CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
22-288

NAME OF APPLICANT/NDA HOLDER
ISTA Pharmaceuticals®, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Bepreve™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Bepotastine Besilate	1.5%

DOSAGE FORM
Ophthalmic solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,780,877	8/24/04	12/25/17

d. Name of Patent Owner
(1) Ube Industries, Ltd.
(2) Tanabe Seiyaku Co. Ltd.

Address *(of Patent Owner)*
(1) 12-32, Nishihonmachi 1-Chome, Ube-Shi
(2) 2-10, Dosho-Machi 3-Chome, Chuo-Ku, Osaka-Shi

City/State
(1) Yamaguchi 755-863, Japan (2) Osaka 541-8505, Japan

ZIP Code
FAX Number *(if available)*

Telephone Number
(908) 607-1950

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Marv Garrett
Vice President Regulatory Affairs, Quality Assurance, and Compliance

Address *(of agent or representative named in 1.e.)*
ISTA Pharmaceuticals, Inc.
15295 Alton Parkway

City/State
Irvine, CA

ZIP Code
92618

FAX Number *(if available)*
(949) 727-0833

Telephone Number
(949) 788-5303

E-Mail Address *(if available)*
mgarrett@istavision.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☑ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☑ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☑ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Maureen Garrett	03 October 2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name ISTA Pharmaceuticals®, Inc.	
Address 15295 Alton Parkway	City/State Irvine, CA
ZIP Code 92618	Telephone Number (949) 788-5303
FAX Number *(if available)* (949) 727-0833	E-Mail Address *(if available)* mgarrett@istavision.com

EXCLUSIVITY SUMMARY

NDA # 22-288 SUPPL # HFD # 520

Trade Name Bepreve

Generic Name bepotastine besilate ophthalmic solution 1.5%

Applicant Name Ista Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

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 ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

(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:

n/a

(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:

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

n/a

==========

Name of person completing form: Raphael Rodriguez & William Boyd, M.D.
Title: Regulatory Project Manager & Clinical Team Leader
Date:

Name of Office/Division Director signing form: Wiley A. Chambers, M.D.
Title: Acting Director, DAIOP, HFD-520

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

RAPHAEL R RODRIGUEZ
09/17/2009

WILEY A CHAMBERS
09/22/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

)A/BLA#: 22-288 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAIOP PDUFA Goal Date: 9/12/09 Stamp Date: 11/12/2008

Proprietary Name: Bepreve

Established/Generic Name: bepotastine besilate ophthalmic solution 1.5%

Dosage Form: topical ophthalmic solution

Applicant/Sponsor: ISTA Pharmaceuticals, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next 'estion):

, NEW ☒ active ingredient(s); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of itching associated with allergic conjunctivits

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply.

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☒ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed$^{\Delta}$
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 0 mo.	2 yr[redacted] mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. *(Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
›pulation		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in ·onducting the studies or, if no progress has been made, evidence and documentation that such studies will be nducted with due diligence and at the earliest possible time. This requirement should be communicated to ,e applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	3 yr. 0 mo.	17 yr. 0 mo.	Yes ☒	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☑	Other	2 yr. __ mo.	2 yr. 11 mo.	☐	☑
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

e the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

ediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

dditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 4/2008)

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 22-288 Supplement Type: Supplement Number:

Product name and active ingredient/dosage form: Bepreve (bepotastine besilate ophthalmic solution) 1.5%

Sponsor: ISTA Pharmaceuticals, Inc.

Indications(s):
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived.

Partially Waived Studies (for selected pediatric subpopulations)
0 months – 2 years 11 months

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

   a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Studies are impossible or highly impractical because the number of pediatric patients age 0 months to 2 years 11 months with allergic conjunctivitis is so small.

   b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. Suggested language includes, "FDA has not required pediatric studies in ages ___ to ___ because (state the safety or effectiveness reason)."

   c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   d. Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22288	GI-1	ISTA PHARMACEUTICALS	BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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

/s/

RAPHAEL R RODRIGUEZ
09/17/2009

WILEY A CHAMBERS
09/22/2009

ISTA Pharmaceuticals

15294 Alton Parkway
Irvine, CA 92618
(949) 788-6000
fax (949) 788-6010

www.istapharm.com

Debarment Certification for NDA 22-288 for
Bepreve™ (bepotastine besilate ophthalmic solution) 1.5%

ISTA Pharmaceuticals®, 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.

Signed:

Marvin J. Garrett
Vice President
Regulatory Affairs, Quality Assurance
& Compliance

02 Oct 08
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-288	NDA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Bepreve Established/Proper Name: Bepotastine ophthalmic solution, 1.5% Dosage Form:		Applicant: Ista Pharmaceuticals, Inc. Regulatory Contact: Paul Nowacki Tel #(949) 789-3109
RPM: Raphael R. Rodriguez		Division:

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	9/12/09
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	5/27/09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	8/10/09 emailed
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	Included 8/12/09
• Original applicant-proposed labeling	Included 11/12/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	8/12/09
• Original applicant-proposed labeling	11/12/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	8/13/09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP 2/5/09, 7/29/09, 9/1/09 ☐ DRISK ☒ DDMAC 8/27/09 ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	2/5/09, 7/29/09, 9/1/09
Administrative / Regulatory Documents	
Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	5/30/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	Included
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	none
❖ Internal memoranda, telecons, etc.	none
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable 5/27/09
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable 8/12/09
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 8/4/08
• EOP2 meeting *(indicate date)*	☐ No mtg 8/15/07
• Other (e.g., EOP2a, CMC pilot programs)	SPA meeting 12/3/07
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	6/26/09
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 9/8/09
Division Director Summary Review *(indicate date for each review)*	☐ None 8/25 /09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/25/09
Clinical Information[5]	
Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	8/18/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	in clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	in clinical review; CDTL review; form 3455 included. n/a
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None n/a
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested enclosed 6/26, 6/29/09
Clinical Microbiology ☐ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 7/31/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5/22/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/21/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 4/21/09
ECAC/CAC report/memo of meeting	☐ None CAC Memo 5/5/09 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 8/13/09
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 7/27/09, and 8/9/09
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	6/17/09 ☐ Not needed n/a
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	7/27/09
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

➢ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 1/26/09 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-288

METHODS VALIDATION MATERIALS RECEIVED

ISTA Pharmaceuticals, Inc.
Attention: Paul Nowacki
Director of Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bepreve (Bepotastine Besilate) ophthalmic solution, 1.5% and to our July 30, 2009, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 4, 2009 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JEANNIE C DAVID
08/04/2009
signing on behalf of James Allgire

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-288

REQUEST FOR METHODS VALIDATION MATERIALS

ISTA Pharmaceuticals, Inc.
Attention: Paul Nowacki
Director of Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bepreve (Bepotastine Besilate) ophthalmic solution, 1.5%.

We will be performing methods validation studies on Bepreve (Bepotastine Besilate) ophthalmic solution, 1.5%, as described in NDA 22-288.

In order to perform the necessary testing, we request the following sample materials and equipments:

Drug Substance
Bepotastine Besilate (Lot 104002 Manufactured 5/1/01 or the oldest batch available) – (b) (4)

Drug Product
Bepreve (Bepotastine Besilate) Ophthalmic Solution 1.5% (Lot W0004236 or the oldest US batch manufactured under GMP) – (b) (4) (if bottle contains more than 3 mL)

Reference Standard
Bepotastine Besilate Reference Standard – (b) (4)

HPLC Columns
(b) (4)

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JEANNIE C DAVID
07/30/2009
signing on behalf of James Allgire

NDA REGULATORY FILING REVIEW

NDA # 22-288 Supplement # 0000 Efficacy Supplement Type SE-

Proprietary Name: Bepreve
Established Name: Bepotastine besilate ophthalmic solution
Strengths: 1.5%

Applicant: ISTA Pharmaceuticals, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: 11/11/08
Date of Receipt: 11/12/09
Date clock started after UN:
Date of Filing Meeting: 12/15/08
Filing Date: 1/13/09
Action Goal Date (optional): User Fee Goal Date: 12 September 2009

Indication(s) requested: Treatment of ocular itching associated with allergic conjunctivitis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1 S
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ N/A NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 66,864

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☐ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 15 August 2007 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 04 August 2008 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 03 December 2007 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☒

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☒

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

NDA #: 22-288

DRUG NAMES: Bepreve (bepotastine besilate opthalmic solution) 1.5%

APPLICANT: ISTA Pharmaceuticals, Inc.

BACKGROUND:

Bepotastine besilate was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as an oral treatment for allergic rhinitis. This product (Talion® tablets, Mitsubishi Tanabe Pharma Corporation [formerly Tanabe Seiyaku Company, Ltd.]) was approved in Japan in July 2000 and launched in Japan in October 2000. Talion® is presently indicated for allergic rhinitis, urticaria, and pruritus associated with skin diseases.

ISTA has studied Bepreve (bepotastine besilate ophthalmic solution) 1.5% as an ocular treatment for allergic conjunctivitis. The proposed indication for Bepreve (bepotastine besilate ophthalmic solution) 1.5% is for the treatment of ocular itching associated with allergic conjunctivitis.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Sonal Wadhwa
Secondary Medical:	William Boyd
Statistical:	Mushfiquer Rashid
Pharmacology:	Theresa Allio
Statistical Pharmacology:	Karl LIn
Chemistry:	Suresh Pagay
Environmental Assessment (if needed):	
Biopharmaceutical:	Kimberly Bergman
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Raphael Rodriguz
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☐ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known 26 June 2009 NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

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

/s/

RAPHAEL R RODRIGUEZ
07/30/2009

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 06-24-2009

TO: Raphael Rodriguez, Regulatory Project Manager
Sonal Wadhwa, M.D., Medical Officer
Division of Anti-Infective and Ophthalmology Products

FROM: Jean Mulinde, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-288

APPLICANT: ISTA Pharmaceuticals

DRUG: Bepreve™ (bepotastine besilate ophthalmic solution) 1.5%

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of ocular itching associated with allergic conjunctivitis in patients 3 years or older.

CONSULTATION REQUEST DATE: 12/15/2008

DIVISION ACTION GOAL DATE: 07/20/2009

PDUFA DATE: 09/11/2009

I. BACKGROUND:

An oral preparation of bepotastine besilate (Talion® tablets, Mitsubishi Tanabe Pharma Corporation [formerly Tanabe Seiyaku Company, Ltd.]) was approved in Japan in July 2000 as a treatment for allergic rhinitis. The successful use of bepotastine besilate as a systemic antihistamine prompted interest in Japan for development as an ophthalmic antihistamine. Senju Pharmaceutical Co., Ltd. is developing an ophthalmic formulation of bepotastine besilate for therapeutic use in allergic conjunctivitis for the Japanese market. This formulation has currently completed two Phase 1 and three Phase 2 trials in Japan. Senju Pharmaceutical Co., Ltd. has sublicensed the U.S. rights for the clinical development of an ophthalmic formulation of bepotastine besilate to ISTA Pharmaceuticals, Inc. (ISTA).

Based on the outcomes of three pivotal clinical studies, ISTA is seeking approval for bepotastine besilate ophthalmic solution 1.5% to treat ocular itching associated with allergic conjunctivitis when dosed twice daily. The clinical safety and efficacy evaluation plan for bepotastine besilate ophthalmic solution in the U.S. has consisted of 3 clinical studies conducted in the U.S., a large 6-week multisite randomized, placebo-controlled safety study and two randomized, placebo-controlled, double-masked efficacy conjunctival allergen challenge (CAC) trials (one Phase 2/3 single site study and one Phase 3 multisite study). The Phase 3 multisite, double-masked, randomized, placebo-controlled, parallel group safety study (CL-SAF-0405071-P) evaluated the safety of bepotastine besilate ophthalmic solution 1.5% administered two times per day (BID) for 6 weeks in healthy, normal volunteers ages 3 years and older. In addition, the two U.S. efficacy CAC trials (ISTA-BEPO-CS01 and CL-S&E-0409071-P) evaluated the safety and efficacy of bepotastine besilate ophthalmic solution (1.0% and 1.5%) in the same clinical trial design using the conjunctival allergen challenge (CAC) model in male and female subjects aged 10 years and older with allergic conjunctivitis.

The protocols inspected include:

1. PROTOCOL NUMBER: CL-S&E-0409071 “A Multi-Center, Double-Masked, Randomized, Placebo-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations of Bepotastine Besilate Ophthalmic Solution (1.0% and 1.5%) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis”

   This study was a multi-center, double-masked, randomized, placebo-controlled study in subjects 10 years and older with a history of allergic conjunctivitis conducted at five centers in the United States. Patients were enrolled in the study from November 16, 2007 through March 2, 2008 (Date of final study report: October 3, 2008).

   The primary efficacy variables for the study were:
   1. Ocular itching evaluated by the subject at 3, 5, and 7 minutes post-challenge at Visits 3B, 4, and 5 (0-4 unit scale, allowing half unit increments).
   2. Conjunctival redness evaluated by the Investigator at 7, 15, and 20 minutes post–challenge at Visits 3B, 4, and 5 (0-4 scale unit, allowing half unit increments)

Safety endpoints included adverse events, distance visual acuity utilizing an ETDRS chart at the beginning of each visit (for subjects under the age of 18, this was also to be performed approximately 15 minutes post investigational product instillation at Visit 3A and Visit 4, and approximately 40 minutes post investigational product instillation at Visit 5), slit lamp biomicroscopy at the beginning of each visit (for subjects under the age of 18, this will also be performed approximately 15 minutes post investigational product instillation at Visit 3A and Visit 4, and approximately 40 minutes post investigational product instillation at Visit 5), intraocular pressure (IOP) following the post-CAC assessments at Visit 1 and Visit 5, dilated fundoscopy following the post-CAC assessments at Visit 1 and Visit 5, urine pregnancy test (for women of childbearing potential) at Visit 1 and Visit 5, and ocular comfort examination 1 immediately after investigational product instillation (within 1 minute) and 5 minutes after investigational product instillation at Visit 3A, Visit 4, and Visit 5. The primary ocular comfort assessment1 is the determination of the absolute comfort grade and the investigational product being tested at each of two time points (immediately after investigational product instillation (within 1 minute) and 5 minutes after instillation) for overall ocular comfort. The grading for overall ocular comfort was to be done on a 0 to 3 scale (with half unit (one step) increments allowed), according to the following:

0 = comfortable; discomfort absent
1 = generally comfortable; mild discomfort
2 = some discomfort, but tolerable; moderate comfort
3 = severely uncomfortable or intolerable

2. PROTOCOL NUMBER: ISTA-BEPO-CS01 "A Single-Center, Double-Masked, Randomized, Placebo-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations (1.0% and 1.5%) Bepotastine Besilate Ophthalmic Solution in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis"

This study was a single-center, double-masked, randomized, placebo-controlled study in subjects 10 years and older with a history of allergic conjunctivitis conducted at one center in the United States. Patients were enrolled in the study from March 1, 2007 through April 4, 2007 (Date of final study report: October 9, 2008).

The primary efficacy variables for the study were:

1. Ocular itching evaluated by the subject at 3, 5, and 7 minutes post-challenge at Visits 3, 4, and 5 (0-4 unit scale, allowing half unit increments).
2. Conjunctival redness evaluated by the Investigator at 7, 15, and 20 minutes post–challenge at Visits 3, 4, and 5 (0-4 scale unit, allowing half unit increments)

Safety endpoints included adverse events, distance visual acuity utilizing an ETDRS chart at the beginning of each visit (for subjects under the age of 18, this was also to be performed approximately 15 minutes post investigational product instillation at Visit 3 and Visit 4, and approximately 40 minutes post investigational product instillation at Visit 5), slit lamp biomicroscopy at the beginning of each visit (for subjects under the age of 18, this will also be performed approximately 15 minutes post investigational product instillation at Visit 3 and Visit 4, and approximately 40 minutes post investigational product instillation at Visit 5), intraocular pressure (IOP) following the post-CAC assessments at Visit 1 and Visit 5, and dilated fundoscopy following the post-CAC assessments at Visit 1 and Visit 5.

3. PROTOCOL NUMBER: CL-SAF-0405071-P "A Multi-Center, Double-Masked, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Safety of Bepotastine Besilate Ophthalmic Solution 1.5% Used Twice Daily in Healthy, Normal Volunteers"

   This study was a multi-center, double-masked, randomized, placebo-controlled, parallel-group safety study in healthy normal adult and pediatric volunteers (≥ 3 years) conducted at six centers in the United States. Patients were enrolled in the study from October 22, 2007 through January 21, 2008 (Date of final study report: October 27, 2008).

   There were no efficacy endpoints for this study. The safety endpoints included:

   - Physical exam (including vital signs) at Visit 1 and Visit 4
   - Adverse events (reported, elicited, and observed)
   - Urine pregnancy test (for women of childbearing potential) at Visit 1 and Visit 4
   - Visual acuity (best corrected if necessary)
   - Biomicroscopy (pre-instillation and 15 minutes post investigational product instillation at Visits 1-3, and once at Visit 4)
   - Ocular endothelial cell counts (age ≥ 10 years old) at Visit 1 and Visit 4 [for approximately 200 subjects]
   - Intraocular pressure (if possible, age ≥ 10 years old) at Visit 1 and Visit 4
   - Ophthalmoscopy (dilated) at Visit 1 and Visit 4
   - Ocular comfort examination (if possible, age ≥ 10 years old) at Visit 2 and Visit 3

Four domestic sites were selected for inspection. This is a re-inspection of Dr. Torkildsen who was previously inspected 10/05/2006 and received a final classification of NAI.

The clinical investigator (CI) sites requested for inspections for CL-S&E-0409071-P were those with the highest enrollment numbers (approximately one half of subjects enrolled in the study). For CL-SAF-040571-P the CI site requested for inspection enrolled greater that one third of all subjects enrolled in the study. For ISTA-BEPO-CS01, the single CI site requested for inspection has previously been inspected by the FDA (inspected 10/05/2006 and received a final classification of NAI), as this site was responsible for all enrolled subjects in this pivotal study a re-inspection of the CI was considered necessary. As the product was a new molecular entity an inspection of the Sponsor was also conducted. Field inspections for these pivotal

studies were considered important as this is a new molecular entity.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Thomas T. Macejko, MD Eye Care Assoc. of Greater Cincinnati, Inc. 563 Wessel Drive Fairfield, OH 45014	CL-S&E-0409071-P Site #1 26 Subjects	05/27/2009-06/01/2009	Pending (Preliminary classification of NAI)
Mark T. Bergmann, MD Eye Care Assoc. of Greater Cincinnati, Inc. 2859 Boudinot Ave, Suite 301 Cincinnati, OH 45238	CL-S&E-0409071-P Site #3 35 Subjects	05/20/2009-05/23/2009	Pending (Preliminary classification of NAI)
Gail Torkildsen, MD ORA Clinical Research and Development, Inc. 797 Turnpike Street North Andover, MA 01845 And Andover Eye Associates 138 Haverhill Street Andover, MA 01810	ISTA-BEPO-CS01 This is only site for this study 107 Subjects	03/03/2009-03/12/2009	VAI
Clifford Michaelson, MD ORA Clinical Research and Development, Inc. 797 Turnpike Street North Andover, MA 01845 And Andover Eye Associates 138 Haverhill Street Andover, MA 01810	CL-SAF-040571-P Site #6 301 Subjects	03/03/2009-03/20/2009	VAI
Sponsor: ISTA Pharmaceuticals 15295 Alton Parkway Irvine, CA 92618	CL-S&E-0409071-P ISTA-BEPO-CS01 CL-SAF-040571-P	02/20/2009-03/10/2009	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.

1. Thomas T. Macejko, MD

Eye Care Assoc. of Greater Cincinnati, Inc.
563 Wessel Drive
Fairfield, OH 45014

Protocol CL-S&E-0409071-P, Site #1

a. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.811 between 05/27/2009-06/01/2009. A total of 64 subjects were screened, 35 subjects were enrolled and 32 completed the study. Informed consent documents for all 35 enrolled subjects were reviewed during the inspection. In addition, complete records for 24 enrolled subjects were reviewed during the inspection. There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of Dr. Macejko's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity**:
Based on communications with the field investigator, data derived from Dr. Macejko's site are considered acceptable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Mark T. Bergmann, MD
Eye Care Assoc. of Greater Cincinnati, Inc.
2859 Boudinot Ave, Suite 301
Cincinnati, OH 45238
Protocol CL-S&E-0409071-P, Site #3

d. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.811 between 05/20/2009-05/23/2009. A total of 60 subjects were screened, 26 subjects were enrolled and 25 completed the study. Records for all 26 enrolled subjects were reviewed during the inspection. There were no limitations to the inspection.

e. **General observations/commentary**:
The inspection of Dr. Bergmann's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

f. **Assessment of data integrity**:
Based on communications with the field investigator, data derived from Dr. Bergmann's site are considered acceptable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions

change upon receipt and review of the EIR.

3. Gail Torkildsen, MD
ORA Clinical Research and Development, Inc.
797 Turnpike Street
North Andover, MA 01845
AND
Andover Eye Associates
138 Haverhill Street
Andover, MA 01810
Protocol ISTA-BEPO-CS01

a. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.811 between 03/03/2009-03/12/2009. A total of 179 subjects were screened, 107 subjects were enrolled and 104 completed the study. Informed consent documents for all enrolled subjects were reviewed, as were random screen failure consents. Records for 49 enrolled subjects were reviewed to verify that subjects met eligibility criteria. Records for 49 enrolled subjects were reviewed to verify other aspects of protocol compliance including: adverse event reporting, completion of visit specific required procedures, and endpoint outcomes. In addition, financial disclosure forms, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of Dr. Torkildsen's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

i. Failure to appropriately document informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of the consent [21 CFR 50.27(a)]. Specifically, for failing to ensure that two subjects (Subject #1105 and Subject #1121), dated informed consent documents when they signed the consents.

ii. Failure to prepare or maintain adequate case histories with respect to data pertinent to the investigation [312.62(b)]. Specifically, for:
   a) Failing to document and adverse event of wisdom tooth pain for one subject (#1150).
   b) Incorrectly documenting one subject (Subject #1104) failed to qualify for the study when they did and were subsequently randomized, treated, and completed the study. Based on review of other source documents and the case report form it appeared that "No" was checked in error.

c) For documenting two Visit 5 assessments for Subject #1099; the first occurring on March 30, 2007 in which apparently only a portion of the visit required procedures were completed and the second occurring on March 31, 2007 at which time all visit procedures appear to have been completed. There was no explanation available as to why two visits are documented to have occurred for Visit 5.

c. **Assessment of data integrity**:
Although regulatory violations were noted, it is unlikely that they significantly affect overall reliability of safety and efficacy data from the site.

4. Clifford Michaelson, MD
ORA Clinical Research and Development, Inc.
797 Turnpike Street
North Andover, MA 01845
AND
Andover Eye Associates
138 Haverhill Street
Andover, MA 01810
Protocol CL-SAF-040571-P, Site #6

a. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.811 between 03/03/2009-03/20/2009. A total of 345 subjects were screened, 301 subjects were enrolled and 258 completed the study. Informed consent documents for all enrolled subjects were reviewed. Records for 146 enrolled subjects were reviewed to verify that subjects met eligibility criteria. Records for 99 enrolled subjects were reviewed to verify other aspects of protocol compliance including: compliance with dosing, adverse event reporting, completion of visit specific required procedures, and primary endpoint outcomes. In addition, financial disclosure forms, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. Of note, the Institutional Review Board used for this study was Coast Independent Review Board LLC (Colorado Springs, CO). Based on review of IRB related documents provided in the Establishment Inspection Report (EIR) and the summary of IRB-site interaction provided in the EIR, it appears that initial and continuing review of the site's conduct of this study was appropriately completed. There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of Dr. Michaelson's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

i. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].

Specifically, for one subject (#6108) two Visit 1 assessments were conducted. The first was halted for undocumented reasons and the subject returned 4 days later and the Visit 1 assessment was performed again, but a visual acuity examination was not performed as required by the protocol during this visit.

ii. Failure to prepare or maintain adequate case histories with respect to data pertinent to the investigation [312.62(b)]. Specifically, for:
   a) Subject #6108, enrolled on October 24, 2007 had a birth date of October 12, 1995 on source documents and the case report form when the correct birth date for the subject was actually October 12, 1985.
   b) For Subject #6120 the Visit 2 source record documents (b) (4) score as -0.10, but the Visit 2 corresponding Case Report Form page documents the (b) (4) as -0.16.

c. **Assessment of data integrity**:
Although regulatory violations were noted, it is unlikely that they significantly affect overall reliability of safety and efficacy data from the site.

5. ISTA Pharmaceuticals
15295 Alton Parkway
Irvine, CA 92618

a. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.810 between 02/20/2009-03/10/2009. The inspection was directed to assess the adequacy of sponsor/monitor/CRO functions for clinical trials, CL-S&E-0409071, ISTA-BEPO-CS01, and CL-SAF-0405071-P. The inspection focused on the selection, monitoring and data validation of clinical investigators, monitoring procedures and activities, adverse event reporting, data collection and handling, test article accountability, and contract responsibilities (CRO, data collection, and laboratory support) related to these studies. A total of six of the Sponsor's CI files were reviewed in depth (Dr. Macejko, Dr. Bergmann, Dr. Torkildsen, Dr. Michaelson, Dr. Kurata, and Dr. Dao). There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of the Sponsor/Applicant, ISTA Pharmaceuticals Inc., did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity**:
Based on the provided Establishment Inspection Report (EIR) for this inspection, data derived from studies CL-S&E-0409071, ISTA-BEPO-CS01, and CL-SAF-0405071-P are considered reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, Protocols CL-S&E-0409071, ISTA-BEPO-CS01, and CL-SAF-0405071-P appear to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Sponsor inspection of ISTA Pharmaceuticals Inc. is NAI.

The final classifications of the Clinical Investigator inspections of Dr. Torkildsen and Dr. Michaelson are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, the safety and efficacy data from these sites are considered reliable.

The preliminary classifications of the Clinical Investigator inspections of Dr. Bergmann and Dr. Macejko are NAI. Upon receipt of the EIRs for Dr. Bergmann and Dr. Macejko an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Jean M. Mulinde, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Jean Mulinde
6/26/2009 10:41:08 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
6/29/2009 08:08:58 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-288

Ista Pharmaceuticals, Inc.
ATTENTION: Mr. Paul Nowacki
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your New Drug Application (NDA) dated November 12, 2008, received November 12, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bepotastine besilate ophthalmic solution.

We also refer to your December 10, 2008, correspondence, received December 10, 2008, requesting review of your proposed proprietary name, Bepreve. We have completed our review of the proposed proprietary name, Bepreve and have concluded that it is acceptable.

The proposed proprietary name, Bepreve will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your December 10, 2008, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Marlene Hammer, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0757. For any other information regarding this application contact Raphael R. Rodriguez at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley Chambers, MD
Acting Director
Division of Anti-Infective and
Ophthalmology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Wiley Chambers

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-288

ISTA Pharmaceuticals, Inc.
Attn: Paul Nowacki
Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your November 12, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bepreve (bepotastine besilate ophthalmic solution) 1.5%. Reference is also made to an FDA filing letter dated January 23, 2009 notifying you of the **Standard** review with the User Fee Goal date of September 12, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to initiate discussion on the proposed labeling and, if necessary, any postmarketing commitment requests by July 31, 2009.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a waiver of pediatric studies in age group ranging from 0 to 3 years old in this application. Once we have reviewed your request, we will notify you of our decision.

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Health Project Manager, at (301) 796-0798.

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

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/s/

Wiley Chambers

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March 6, 2009

The attached "Filing Communication - No Issues Identified" letter did not include information related to internal review timelines or PREA. This information was provided to the sponsor in the “General Advice Letter” issued 3/6/09. Refer to this letter for specifics.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-288

ISTA Pharmaceuticals, Inc.
Attn: Paul Nowacki
Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your November 12, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bepreve (bepotastine besilate ophthalmic solution) 1.5%.

We acknowledge receipt of your submissions dated December 10, 11, 17 and 18, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is September 12, 2009.

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

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

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/s/

Wiley Chambers

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DSI CONSULT: Request for Clinical Inspections

Date: December 15, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
ATTN: Jean Mulinde, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

From: Sonal D. Wadhwa, MD, Medical Officer, (301) 796-2446
Raphael R. Rodriguez, RPM, (301) 796-0798
Division of Anti-Infective & Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: **NDA-22-288**
Sponsor: **Ista Pharmaceuticals** POC:**Paul Nowacki 949) 789-3109**
Drug: **Bepreve (bepotastine besilate ophthalmic solution) 1.5%**
NME (Yes/No): **Yes**
Review Priority (Standard or Priority): **Standard**

Study Population includes < 18 years of age (Yes/No): **Yes**
Is this for Pediatric Exclusivity (Yes/No): **No**

Proposed New Indication for Supplement: **Treatment of ocular itching associated with allergic conjunctivitis in patients 3 years or older.**

PDUFA: **September 11, 2009**
Action Goal Date: **July 20, 2009**
Inspection Summary Goal Date: **June 25, 2009**

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Thomas T. Macejko, MD Eye Care Assoc. of Greater Cincinnati, Inc. 563 Wessel Drive Fairfield, OH 45014	CL-S&E-0409071-P	38	Treatment of ocular itching associated allergic conjunctivitis
Mark T. Bergmann, MD Eye Care Assoc. of Greater Cincinnati, Inc. 563 Wessel Drive Fairfield, OH 45014	CL-S&E-0409071-P	25	Treatment of ocular itching associated allergic conjunctivitis
Fred K. Kurata, MD East West Eye Institute 420 Wast Third Street Los Angeles, CA 90013	CL-S&E-0409071-P	24	Treatment of ocular itching associated allergic conjunctivitis
Gail Torkildsen, MD 797 Turnpike Street North Andover, MA 01845 And Andover Eye Associates 138 Haverhill Street Andover, MA 01810	ISTA-BEPO-CS01	107	Treatment of ocular itching associated allergic conjunctivitis
Clifford Michaelson, MD ORA Clinical Research and Development, Inc. 797 Turnpike Street North Andover, MA 01845 And Andover Eye Associates 138 Haverhill Street Andover, MA 01810	CL-SAF-040571-P	301	Treatment of ocular itching associated allergic conjunctivitis

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Eugene E. Protzko, MD Seidenbery-Protzko Eye Associates 520 Upper Chesapeak Drive #401 Bel Air, MD 21014 And 930 Revolution Street Havre de Grace, MD 21078	CL-SAF-040571-P	126	Treatment of ocular itching associated allergic conjunctivitis
Stacy L. Ackerman, MD Philadelphia Eye Associates 1703 S. Broad Street Philadelphia, PA 19148	CL-SAF-040571-P	110	Treatment of ocular itching associated allergic conjunctivitis

III. Site Selection/Rationale

The highest enrollers for the three protocols are identified in the preceding table. An inspection is requested for at least one site for each of these clinical trials as your resources permit.

There are no specific safety or efficacy concerns for any of the sites for either of the two clinical trials identified in this consult request. There are no fraud or misconduct concerns currently identified at any of the investigational sites in either of the three clinical trials.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__x__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

Not applicable.

Should you require any additional information, please contact Sonal D. Wadhwa, MD at (301) 796-2446.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Director, Division Director (for foreign inspection requests only)

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/s/

Raphael Rodriguez
12/15/2008 11:19:53 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, DDMAC
Attn: Paul Loebach,RPM

FROM:
Wiley Chambers, MD, Acting Director, DAIOP
Raphael Rodriguez, RPM phone 796-0798

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/20/2008	66,864	22-288		11/12/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
bepotastine besilate ophthalmic solution 1.5%	Standard Review	5HT antagonist ophthalmics	6/1/09

NAME OF FIRM: Ista Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- X ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS:

Please provide a labeling reviews for the Bepreve (bepotastine besilate ophthalmic sol) 1.5%. This is an NME and anticipating for Advisory Committee.

This entire submission was sent via Electronic Submissions Gateway (ESG), eCTD which means there are NO jackets to distribute.

Please let me know if you need any additional information to complete this trade name review.

Thanks in advance. Raphael

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Raphael Rodriguez 11/20/08	Via: Interoffice Mail
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Raphael Rodriguez
11/20/2008 11:26:32 AM