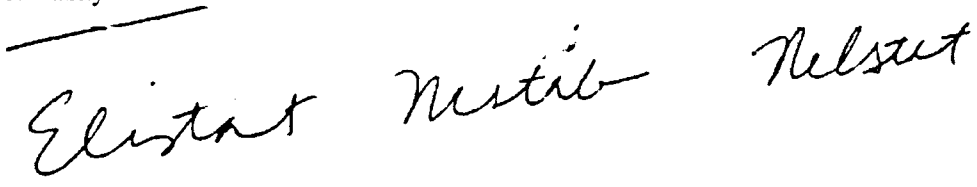
This memorandum is in response to a October 2, 2003 request from your Division for a review of the proprietary name, Elestat. This is the second proposed proprietary name for this application. The sponsor, Allergan, initially submitted the name Relestat. In a consult dated December 11, 2003, DMETS expressed concern with the use of Relestat due to its similarity Allergan's ophthalmic preparation, Restasis. Consequently, the sponsor submitted the alternate proprietary name Elestat.

The standard DMETS proprietary name review was not performed for this product due to the expedited nature of this consult. An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Elestat. 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.

The Expert Panel identified two proprietary names as having the potential for confusion with Elestat. These comparision of these names are provided in the chart below.

Proprietary Name	Elestat	Nestab CBF or FA	Nilstat
Writing sample			
Established Name	Epinastine Ophthalmic Solution	Multivitamin	Nystatin Oral Suspension
Indication	Allergic conjunctivitis	Nutrition	Treatment of Oral Candidiasis
Dosage Strength	0.05%	Multiple vitamins with Folic Acid	100,000 units/mL
How Supplied	5 mL/bottle	100 count bottle	60 mL
Usual Dose and Range	1 drop twice daily to affected eye(s)	1 tablet once daily	Use 2 mL in each side of mouth four times daily
Route of Administration	Ophthalmic	Oral	Oral
Storage conditions	Room temperature	Room temperature	Room temperature

DMETS believes that the potential for confusion between Nestab and Elestat is minimal due to differences in sound and script as well as differences in dosage form, route of administration, dosing schedule, and indication of use. However, the potential for confusion is possible between Nilstat and Elestat due to a look-alike (see writing sample below) and sound-alike similarity.



The similarity in sound stems from the "el" and "stat" sound. Elestat, if pronounced as "el-stat" rather than "ele-stat" may sound similar to Nilstat. However, the "N" sound in the beginning of the name in Nilstat may distinguish this name pair phonetically. Since both products are available in only one strength, differences in strength may not distinguish these products if a prescription a prescription for either product is written without a strength. The products may also be ordered in quantities of one. A prescription for either one of these products may also be scripted with the directions "Use as directed" thereby contributing to confusion. Although reference to Nilstat may be found in the Agency's "Orange Book", this product is not found in the 2003 Drug Topics *Red Book*, and therefore may no longer be available in the marketplace. Despite sound-alike and look-alike similarities, probability of confusion between Elestat and Nilstat is minimal due to product differences including dosage form and route of administration (Ophthalmic solution vs. oral suspension), expression of strength (0.5% vs. 100,000 units per mL), dosing schedule (twice daily vs. four times daily), indications (allergic conjunctivitis vs. oral candidiasis), and lack of availability in the U.S. marketplace. Therefore, DMETS has no objections to the use of the proprietary name Elestat.

We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Charles Hoppes
10/14/03 09:45:11 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/14/03 09:50:21 AM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

MEMO

To: Lee Simon, M.D.
Director, Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

From: Linda Y. Kim, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Denise P. Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Raphael Rodriguez
Project Manager, Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550

Date: August 27, 2003

Re: ODS Consult 01-0022-1 Relestat (Epinastine Hydrochloride Ophthalmic Solution) 0.05%, NDA 21-565

*****NOTE: This review contains proprietary and confidential information that should not be released to the public. These names are pending approval.*****

This memorandum is in response to a August 21, 2003 request from your Division for a final review of the proprietary name, Relestat. The carton and insert labeling were also submitted for review and comment. The proposed proprietary name was found acceptable by the Division of Medication Errors and Technical Support (DMETS) on November 14, 2001 (ODS Consult 01-0022-1). Since that review, DMETS has identified one additional proprietary name, [redacted] as having potential look-alike confusion with Relestat.

[redacted] was reviewed by DMETS on August 1, 2002 and found unacceptable (see ODS consult # 00-0137-1). On August 19, 2003, the sponsor of [redacted] submitted an alternate name which is pending review by DMETS. Therefore, [redacted] is no longer a potential problem.

The Relestat labels and labeling were submitted in draft format, which did not allow for a comprehensive evaluation of the color, format, etc. However, DMETS has attempted to focus on safety issues relating to possible medication errors and identified the following areas of possible improvement, which might minimize potential user error.

A. CARTON LABELING (5 mL, and 10 mL bottles)

B. INSERT LABELING

In the WARNINGS section, the statement " should be revised to delete references to the . and state that " is for **ophthalmic use** only...".

We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Linda Kim-Jung
9/5/03 10:16:12 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/9/03 12:09:53 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/9/03 12:12:40 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: September 20, 2001	DUE DATE: November 27, 2001	OPDRA CONSULT #: 01-0022-1

TO: Lee Simon, MD
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550

THROUGH: Raphael Rodriguez, Project Manager
HFD-550

PRODUCT NAME:	Manufacturer: Allergan, Inc.
Relestat (epinastine HCl ophthalmic solution) 0.05% IND #: 61,025	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550), OPDRA conducted a review of the proposed proprietary name "Relestat" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not object to the use of the proprietary name "Relestat".

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 14, 2001

IND NUMBER: [redacted]

NAME OF DRUG: Relestat
(epinastine HCl ophthalmic solution)
0.05%

IND HOLDER: Allergan, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550), for assessment of the tradename "Relestat", regarding potential name confusion with other proprietary/generic drug names.

The sponsor had previously proposed the tradename [redacted]. OPDRA found the name unacceptable (see OPDRA consult 01-0022).

PRODUCT INFORMATION

[redacted] ophthalmic solution contains epinastine HCl and is indicated for the prevention [redacted] allergic conjunctivitis. The recommended dosage is one drop twice daily.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound-alike or look-alike to "Relestat" 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[v] and Thomson

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[v] WWW location http://www.uspto.gov/tmdb/index.html.

and Thomson[vi] were also conducted. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Relestat". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising 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.

- Five product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with "Relestat". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.
- DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Relestat	Epinastine HCl opthalmic solution	1 drop twice daily	
Periostat	Doxycycline tablets and capsules 20 mg (Rx)	20 mg twice daily	S/A, L/A per OPDRA
Allerest	Antihistamine and decongestant combinations (otc): • 12 Hour Nasal Spray • Eye drops • Headache Strength Advanced. Formula • Maximum Strength • Maximum Strength 12 Hour • No Drowsiness Caplets • Sinus Pain Formula	Varies according to product	S/A, L/A per OPDRA
Orlistat (Xenical®)	Orlistat 120 mg capsule (Rx)	1capsule 3 times daily	S/A, L/A per OPDRA
Helistat	Absorbable collagen sponge	No longer marketed	S/A, L/A per OPDRA
[redacted]	[redacted]	[redacted]	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

*****NOTE: This review contains proprietary and confidential information that should not be released to the public. *****

[vi] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com."

B. STUDY CONDUCTED BY OPDRA

1. Methodology

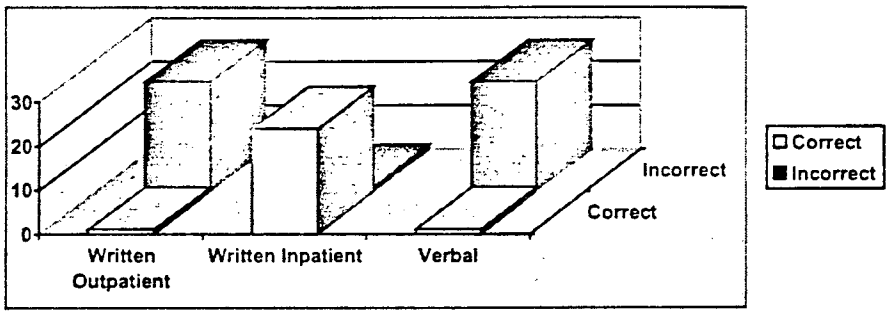
A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Relestat" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 117 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for "Relestat" (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Relestat # 1 Sig: 1 gtt OU BID prn	Relestat Instill 1 drop in both eyes twice daily as needed Dispense #1
Inpatient: Relestat 1 gtt OU BID prn	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Relestat" response	Other response
Written: Outpatient	39	26 (67%)	1 (4%)	25 (96%)
Inpatient	39	25 (64%)	24 (96%)	1 (4%)
Verbal	39	26 (67%)	1 (4%)	25 (96%)
Total:	117	77 (66%)	26 (34%)	51 (66%)



Among participants in the two written prescription studies, 26 of 51 respondents (51%) interpreted the name incorrectly. The participants provided interpretations such as *Relistat, Retestat, Retistat, Retestol, Ritistat, Relestol, Retestot,* and *Retestal.*

Among verbal prescription study participants, 25 out of 26 study participants (96%) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Relestat" such as *Relostat, Relastat, Rolostat, Rilstat,* and *Relistat.* Other interpretations included *Velastad, Orlostat, Willestat, Olistat, Prilostat, Wellistat, Relafstat,* and *Brilostat.*

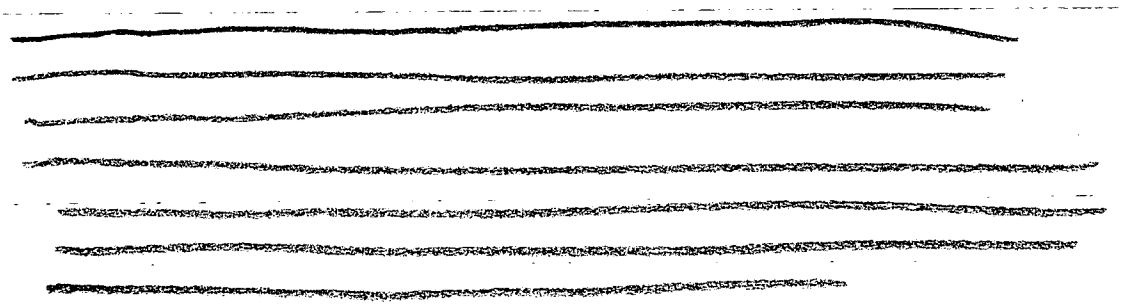
C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Relestat", the primary concerns raised were related to a few sound-alike, look-alike names that already exist in the U.S. marketplace. Three products, Orlistat, Periostat, and [redacted] were believed to be the most problematic in terms of potential medication errors.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Relestat could be confused with Orlistat, Periostat, or [redacted] However, two study participants from the verbal prescription study provided *Olistat* and *Orlostat* as an interpretation, which is strikingly similar the approved drug product *Orlistat.* Although there are limitations to the predictive value of these studies primarily due to sample size, we have acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Orlistat is the established name for the proprietary name Xenical. Orlistat is for management of obesity including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Orlistat is also indicated to reduce the risk for weight regain after prior weight loss. Each capsule contains 120 mg of Orlistat. The recommended dose of Orlistat is one 120 mg capsule 3 times a day with each main meal containing fat (during or up to 1 hour after the meal). Although Relestat and Orlistat do not look similar when scripted, the names sound somewhat similar. In addition, both drugs will be available in only strength, which adds to the confusion as prescribers often omit the strength on a prescription when only one strength is available for a product. However, Relestat and Orlistat differ in dosage form, dosing frequency and route of administration. Furthermore, Relestat will be ordered in quantities of one, whereas Orlistat will be ordered in larger quantities because of its dosing regimen of 3 capsules per day for extended periods of time.

Periostat contains doxycycline and is indicated as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis. Although Periostat and Relestat do not sound similar, the names have the potential to look similar when scripted. Additionally, the drug products share an overlapping dosing regimen (twice daily). However, the drug products differ in route of administration (oral vs. topical ophthalmic) and post-marketing experience has not demonstrated medication errors occurring between ophthalmic and oral drug products.



***NOTE: This review contains proprietary and confidential information that should not be released to the public. ***

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Please submit for evaluation.

IV. RECOMMENDATION:

OPDRA does not object to the use of the proprietary name "Relestat".

OPDRA would appreciate feedback of the final outcome of this. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Alina Mahmud, R.Ph. at 301-827-0916.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment (OPDRA)

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

/s/

Alina Mahmud
11/19/01 09:26:19 AM
PHARMACIST

Jerry Phillips
11/19/01 04:20:38 PM
DIRECTOR

Martin Himmel
11/20/01 09:58:40 AM
MEDICAL OFFICER

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