CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-290 SUPPL # HFD # 160

Trade Name AdreView

Generic Name Iobenguane I-123 Sulfate

Applicant Name GE Healthcare

Approval Date, If Known September 19, 2008

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)(2)

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?

7 years-For Orphan Drug Designation, 5-Years Regular Exclusivity

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?

No

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:

(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:

Name of person completing form: James Moore
Title: Project Manager,
Date: September 17, 2008

Name of Office/Division Director signing form: Richard Pazdur, M.D.
Title: Office Director

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

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

/s/

Richard Pazdur
9/17/2008 12:06:00 PM

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

NDA/BLA#: 22-290 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

vision Name:Medical Imaging and ematology PDUFA Goal Date: September 19, 2008 Stamp Date: 3/21/2008

Proprietary Name: Adreview

Established/Generic Name: Iobenguange I-123 Sulfate

Dosage Form: Injection

Applicant/Sponsor: GE Healthcare

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

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: Use as an adjunct to other diagnostic tests to detect the presence of neuroblastomas — pheocchromocytomas. b(4)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

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

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

☐ Yes. Please proceed to Section D.

☐ 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 question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ 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.***

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 some or all 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 for the reason(s) selected)**

- ☐ 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 unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and 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.

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[Δ]
☐	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 unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*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 complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section 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 selected pediatric subpopulations).

Check pediatric subpopulation(s) 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)*	Received
☐	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): _____						

re 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 partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

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	__ 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 ☐

re 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 there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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

opulation		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 all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or 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 pediatric subpopulation for which information will be extrapolated. 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. Under the statute, safety cannot be extrapolated.

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 complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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: _____

1: 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 some or all 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 for the reason(s) selected**)

☐ 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 unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and 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.

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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 unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*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 Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section 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 some or all pediatric subpopulations).

ıeck pediatric subpopulation(s) 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)*	Received
☐	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): _____						

.re 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 partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

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	__ 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: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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

opulation		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 all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or 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 pediatric subpopulation for which information will be extrapolated. 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. Under the statute, safety cannot be extrapolated.

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.

e 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 or DARRTS as appropriate after clearance by PeRC.

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: 6/2008)

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

/s/

James Moore
9/17/2008 07:50:55 AM

1.3.3 Debarment Certification

GE Healthcare 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.

6. Sept. 2008

Donald Black MD
Head of Global Research and Development
Medical Diagnostics

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-290 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: AdreView Established/Proper Name: Iobenguane I 123 Sulfate Dosage Form: Injection		Applicant: GE Healthcare Agent for Applicant (if applicable):
RPM: James Moore		Division: Medical Imaging and Hematology

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)): 20-084, Iobenguane Sulfate I-131 Provide a brief explanation of how this product is different from the listed drug. The listed product is I-131Iobenguane Sulfate and the pending application is I-123 Iobenguane Sulfate ☐ 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)	September 19, 2008
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

[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): 1

☐ 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:

❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative/Regulatory Documents *section, with* Administrative Reviews*)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative/Regulatory Documents *section with* Administrative Reviews*)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: ☒	This application has Orphan Drug status and does not require PeRC review
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date N/A
❖ 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	☒ 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 the 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]	x
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/nonconsent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval September 19, 2008
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)	September 16, 2008
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	September 17, 2008
❖ Original applicant-proposed labeling	March 20, 2008
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ 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
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA

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

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	NA
❖ Original applicant-proposed labeling	NA
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ 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	September 4, 2008
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEDP ☐ DRISK ☒ DDMAC ☐ CSS ☒ Other reviews September 8, 2008
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Septebmer 17, 2008
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	☒ Not on AIP
❖ 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	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	NA
• Incoming submission documenting commitment	NA
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	September 21, 2008 December 20,

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

	2007, August 9, 2007
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None September 19, 2008
Division Director Summary Review *(indicate date for each review)*	☐ None September 17 , 20008
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	September 9, 2008
• Clinical review(s) *(indicate date for each review)*	September 11, 2008
• 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)*	See Medical 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	See Medical Review,Page 13
❖ 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
❖ REMS • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • Review(s) and recommendations (including those by OSE and CSS) *(indicate location/date if incorporated into another review)*	☒ None
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	September 4, 2008
• Bioequivalence Studies	NA
• Clinical Pharmacology Studies	NA
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None September 14, 2008
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None September 12, 2008
Statistical Review(s) *(indicate date for each review)*	☐ None September 12, 2008
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None September 11, 2008

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

Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None September 11, 2008
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None September 11, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None September 19, 2008
• Supervisory Review(s) *(indicate date for each review)*	☐ None September 16, 2008
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None September 16, 2008
❖ 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
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None September 10, 2008
• Branch Chief/TeamLeader Review(s) *(indicate date for each review)*	☐ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None September 5, 2008
• 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	September 3, 2008 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for 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)*	See Chemistry Review
☐ Review & FONSI *(indicate date of review)*	NA
☐ Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: June 26, 2008 ☒ Acceptable ☐ Withhold recommendation
• BLAs: ➢ TBP-EER ➢ 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: NA ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

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.

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

/s/

James Moore
9/19/2008 09:27:25 AM

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-290	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Adreview Established/Proper Name: I-123 MIBG Dosage Form: Injection Strengths: 2miC/mL		
Applicant: GE Health Care		
Date of Receipt: March 21, 2008		
PDUFA Goal Date: September 19, 2008	Action Goal Date (if different):	
Proposed Indication(s): A diagnostic radiopharmaceutical containing a radioiodinated benzylguanidine indicated as an imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas.		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

   YES ☐ NO x

   *If "**YES**," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

   YES ☐ NO x

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature I-131,I-123	Efficacy,Limited Safety information

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

No bridge provided, Applicant suggested activity same base on composition and activity

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES X NO ☐

Results of a single clinical study are also provided. The applicant does not rely on literature alone for approval.

*If "**NO**," proceed to question #6.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES X NO ☐

*If "**NO**", proceed to question #6*

*If "**YES**", list the listed drug(s) identified by name and answer question #5(c).*

I-131MIBG

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO ☐

*If "**NO**," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
I-131 MIBG	20084	Y, Plus clinical study

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES ☐ NO ☐

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:
   a. Approved in a 505(b)(2) application?

YES ☐ NO x

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b. Approved by the DESI process?

YES ☐ NO x

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

   c. Described in a monograph?

YES ☐ NO x

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO x

*If "**YES**", please list which drug(s) and answer question d.1.*
*If "**NO**", proceed to question #10.*

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO x

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Product is new molecular entity.

The change in product (proposed vs listed) is the radionucleotide label on the MIBG ligan, I-123 instead of I-131

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO x

*If "**NO**," to (a) proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO x

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO x

*If "**YES**" and there are no additional pharmaceutical equivalents listed, proceed to question #13.*

*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES x NO ☐

*If "**NO**", proceed to question #13.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO x

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES x NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #13.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

    Listed drug/Patent number(s): No Patent information is available in the Orange book for the list drug product

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

    YES ☐ NO x

    If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

    Listed drug/Patent number(s): NA

15. Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

    ☐ No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

    ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

    ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

    Patent number(s):

    ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

    Patent number(s):

    ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

    Patent number(s):

    If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

    YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO x

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO x

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):
If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES ☐ NO x

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO x

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO x

☐ Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

x 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

/s/

James Moore
9/19/2008 09:04:09 AM
CSO

Kyong Kang
9/19/2008 09:07:48 AM
CSO

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-290 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Adreview® Established/Proper Name: Iobenguane I123 Sulfate Dosage Form: Injection Strengths: 2mCi/mL at calibration time		
Applicant: GE Healthcare Agent for Applicant (if applicable):		
Date of Application: March 21, 2008 Date of Receipt: March 21, 2008 Date clock started after UN:		
PDUFA Goal Date: September 19, 2008	Action Goal Date (if different):	
Filing Date: May 20, 2008 Date of Filing Meeting: May 8, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication: A diagnostic radiopharmaceutical containing a radioiodinated benzylguanidine indicated as an ——— for the detection of primary or metastatic pheochromocytomas — neuroblastomas.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☐ 505(b)(1) x 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☐ Standard x Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐ N/A		
Part 3 Combination Product? No		☐ Drug/Biologic Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review x Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify

b(4)

Other:	clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 62,669	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	x YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	x YES NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes,** explain: **If yes,** has OC/DMPQ been notified of the submission? **Comments:**	☐ YES x NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	x YES ☐ NO
User Fee Status **Comments:**	☐ Paid x Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes,** is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments:**	☐ YES x NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☐ YES # years requested: 7 years as Orphan Drug 5 years other Exclusivity NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	x Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES x NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES x NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES x NO

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes,** please list below:	☐ YES x NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	x YES NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	X YES ☐ NO XYES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	X YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain:	X YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments:**	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	NA ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments:**	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? Certificate is unsigned ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	xYES NO

Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) 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..." **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***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.* **Comments:**	x YES ☐ NO
Pediatrics	
PREA *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments:**	x Not Applicable ☐ YES NO ☐ YES x NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES x NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** x Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide x Carton labels(shield) x Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	x YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, 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 no, request in 74-day letter.*** **Comments:**	x YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	x YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	x Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	x Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable x YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	**x Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☐ YES Date(s): x NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	YES Date(s): x NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): x NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 8, 2008

NDA/BLA #: 22-290

PROPRIETARY/ESTABLISHED NAMES: Adreview

APPLICANT: GE Healthcare

BACKGROUND: This product is a new molecular entity. It has been designated for priority review. It is a radiopharmaceutical I-123. It has Orphan designation.
(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.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Moore	Y
	CPMS/TL:	Kyong Kang	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Robert Yaes	Y
	TL:	Alexander Gorovets	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:		
OSE	Reviewer:	Cathy Miller	N
	TL:	Linda Kim-Jung	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	
	TL:	NA	

Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Young Moon Choi	N
Biostatistics	Reviewer:	Jiang Xiaping	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Siham Biade	Y
	TL:	Adebayo Laniyonu	Y
Statistics, carcinogenicity	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Eldon Leutizinger	Y
	TL:	Ravi Harapanhalli	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	Unknown	N
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	Robert Mello	Y
	TL:	Bryan Riley	N
Bioresearch Monitoring (DSI)	Reviewer:	Unknown	N
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES x NO
Per reviewers, are all parts in English or English translation? **If no,** explain:	X YES ☐ NO

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason: The application did not raise significant public health questions on the role of the drug in diagnosis of pheochromocytoma/neuroblastomas
• 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? **Comments:**	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s)	☐ YES

needed?	☐ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES x NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ Not Applicable X YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	X YES ☐ NO X YES ☐ NO
FACILITY (BLAs only)	x Not Applicable ☐ FILE

Comments: Chemisty and Microbiolgy Comments sent in 74-day letter	☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: James Moore/Kyong Kang

GRMP Timeline Milestones:

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review X Priority Review

ACTIONS ITEMS

X	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appears This Way
On Original

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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 OND ADRA or OND IO.

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/s/

James Moore
9/17/2008 09:06:33 AM
CSO

Kyong Kang
9/17/2008 09:13:31 AM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology

Application Number: NDA 22-290

Name of Drug: AdreView®, (Iobenguane I-123) Injection

Applicant: GE Healthcare

Material Reviewed:

Submission Date: March 21, 2008

Receipt Date: March 21, 2008

Submission Date of Structure Product Labeling (SPL): March 21, 2008

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies were identified in the proposed labeling.

b(4)

———— should be removed from highlights and the remainder of the package insert.

Recommendations

The requested change was noted in the draft labeling sent to GE HealthCare on Friday, September 12, 2008. It was requested that the label be returned to the Division as soon as possible.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Supervisory Comment/Concurrence:

_____

Kyong Kang, PharmD.
Chief, Project Management Staff

Drafted: JM/September 13, 2008
Revised/Initialed:
Finalized: JM/September 15, 2008
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

James Moore
9/17/2008 07:17:34 AM
CSO

Kyong Kang
9/17/2008 08:45:27 AM
CSO

Minutes of Telephone Conference between the Division of Medical Imaging and Hematology and GE Healthcare, Thursday, August 21, 2008

Subject: N 22-290, AdreView®, (Iobenguane I-123 Sulfate) Injection

GE Health Care Attendees:

Fred Longenecker, Director, Regulatory Affairs
Susan White, Manager, Regulatory Affairs
Arnold Jacobson, M.D., Director, Clinical Research

FDA Attendees:

Robert Yaes, M.D., Clinical Reviewer, DMIHP
Alexander Gorovets, M.D., Clinical Team Leader, DMIHP
James Moore, PharmD., M.A., Project Manager, DMIHP

Background

This meeting was requested by FDA to discuss the levels of sensitivity and specificity for SPECT imaging and planar images observed in clinical trial MBG308 for AdreView®.

Discussion

FDA and GE Healthcare discussed the decrease in sensitivity and specificity seen in images captured using SPECT + planar vs planar alone in the MBG308 trial using AdreView® (I-123 Iobenguane Sulfate). FDA queried GE on the reason for a decrease in performance of SPECT + planar versus planar alone imaging using I-123. GE Healthcare described the trial in detail and stated that they could not provide a definitive answer regarding the decline in performance of SPECT + planar versus planar imaging alone but did say it probably was related to training and the inability to evaluate the SPECT images accurately.

FDA asked GE Healthcare to provide a listing of sensitivity and specificity tables that displayed the sensitivity/specificity data obtained from patients who had planar images and SPECT together, and those that had SPECT alone and planar alone.

Summary

GE Healthcare will provide the sensitivity and specificity data on patients who had SPECT images alone, those who had SPECT plus planar and those that only had planar images alone. FDA asked that this information be provided as soon as possible.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
9/16/2008 04:41:21 PM
CSO

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: September 4, 2008

TO: James Moore, Regulatory Project Manager
Robert Yaes, Medical Officer
Division of Medical Imaging and Hematology

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

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

SUBJECT: Evaluation of GE Healthcare Ltd, Image Core Laboratory.

NDA: 22 290

APPLICANT: GE Healthcare Ltd.

DRUG: iobenguane I^{123} [USP] (AdreView) {I^{123} mIBG}

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: ———— for the detection of primary or metastatic pheochromocytomas ___ neuroblastomas.

b(4)

CONSULTATION REQUEST DATE: July 30, 2008

DIVISION ACTION GOAL DATE: September 19, 2008

PDUFA DATE: September 19, 2008

I. BACKGROUND:

Meta-iodobenzylguanidine (mIBG) is an arylalkylguanidine norepinephrine analog. The drug enters adrenergic neurons and chromaffin cells by active transport for catecholamines into adrenergic storage granules. Neuroectodermally derived tumors also take up the drug. I-131 mIBG is the subject of an approved NDA20 084 (1994). It had been used as a diagnostic agent since the 1980s.

I-123 mIBG is the subject of this NDA. It has been used as a diagnostic agent for more than 20 years for tumors of neural crest and neuroendocrine origin. It has several advantages over I-131 mIBG including: greater gamma camera efficiency, option to perform single-photon emission computed tomography (SPECT), and a shorter half life.

One protocol study has been submitted in support of this application: MBG 308: An Open-Label Multicentre, Phase 3 Scintigraphy Study Assessing ^{123}I-mIBG Uptake in Subjects Being Evaluated for Phaeochromocytoma or neuroblastoma. There were 24 centers involved in this study which enrolled 251 subjects – 179 in the US and 72 in Europe. Images obtained were sent to the Image Core Laboratory digitally. These were read by 3 independent blinded readers.

The Image Core Laboratory is a dedicated unit within GE Healthcare, the NDA sponsor.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Image Core Laboratory Princeton, NJ	MBG 308	August 21, 2008	pending, Interim classification NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Image Core Laboratory
   101 Carnegie Center
   Princeton, NJ 08540

   Note: EIR has not been received by DSI. Observations reported are based on a discussion with the field investigators who conducted the inspection.

   a. What was inspected: Facility, and method of doing image reviews and readings.

b. General observations/commentary: The facility was well organized and appropriate. Relevant SOPs were available and reviewed. Procedures were followed. Readers did their assessments independently and attendance could be verified. Generally readers were not at the facility at the same time. Data obtained was secured. The sponsor has custody of the data.

No 483 was issued and the district considers the inspection NAI.

c. Assessment of data integrity: Data is acceptable and/reliable in support of the pending application

Note: An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by this facility is acceptable for the review of the application.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch *II*
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Tejashri Purohit-Sheth
9/4/2008 02:21:17 PM

September 2, 2008

In reference to your responses to the labeling comments of August 28, 2008 for your pending NDA 22-290 for Adreview you added the phrase [redacted] to the storage statements in the package insert and the container labels (immediate vial and shield container). What is the basis for the addition of this phrase to the above labeling, and what information/data do you have that supports and make it necessary to add this phrase to the storage statement?

b(4)

Please respond to this comment by COB Thursday, September 4, 2008.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
9/2/2008 05:59:44 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-290

INFORMATION REQUEST LETTER

GE Healthcare-Medical Diagnostics
Attention: Susan White
Regulatory Manager
101 Carnegie Center
Princeton, NJ 08540

Dear Ms. White:

Please refer to your March 20, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AdreView (Iobenuane I^{123}) Injection.

We also refer to your submission dated June 18, 2008.

We are reviewing the Labeling section of your submission and have the following comments regarding the labeling. We request a prompt written response in order to continue our evaluation of your NDA.

b(4)

b(4)

If you have any questions, call James Moore, Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Eldon Leutzinger, Ph.D.
Pharmaceutical Assessment Lead for the
Division of Medical Imaging and Hematology
Products, HFD-160
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
8/27/2008 04:31:22 PM
CSO

Diane V Leaman
8/27/2008 04:32:04 PM
CSO

Eldon Leutzinger
8/28/2008 06:53:52 AM
CHEMIST

Regarding you pending NDA 22-290 for Adreview the reviewing chemist has the following comments.

1. [redacted] b(4)

2. The formulation in the DESCRIPTION section also lists "74 MBq (2 mCi) of I 123 [redacted] This should be listed as iobenguane sulfate I 123, as in USAN, or in terms of the chemical name, (m-iodo-^{123}I-benzylguanidine) sulfate (2:1). Also, there should be a time point associated with the measured quantity of radioactivity, e.g., "74 MBq (2 mCi) of I 123 as iobenguane sulfate I 123 at calibration." b(4)

3. The last sentence in the DESCRIPTION says that ' [redacted] is also known as [redacted] and has the following formula." Sulfate should be included after iobenguane and before I 123. If iobenguane sulfate I 123 is to be translated into a chemical name, it should be consistent with that in USAN, e.g., (m-iodo-^{123}I-benzylguanidine) sulfate (2:1). Also, the structure shown [redacted] This structure should be drawn to include sulfate, since sulfate is the counter ion associated with [^{123}I] MIBG, and a component of the formulation. b(4)

4. We have also noted inconsistencies between the DESCRIPTION section of the package insert and the label for the product vial. The description of the formulation in the DESCRIPTION section of the package insert should be the same as that on the vial label. The vial label reads [redacted] If chemical names are going to be used, they should be spelled out, e.g.. [redacted] b(4)

We are requesting that you make the requested changes and submit the revised label to the Division by COB Wednesday, August 13, 2008.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD, M.A.
Project Manger, DMIHP

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/s/

James Moore
8/8/2008 06:09:54 PM
CSO

July 21, 2008

Regarding your pending NDA for Adreview®, NDA 22-290, the reviewing chemist has the following comment and request.

[redacted] b(4)

Since extractables/leachables are not related to the drug, but originate from the container closure system, tighter thresholds than those identified in the EMEA guidance on genotoxic impurities are applicable. Because extractables/leachables originate from container closures, they could in principle be avoided or minimized by choosing an appropriate container closure system to accomplish those ends.

Do you know, or have you investigated any current stoppers that would be compatible with [redacted] but avoid or at least minimize the level of this unknown impurity below the levels seen in the [redacted] b(4)

Please respond to this request by COB, Wednesday, July 23, 2008.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
7/21/2008 05:20:38 PM
CSO

July 2, 2008

Regarding your pending NDA 22-290 for Adreview I^{123}MIBG, the reviewing chemist has the following comments and requests.

In the section on compatibility (3.2.P.2.6), there is a very brief discussion of a leachate impurity _____ found in the drug product, the origin of which is the _____ stoppers following _____ The leachate impurity is indicated to belong to _____ although its actual identity remains unknown. We have the following comments: b(4)

1. Although in your IND 62,669 a range was indicated to be _____, no information is provided in the NDA on what basis the figure _____ was chosen as the limiting amount of the leachate impurity in any batch of drug product packaged in vials closed with _____ stoppers. Provide this information. b(4)

2. It is stated that the level of the leachate impurity should not exceed _____ but few details are given on its determination. Provide these details, including analytical instrumentation, procedure, preparation of standard solutions, standard curves and calculations. Also, provide your evidence that the impurity belongs to _____ b(4)

3. In the procedure for estimation of the amount of leachate impurity, you indicate that _____ analyzed by HPLC. Provide the HPLC chromatogram showing the full impurity profile. Include all HPLC peaks, clearly labeled and quantitative estimates of their levels in the leachate. b(4)

4. Also, provide the HPLC chromatogram of the impurity profile of the drug product, and compare with that obtained with _____ b(4)

5. Do you know whether this leachate impurity _____ once formed, increases with time as the drug product approaches its expiration date? Provide evidence in support of your response. b(4)

Please respond to these comments by COB Wednesday, July 16, 2008.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
7/2/2008 03:53:57 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-290

GE Health Care
Attention: Fred E. Longenecker
U.S. Regulatory Site Head
101 Carnegie Center
Princeton, New Jersey 08540

Dear Mr. Longenecker:

Please refer to your new drug application (NDA) dated March 20, 2008, received March 21, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adreview [^{123}I]MIBG, Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is September 19, 2008.

During our filing review of your application, we identified the following potential review issues:

1. Absence of current copies of the sterility test method and the bacterial endotoxin test (BET) method. This is needed for the reviewer to adequately assess the sterility and BET specifications.

2. Absence of drug product specific assay validation reports for the sterility test.

3. Absence of drug product specific assay validation reports for the bacterial endotoxin test.

b(4)

4. Absence of the protocol and a summary report for the _____ validation for the drug product.

5. Absence of summary reports of the validation of container closure integrity for the maintenance of sterility of the drug product following _____

b(4)

To address the above deficiencies please provide the items identified as absent in items 1-5.

6. Although there are defined procedures (tests/acceptance criteria) for receiving [redacted] any future changes that might be made in the process or controls at [redacted] could potentially affect its purity and quality, and hence impact the [^{123}I]MIBG drug product. We also note that [redacted] does not have a DMF, and such changes could be made without notice. Hence, such changes present a potential risk for not being factored into your acceptance criteria. b(4)

   To address this issue, we request that you put into place a change control protocol for covering any future changes that might be made to the manufacturing process at [redacted]

7. In the finished product specifications and test methods, the reliability of an accurate determination of radiochemical purity depends in part on accurate location of the radioactive peak corresponding to [^{123}I]MIBG. Although radiolabeling is via [redacted] you still should have a formal procedure for radiochemical identity (e.g., an appropriate range around the retention time for the standard, a percentage of the reference standard, etc.). b(4)

   To address this issue, revise the analytical procedures/finished product criteria to include radiochemical identity.

8. You indicate that specific activity is determined by HPLC, but do not include the procedures for its determination (e.g., via calibration with respect to the standard).

   To address this issue, provide a description of these procedures.

9. In Section 3.2.P.6, you indicate that reference standards (e.g., that for MIBG) are controlled per GE Healthcare Internal Procedures.

   To address this issue, provide a description of these procedures.

10a. The limit for radiochemical impurities in the finished product is indicated to be NMT [redacted] b(4)

   To address this point state how this is determined.

10b. Considering that if a batch of final product were to contain [redacted] impurities, we assume that most of it would be [redacted] b(4)

   Is this a correct assumption? If not, explain.

10c. FDA needs to know the impurity distribution profile for bathes of the product produced at the Arlington Heights facility.

To address this point, state the distribution profile for batches of your product produced at the Arlington Heights facility.

10d. Have you seen any organic radiochemical impurities in any batches of finished product produced by the procedures at Arlington Heights?

To address this point, you should describe these radiochemical impurities and the amounts present.

11. Your limit for radionuclidic purity of the finished product is indicated to be NLT ——— by gamma spectroscopy. b(4)

To address this point, you must state what the other ——— radionuclides were at the time of calibration for batches of finished product at the Arlington Heights facility.

12. Total radioactivity is indicated to be measured by ——————— b(4)

To further clarify and address this point state the type of ——————— that is being used and provide a brief description of its calibration.

13. The limit for ——— in the finished product specifications is indicated to be ———

It is assumed that you mean ——— in terms of the mass of ——— not including the ——————— Is this a correct assumption? Explain. b(4)

14. We assume that appropriate NIST standards are used in all radioactivity measurements (e.g., total radioactivity, radioactivity concentrations, etc.).

To address this point, you should clarify whether NIST standards are used in your radioactivity measurements.

We recommend that you participate in the NEI-NIST Measurement Assurance Program (MAP) that allows manufacturers to verify the accuracy of their measurements through exchange and measurement of samples from NIST.

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Rieves, M.D.
Director
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves
6/4/2008 05:30:46 PM

May 23, 2008

The reviewing statistician has the following request regarding your pending NDA 22-290 for Adreview (I-123 MIBG).

1) Please provide a document that indicates which datasets and which variables were used to obtain the primary efficacy results. For each efficacy variable, please indicate which dataset the variable locates. The file define.pdf in the submission does not provide enough information.

2) Please provide the datasets and variables that were used to obtain the estimates of sensitivity and specificity in Table 4, 7 and 11 in the submission 2.7.3 Summary of Clinical Efficacy as soon as possible. The dataset(s) should contain one row for one subject and include the following variables:

   Demographics:
   Patients ID #
   Center
   Age
   Gender
   Race

   Truth Results
   SOR Source (Truth Standard used for Disease Determination)
   SOR Results-Which of the two Disease was present, or was the patient Normal

   Reader Results
   Reader # J (J=1,2,3) Diagnosis Result—Four possibilities: Disease Type/Normal/Missing/Uninterpretable
   Variable that indicates standard sub-populations (Category A, B, C)

   If the dataset(s) is/are included in the NDA submission, please provide the names of datasets and variables. For each variable, please indicate which dataset the variable locates.

Please respond to the request as soon as possible.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A
Project Manager, DMIHP

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/s/

James Moore
5/28/2008 11:18:21 AM
CSO

May 13, 2008

In reference to your pending NDA 22-290 and to the Applicant's Briefing scheduled for 05/15/08, we have the following clinical comments and requests for information. Please note that addressing these at the Briefing could be helpful to the review process which is currently in its early stages.

1) If approved, I-123-MIBG may be regarded as an alternative to I-131-MIBG. Please clarify the difference in the wording of the indication in the I-131 labeling and the indication that you are requesting for I-123-MIBG, specifically in relation to the use of the words "adjunctive" and "localization" vs. "detection":

   "I-131-"Iobenguane sulfate, I-131 injection is indicated as an adjunctive diagnostic agent in the localization of primary or metastatic pheochromocytoma or neuroblastoma" vs.
   "123- AdreView is a radiopharmaceutical _____ *the detection of primary or metastatic pheochromocytomas* ___ *neuroblastomas"*

   b(4)

2) On pages 24 and 27 of the case report form the reader is asked whether the scans are consistent with active tumor, yes or no. The answers form the basis of your calculation of sensitivity and specificity. The next query contains a table where the reader is asked questions concerning the extent of disease. Please clarify whether you have analyzed these additional data to determine the sensitivity and specificity of detecting either primary or metastatic pheochromocytoma or neuroblastoma.

3) Please clarify whether you have submitted, in this application, the analysis and the summary of each individual study used in the meta-analysis, and whether you have commented on each study as well as on the meta-analysis itself.

4) You have commented on "publication bias" as a possible explanation of the discrepancy of the results of the meta-analysis and of the prospective study. Do you mean to imply that the published data might be unreliable because of this bias and that therefore emphasis should be placed on the results of the prospective study?

5) The results for SPECT plus planar images apparently do not give much better sensitivity and specificity results than reading of the planar images alone. Does this imply that there is no advantage in having the SPECT images as well as the planar images?

6) You have performed no Phase 2 dose ranging studies but claim that 10 mCi is an optimal dose for adults and for pediatric patients weighing > 70kg and you propose dosing for patients weighing < 70 kg according to a table. Can you refer to any dose ranging study performed in Europe or elsewhere where this optimal dosing

schema was assessed in humans?

7) Apparently no superiority over I-131-MIBG, as an imaging agent, has been demonstrated in your prospective study or in your meta-analysis. Please confirm and comment.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
5/13/2008 11:54:21 AM
CSO

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May 13, 2008

This note is confirmation of the Regulatory Briefing with GE Healthcare scheduled for Thursday, May 15, 2008 from 2:30PM-4:00PM in Conference Room 1313, Building 22, FDA White Oak Campus, 10903 New Hampshire Avenue, Silver Spring, Maryland 20903. Here is the list of FDA personnel that have been invited to attend this meeting.

1. Richard Pazdur, M.D., Office Director, Office of Oncology Drug Products
2. Karen Weiss, M.D., Deputy Office Director, Office of Oncology Drug Products
3. Rafel Rieves, M.D., Acting Division Director, DMIHP
4. Libero Marzella, M.D., Ph.D., Acting Deputy Division Director, DMIHP
5. Alexander Gorovets, M.D., Clinical Team Leader, DMIHP
6. Robert Yaes, M.D., Sc.D., Clinical Reviewer, DMIHP
7. Siham Biade, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP
8. Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader, DMIHP
9. Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA
10. Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB
11. Anthony Mucci, Ph.D., Statistical Reviewer, OB
12. Jiang Xiaoping, Ph.D., Statistical Reviewer, OB
13. Elba Ali-Ibrahim, M.S., Project Manager, DMIHP
14. Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP
15. Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP
16. James Moore, PharmD., M.A., Project Manager, DMIHP
17. Janet Anderson, PharmD., Project Manager, OSE
18. Janos Bacsanyi, M.D., Safety Evaluator, OSE
19. Susan Lu, PharmD., Team Leader, OSE
20. Kyong Kang, PharmD., Chief, Project Management Staff, DMIHP
21. James McVey, Ph.D., Microbiology Team Leader, OPS

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
5/13/2008 11:50:37 AM
CSO

May 9, 2008

In review of your application NDA 22-290 (Adreview), the clinical team noted that additional information is needed regarding your study sites. Therefore, FDA is requesting the following information.

1. The investigational site numbers and locations including the number of patients per site, efficacy and safety data per site, availability of histology for SOT assessment per site, protocol violations and patient withdrawals per site, financial disclosure per site.

Please provide this information by COB Wednesday May 14, 2008. If the information is present in the NDA, please cite the locations where this information may be found.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
5/9/2008 01:29:38 PM
CSO

April 23, 2008

Regarding your pending NDA 22-290 for Adreview, the reviewing chemist has the following comments.

Again, it is emphasized that we consider [redacted] However, as an intermediate, it could also be considered an API starting material (ICH Q7A). Either way, because of its position in the process it will be considered with a similar level of scrutiny as a drug substance. b(4)

We continue to be concerned that [redacted] meets identity, quality and purity criteria that it is purported to possess. Does [redacted] have a Drug Master File that describes their process and controls for release to GE? Also, we do not understand the role and implication of the list of tests/test criteria provided in Section 2.3.S.4. Is this testing which [redacted] performs at release from their facility, or is this testing which GE does in accepting [redacted] b(4)

Please respond to these comments by COB Friday, April 25, 2008.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
4/23/2008 05:00:47 PM
CSO

April 15, 2008

Regarding your pending NDA 22-290 for AdreView, the reviewing chemist has the following comments.

1. You state that the manufacturer of _____ will be _____ who will use a validated process to GMP quality in its production. Be advised that the Agency considers _____ _____ Furthermore, because the drug substance, _____ the final intermediate will be considered with the same level of scrutiny as the drug substance, and the manufacturing facilities _____ may need to be inspected for CGMP compliance. b(4)

   Hence, provide the exact address of the _____ facility where _____ _____ will be manufactured and tested for release. b(4)
   Also include (1) the contact person for that facility and (2) the drug establishment number (CFN number, etc.).

2. For the Arlington Heights facility, please confirm that the address of the manufacturing site is as indicated in the NDA, as 3350 North Ridge Avenue, Arlington Heights, Ill 60004. Also please confirm that the drug establishment number is _____ b(4)

3. Finally, confirm that there are no other manufacturing sites used in the production of drug product other than the ones listed above.

4. Are all facilities cited in the application ready for a CGMP inspection?

Please respond to these comments by COB Friday April 18, 2008.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
4/15/2008 10:45:35 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-290

NDA ACKNOWLEDGMENT

GE Health Care
Attention: Fred E. Longenecker
U.S. Regulatory Site Head
101 Carnegie Center
Princeton, New Jersey 08540

Dear Mr. Longenecker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: AdreView (Iobenguane I-123 Injection)

Date of Application: March 20, 2008

Date of Receipt: March 21, 2008

Our Reference Number: NDA 22-290

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 20, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD., M.A.
Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

James Moore
4/2/2008 10:00:06 AM

Industry Meeting, Thursday, December, 20, 2007, 12:30 PM- 2:00 PM, White Oak Campus, Building 22, Conference Room 1415, 10903 New Hampshire Avenue, Silver Spring, Maryland

Subject: IND 62,999 (Iobenguane I-123)

Don Black, M.D, Global Head Research and Development
Pamela S.Cohen, M.D., Global Therapeutic Head, Oncology
JoAnne Harla, Project Director, Project Management
Arnold Jacobson, M.D., Ph.D., Director, Clinical Research
Natalie Khoutryansky, Statistician, Statistics and Programing
Fred Leongenecker, Director, Regulatory Affairs

b(4)

FDA Attendees:

Rafel Rieves, M.D., Acting Division Director, DMIHP
Libero Marzella, M.D., Ph.D., Acting Deputy Division Director, DMIHP
Alex Gorovets, M.D., Ph.D., Clinical Team Leader
Robert Yaes, M.D., Sc.D., Clinical Reviewer, DMIHP
Anthony Mucci, Ph.D., Statistical Reviewer, OB
Joyti Zalkikar, Ph.D., Statistical Team Leader, OB
Qing XU, Ph.D., Statistical Reviewer, OB
Richard Fejka, M.S., Radiopharmacist,OODP
James Moore, PharmD., M.A., Project Manager, DMIHP

Background

The meeting was scheduled at the request of GE Health Care in their meeting request of October 10, 2007. A fax was sent to them on December 19, 2007 providing responses to their meeting packages of October 10 and November 6, 2007. FDA's response to GE's meeting package is provided below.

FDA PRELIMINARY COMMENTS

This material consists of the reviewers' preliminary notes in preparation for the discussion at the December 20, 2007 meeting between GEHC and the FDA's Review Team. This material may not have been fully vetted internally and should not be considered as an official position of the FDA. This material is shared with the Sponsor solely to promote a collaborative and successful discussion at the meeting. The minutes for the meeting will reflect agreements and discussion at the meeting and may not be consistent with these preliminary notes. The draft comments by FDA to GEHC are being communicated to Ms. Susan White on December 19, 2007.

We refer to IND 62,669 for Iobeguane I^{123} and to your submissions, dated 10-03-07, 10-10-07 and 11-16-07, which contain the Meeting Information for the 12-20-07 meeting. The Division of Medical Imaging and Hematology Products (DMIHP) reviewers have reviewed the submissions and provide the following General Comments:

1. We remain concerned that Study MBG 308 may not provide persuasive evidence of diagnostic efficacy. Apparently, one of the concerns regarding Study MBG 308 results related to a potentially faulty standard of truth definition. Your meeting packages contain proposals intended to better characterize the performance characteristics of your product, based upon new analyses and new source data that are used to "redevelop" the truth standard. Paramount in these attempts to "redevelop" the findings from Study MBG 308 is the ability for you and FDA to verify that the "redeveloped" findings are not biased due to knowledge of the study's original results.

   If we understand correctly, you currently have a locked dataset (case report forms and data tabulations) for Study MBG 308. You now intend to develop a new dataset that will contain more information than is currently contained within the locked dataset. We will refer to this second source dataset as the "post-hoc" dataset and the original, locked dataset as the "locked" dataset. New analyses of your product's performance characteristics will be applied to the post-hoc dataset. We make the following points:

   a) Conceivably, the redevelopment of a truth standard based upon the locked dataset may be useful in meaningfully analyzing your product's performance characteristics. In this situation, multiple redeveloped truth standards can be developed using the locked dataset and multiple analyses performed to assess your product's performance characteristics. Consistent findings from these multiple analyses may provide persuasive evidence of your product's diagnostic efficacy. Using the locked dataset, we suggest that you develop a proposal for a primary endpoint standard of truth and other exploratory endpoints that use alternative standard of truth definitions.

   b) Redevelopment of a truth standard based upon the post-hoc dataset presents special challenges since it will be impossible to verify that knowledge of the original study results did not influence the ascertainment of the new data, especially if any data are missing for subjects. While we do not object to this proposal, we regard analyses of this post-hoc dataset as useful exploratory information that would require confirmation within another clinical study.

2. Please clarify the rationale for proposing an image re-read, as we do not find, at this time, that the re-read is necessary. However, we may misunderstand the purpose of this reread.

Questions from GE Amended Meeting Package Dated, November 16, 2007

Clinical

Sponsor's Question 1

Does the Division concur with the proposed standard of truth redefinition regarding diagnosis of absence or presence of active pheochromocytoma or neuroblastoma?

FDA response

The proposed Truth Standard redefinition appears complex and apparently applies to the post-hoc dataset (not the locked dataset). The description refers to four "levels of evidence" as if to imply these levels have some form of hierarchy. However, the hierarchy is not readily evident in the truth standard redefinition. We request clarification of these plans. Also, see our prior comments.

Sponsor's Question 1a

Does the Division have any comments regarding the Statistical Analysis Plan for the redefined standard of truth post hoc analysis contained in Attachment 2 of this submission?

FDA response

No. We have no additional comments.

Sponsor's Question 2

Does the Division have any comments regarding the proposal to conduct a post hoc, fully blinded evaluation followed by a sequential unblinded read?

FDA response

No. Please refer to prior general comments. Please also note that the sequential unblinding proposed by you would apparently unblind the readers to clinical information contained in the standard of truth, and it appears that you would in effect be comparing the standard of truth to itself.

Sponsor's Question 2a

Does the Division see value in conducting this post hoc re-read as additional documentation in conjunction with the revised standard of truth to enable appropriate labeling to be drafted and eventual approval of the product?

FDA response

We are unclear of the purpose of the proposed re-read, in light of your concern about the standard of truth.

Sponsor's Question 2b

What comments does the Division have regarding the varying degree of availability of the correlative imaging information per subject?

FDA response

We have no additional comments. Please refer to the General Comments and clarify what you mean by "correlative imaging information".

Sponsor's Question 2c

As an additional option, would the Division consider it acceptable to have the sequential unblinded readings performed by the same readers who performed the original fully blinded reviews, thereby making a second fully-blinded read unnecessary?

FDA response

The sequential unblinded read may provide useful exploratory or supportive information. However, we do not regard the information from this reread, alone, as capable of supplanting the original study findings.

Sponsor's Question 3

Does the Division have any comments regarding the proposed statistical analyses for the BIE Protocol - Sequential Unblinded Reread contained in Attachment 5?

FDA response

No.

Format

Sponsor's Question 1

GEHC has made the decision to submit the NDA as an electronic CTD. GEHC has retained the services of a CRO to compile the submission on our behalf. What comments does the Division have in regard to our use of this submission format?

FDA response

Submitting an NDA in an electronic CTD format is acceptable. We have no additional comments at this time.

Sponsor's Question 2

GEHC has made the decision to submit the clinical data in SDTM format within the eCTD structure. has been retained by GEHC to convert the data into this standardized format according to the CDISC requirements. In addition, GEHC will supply analysis datasets in 1999 compliant format. Because the data will be provided in SDTM format, GE Healthcare would like to know whether the Agency will want to receive data listings or if the presentation in SDTM format is sufficient for review.

FDA response

We defer comment at the present time.

Sponsor's Question 3

The current submission will involve a Phase 3 study with three independent blinded readers (each subject's images were provided to each reader). GEHC has created efficacy analysis datasets with one record for each subject and reader combination. GEHC feels this structure is optimal for performing analyses by the individual reader. What comments does the Division have regarding this presentation of the efficacy analysis data?

FDA response

Data from each reader should be analyzed separately. Sensitivity, specificity PPV and NPV should be calculated for each reader.

Sponsor's Question 4

It is the sponsor's intent to make the AdreView images available to the Division upon request. Planar images, tomographic projections and reconstructed transaxial slices will be provided in DICOM 3 part 10 format. The images should be able to be viewed with any DICOM-compliant viewer or workstation. The sponsor will provide a copy of eFilm Lite (Merge Healthcare - Milwaukee, WI) software with the images for the Division's convenience in viewing them. Alternatively the images can be provided as JPEG format static images and digital cine loops for the tomographic projections at the reviewer's request. What comments does the Agency have to this proposal?

FDA response

Please note that we do not routinely examine images as part of the NDA review process. We may wish to see examples of images in some specific cases but not the entire image sets. If we request an image examination, we will notify you and request that you bring all necessary equipment for a meeting in which the images are displayed.

Sponsor's Question 5

The Sponsor plans to include the MBG308 (single pivotal efficacy trial) clinical study report in CTD module 5 section 5.3.5.1 and the report generated based on the document entitled "Guidance for MBG308 Post Hoc Analysis" in section 5.3.5.4, Other Study Reports. Does the Agency accept this proposal?

FDA response

Commenting on this question appears to be premature at this time. Distinguishing any post-hoc analyses (including a "redeveloped" standard of truth that uses the locked dataset) from pre-specified analyses is essential in all documents and formats.

Sponsor's Question 6

The final diagnosis/standard of truth for all subjects enrolled in clinical protocol MBG308 will be recorded on the 2 page case report form contained on pages 22 and 23 of the background package dated October 10, 2007. The sponsor does not intend to include copies of the source documents supporting completion of the final diagnosis case report form pages. Does the Agency accept this proposal?

FDA response

FDA may request copies of medical record/or other source documents. In general, these types of source documents are not anticipated for submission within an NDA.

Discussion

GE Healthcare opened the meeting with a presentation. According to GE Healthcare the presentation highlighted the findings from studies performed using the product for neuroblastoma. GE Healthcare sought to convey in their presentation the practice community's need and desire for approval of this agent because of its distinct advantages over the approved I-131 product. FDA expressed its concern about the revised standard of truth presented in the meeting package and at the meeting. GE Healthcare conveyed that the locked database has remained locked and the revisions only affect the standard of truth that will be used for the analysis.

FDA inquired about the introduction of new case report forms for the patients that would be included in a subset analysis using the new standard of truth and GE Healthcare

replied that no new case report forms will be submitted. According to GE Healthcare the case report forms in the NDA would be those of patients from the locked database.

GE HealthCare said they planned to reference the pharmacology/toxicology information from the CIS-US New Drug Application for I-131 (NDA 20-084) to support the approval of their NDA. FDA then asked GE Healthcare if they had right of reference for CIS-US's NDA. GE Healthcare then replied that they did not. FDA cautioned GE Healthcare about using this approach since it is unclear if this is acceptable regulatory practice under the 505 (b)(2) regulation. GE Healthcare stated that their product was superior to the CIS-US's product because of its emission of gamma rays only. FDA then questioned GE Healthcare about the use of the CIS-US pharmacology/toxicology data since GE Healthcare [redacted] b(4)

GE Healthcare asked FDA to provide feedback on its findings regarding the preclinical proposal so that they could move forward with their plan to submit their NDA for I-123. GE Healthcare stated that they planned to submit their NDA during the first quarter of 2008.

FDA requested that GE Healthcare redefine the truth standard for the trial and GE Healthcare stated that the truth standard would be a combination of an expert panel using clinical diagnoses criteria and histology to provide the standard of truth for the trial.

FDA asked GE Healthcare about the availability of I-123 at various sites around the country and GE Healthcare responded that it is available under an IND and pharmacists compound the product for use at various sites. FDA asked GE Healthcare if they had access to the data from any of these sites and GE Healthcare replied that they did not. FDA noted that the goal established for sensitivity in the statistical analysis plan for I-123 was not achieved in study 308. GE Healthcare agreed but stated that their accuracy goal was achieved in the trial. FDA asked GE Healthcare the percentage of false positives seen in the study and GE Healthcare replied that the percent of false positives was less than 10%.

FDA inquired about the percentage of patients in the study that had histology and GE Healthcare replied that 82% of the patients in the study had histology.

FDA inquired about the data that would be submitted in support of the NDA and GE Healthcare stated that the data would be a combination of a metaanalysis from the literature and the data obtained from the clinical trial 308.

FDA inquired why histology was not performed on more patients given I-123 and GE Healthcare replied, because neuroblastoma is a disease seen in children histology is sometimes not done because of concerns about safety of the biopsy procedure.

GE Healthcare stated that they planned to submit the efficacy data from study 308 in the STDM format and asked if that was acceptable. FDA replied that it was, but FDA cautioned GE Healthcare that any dataset submitted must be formatted properly.

Summary

Following a general discussion of analytical plans, GE Healthcare agreed to provide persuasive evidence of safety and efficacy and plans to submit their NDA to FDA during the first quarter of 2008.

FDA will provide guidance on whether it is acceptable for GE Healthcare to reference the pharmacology/toxicology data from CIS-US's I-131 application under the 505 (b)(2) regulation.

The meeting adjourned at 1:35PM.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Appendix

071220-AdreVie
/FDA Slides_fina.

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Linked Applications	Sponsor Name	Drug Name
IND 62669	GE HEALTHCARE	123 I-MIBG INJECTION

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/s/

JAMES W MOORE
02/26/2008
Fax of minutes for IND 62,699 (I-123, MIBG) GE

MEMORANDUM OF MEETING REPORT

Meeting Date: August 9, 2007
Time: 11-12:30 PM
Location: FDA, White Oak Building 22, Room 1415

Application: IND 62,669, AdreView (^{123}I-*m*IBG)

Type of Meeting: End-of-Phase 3 meeting

Meeting Chair: Dr. Alex Gorovets

Meeting Recorder: Ms. Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Medical Imaging and Hematology Drug Products

Dwaine Rieves, M.D.; Acting Division Director
Louis Marzella, M.D.; Acting Deputy Director
Alex Gorovets, M.D.; Medical Team Leader
Robert Yaes, M.D.; Medical Reviewer
Jyoti Zalkikar, Ph.D.; Statistical Team Leader
Eldon Leutzinger, Ph.D; CMC Pharmaceutical Lead
Adebayo Laniyonu, ph.D.; Pharm/Tox team Leader
Siham Biade, Ph.D.; Pharm/Tox Reviewer
Alice Kacuba, R.N., MSN; Regulatory Project Manager Team Leader
James Moore, Pharm.D.; Regulatory Project Manager

External Constituent Attendees and Titles:

GE Healthcare
Larry Bell, M.D.; Global Head, Regulatory Affairs
Giles Campion, M.D.; Head, Global Medicine
Pamela S Cohen, M.D.; Global Therapeutic Head, Oncology
JoAnne Harla; Project Director, Project Management
Arnold Jacobson, M.D., Ph.D.; Director, Clinical Research
Fred Longenecker; Director, Regulatory Affairs
John Ventre; Global Head, Statistics and Programming
Susan White; Manager, Regularly Affairs

b(4)

Background:
IND 62,669 is being investigated for use as a radiopharmaceutical that is administered by intravenous injection to detect tumors of neuron crest or neuroendocrine origin (most often for assessment of patients with neuroblastoma and suspected pheochromocytoma). On May 31, 2007, the sponsor submitted a Pre-NDA Meeting Request with subsequent Background Packages (BGP) submitted on July 11 and July 25, 2007. Prior to the meeting, FDA communicated to the sponsor that because the BGP stated that the Phase 3 study did not meet the prespecified endpoints, the scheduled meeting would be more appropriate as an End-of-Phase 3 meeting and requested the sponsor present the regulatory history and a review of the Phase 3 study. On August 8, 2008, FDA sent by facsimile to the sponsor, FDA preliminary responses to the questions posed in the sponsor's July 11, 2007 BGP. The content of the facsimile is reproduced below.

"In reference to your product I-123-MIBG, the IND 62-629, and the pre-NDA meeting scheduled on 08-09-07, we have reviewed the meeting package submitted on 07-11-07. The supplied information does not appear to provide evidence of efficacy and safety of your product to successfully support an NDA. Most notably, statistical success was not demonstrated on the single confirmatory study's primary endpoint and the supplied information does not include summarized safety data.

Regarding the primary endpoint failure, we recommend that you analyze your data to determine the basis for the failure to demonstrate diagnostic efficacy. Based upon these analyses, we recommend that you supply confirmatory efficacy data from at least one additional clinical study. Alternatively, please justify the appropriateness of concluding you have demonstrated diagnostic efficacy for your product despite the statistical failure of the confirmatory study's primary endpoint. We also request a summary of the safety data from your clinical development program.

We have the following Clinical Comments (Sponsor's questions and the proposed FDA responses are listed in the Appendix):

1) **As noted above, the prospective criterion for demonstration of efficacy, a lower confidence limit for sensitivity and specificity of > 80% for 2 out of 3 readers has not been achieved in study MBG308.**
2) **In the clinical/statistical summary in this pre-meeting package, safety data is not discussed. Although theoretically ^{123}I-MIBG might be safer than ^{131}I-MIBG *at equal doses*, safety data from this study will still have to be reviewed. Please comment on the relative safety of ^{131}I-MIBG and ^{123}I-MIBG.**
3) **Please perform a dosimetry calculation and provide a table of estimated radiation absorbed doses to the whole body and to those normal organs listed in table 3.17, vol. 2 p. 36 of your submission from the recommended imaging dose of ^{123}I-MIBG (370 MBq) and also for the recommended dose (0.5mCi) of ^{131}I-MIBG in a 70 kg man. If old biodistribution data is used, please perform a new dosimetry calculation using the FDA approved OLNDA software package. Since the pharmacokinetics and biodistribution of ^{123}I-MIBG and ^{131}I-MIBG will be the same, ^{131}I-MIBG biodistribution data could be used in such a calculation for both agents.**
4) **Apparently only 20% (50/250) subjects had a histological diagnosis. In most circumstances histology is considered THE gold standard for the diagnosis of malignancy. In clinical practice the conclusion of an "expert panel" based on other**

clinical information would likely be considered a poor substitute (or unacceptable substitute) for a histological diagnosis of malignancy. In the US, with a few well circumscribed exceptions, the approach of most oncologists is not to treat a cancer patient until a histological diagnosis is obtained. Since antineoplastic therapy is frequently associated with serious adverse reactions, the consequences of being wrong in even a small number of cases would be unacceptable. At the time that the protocol was submitted it might have been implicitly assumed that most of the subjects would have a histological diagnosis and that the expert panels would be required in only a small number of cases. If the expert panel diagnoses were inaccurate, this could in part explain why confidence intervals were so wide and the target values were not reached. Of note, the subset of patients who did have a histological diagnosis showed an attainment of point estimates for the measured performance characteristics >80%, although target confidence intervals might not have been reached because the sample size for this subset was too small.

5) In study MBG308 the readers were asked to determine the presence or absence of active tumor. The readers were not asked to provide any spatial information (location of tumor, single vs. multiple foci of increased uptake etc.) and there was apparently no standard of truth diagnosis for spatial information. [redacted] This indication, as worded, is not supported by the results of MBG308. b(4)

6) It is stated that the expert panel would make the final determination of the standard of truth diagnosis in patients without "current histology" Under what circumstances would histology be considered "current"? Were histological results that were not considered to be "current" provided to the expert panel?

7) The ^{131}I MIBG package insert mentions 4 clinical trials: 3 trials of subjects with suspected pheochromocytoma and one trial of subjects with suspected neuroblastoma. For ^{123}I MIBG, you are proposing to submit a single trial with subjects having either suspected pheochromocytoma or neuroblastoma. Without data, there is no reason to believe that ^{123}I-MIBG is equally effective in imaging neuroblastoma and pheochromocytoma. Please provide a subset analysis of sensitivity and specificity for subjects with each tumor type separately. Additional clinical data may be necessary to support the proposed indications (see prior comments).

8) In study MBG308 there was no comparison of ^{123}I-MIBG to ^{131}I-MIBG. Thus the results of MBG308 would not support any comparative claim of ^{123}I-MIBG in relation to ^{131}I-MIBG.

9) Please justify the proposed adult dose of ^{123}I MIBG in comparison to the recommended dose of ^{131}I MIBG in the package insert.

10) Please justify the timing of image acquisition for ^{123}I-MIBG and provide supporting data.

11) Of the 251 patients imaged, how many were imaged in the US and how many were imaged in other countries? Of the 50 patients with a histological diagnosis, how many were imaged in the US and how many in other countries? Please provide a list of the countries where patients were imaged and specify the number imaged in each country.

LIST OF QUESTIONS

ADMINISTRATIVE

(1) Clinical safety and efficacy for the AdreView (Iobenguane I 123 Injection) NDA will be based on clinical trial MBG308 and cross reference to CIS NDA 20-084 for Iobenguane I 131 Injection (referencing preclinical and clinical safety and efficacy data). Based on previous agreements reached with the Division we intend to file the NDA as a 505(b)(2) application. Does the Division concur?

FORMAT

(1) GE Healthcare intends to submit the NDA for AdreView (Iobenguane 1123 Injection) in eCTD format. GE Healthcare has retained the services of ——————————————— to compile the eCTD on our behalf. Since——has successfully submitted pilots and submissions in the eCTD format to the Agency, GE Healthcare will not be submitting a pilot for this submission. What comments does the Division have in regard to our use of this submission format? (2) GEHC has made the decision to submit the clinical data in SDTM format within the eCTD structure. ——————————— has been retained by GEHC to convert the data into this standardized format according to the CDISC requirements. In addition, GEHC will supply analysis datasets in 1999 compliant format. What comments does the Division have regarding this plan?

b(4)

(3) The current submission will involve a Phase 3 study with three independent blinded readers (each subject's images were provided to each reader). GEHC has created efficacy analysis datasets with one record for each subject and reader combination. GEHC feels this structure is optimal for performing analyses by the individual readers. What comments does the Division have regarding this presentation of the efficacy analysis data?

(4) It is the sponsor's intent to make the AdreView images available to the Division upon request. Planar images, tomographic projections and reconstructed trans axial slices will be provided in DICOM 3 part 10 format. The images should be able to be viewed with any DICOM-compliant viewer or workstation. The sponsor will provide a copy of eFilm Lite (Merge Healthcare - Milwaukee, WI) software with the images for the Division's convenience in viewing them. Alternatively the images can be provided as JPEG format static images and digital cine loops for the tomographic projections at the reviewer's request. What comments does the Agency have to this proposal?

Proposed FDA response:

In view of the failure of the single Phase-3 trial it is premature at this time to comment on the Administrative and Format questions.

CONTENT

(1) What comments does the Division have based on their review of the Clinical section of the pre-meeting package?

Proposed FDA response:

Please see the Clinical Comments above.

(2) GE Healthcare believes that the nonclinical safety information based on the CIS-US NDA 20-084 (1994) and supplemented by GE Healthcare with a standard Genotox study package and a bERG study is a complete preclinical package. Does the Division concur?

Proposed FDA response:

Yes.

(3) Since reproductive toxicity studies are not normally required for the development of a single dose diagnostic radiopharmaceutical, GE Healthcare requested a waiver from conducting such studies in our original IND dated December 2, 2004. The waiver request was contained in both the cover letter accompanying the original IND (62, 669, serial number 0000) and in section 8.3.3.5 Reproductive Toxicity studies. GE Healthcare has followed up periodically with the Division. Although we have not received a formal response we have understood that a waiver would be granted. Does the Division concur?

Proposed FDA response:

A request for waiver and adequate justification must be presented in the NDA submission (see 21CFR § 314.90).

(4) What comments does the Division have based on their review of the CMC technical summary section of the pre-meeting package?

Proposed FDA response:

a. Be advised that because the drug substance (^{123}I-meta-iodobenzylguanidine) is produced [redacted] the final intermediate [redacted] will be held to the same purity and quality standards as a drug substance. Also, the facilities responsible for production of [redacted] may be subject to CGMP inspection. b(4)

b. In December of 2004, you had indicated that an impurity was detected in the product in the likely content range [redacted] This range was based on HPLC-UV peak area and the UV extinction coefficient of [redacted] had determined that this impurity was likely structurally similar [redacted] As we recall, this content range was somewhat uncertain, due to the uncertainty in the extinction coefficient / identity. Since you are proposing to use the same stopper in the marketed product, have you better defined this range of impurity content so that is known with reasonably good accuracy? b(4)

c. On page 79 (vol 1) of the meeting package, you indicate that batches of [redacted] are analyzed on production and have a retest date of [redacted] You also indicate that re-testing does not include [redacted] It is presumed that the re-testing will include a meaningful test for chemical purity, that will detect and b(4)

estimate any impurity / degradant that might arise during storage. Please explain.

Discussion Points:

I. Introductions

II. Sponsor presentation: The bulk of the meeting was the sponsor's presentation. See attached slides.

Mr. Lonenecker began the sponsor's presentation with a summary of the discussion topics and a brief review of the regulatory status of *m*IBG. Mr. Longenecker added that GEHC understood the FDA comment regarding the term "localization" in the proposed indication statement and commented that the clinical study was not designed to collect spatial information however as far as we believe neither did CIS. Mr. Longenecker concluded by briefly reviewing the previous interactions between GEHC and the Division.

Next, Dr. Jacobson provided information regarding the product. He described the *m*IBG molecule emphasizing that the isotope of iodine in a molecule of *m*IBG has no influence on the compound's chemical or physiological characteristics. After an explanation how *m*IBG recirculates in the noradrenergic axonal terminal, Dr. Jacobson showed 2 sets of images comparing ^{123}I-*m*IBG and ^{131}I-*m*IBG.

——— introduced herself and stated ^{123}I-*m*IBG has become the standard of care in the diagnosis and staging of neuroblastoma. ——— is a member of the ——————————————— ———and commented that the group is in the process of developing a new staging system in which ^{123}I-*m*IBG imaging will be mandatory for staging of disease. ———added that ^{123}I-*m*IBG is also very useful in assessing response to therapy. The presence of ^{123}I-*m*IBG in serial follow-up scans relates to poorer outcomes and ^{123}I-*m*IBG is the most useful modality for detecting skeletal metastases. Dr. Yaes inquired if it is standard of care to have histological diagnoses. ———explained that most patients do have histological confirmation of disease however there is a subset of infants where an adrenal mass is picked up on ultrasound and these patients do not have histology. Dr. Yaes asked ———to quantify the number of cases in which disease was histologically confirmed. ——— replied stating that well over 90% of tumor diagnosis has histological confirmation but then they don't get repeat biopsies at the time of sequential scans. Finally, ——— provided image examples depicting metastatic disease, positive response to therapy, and a ^{123}I-*m*IBG scan associated with a very poor prognosis after induction chemotherapy.

b(4)

Next, Dr. Jacobson provided an overview of clinical trial MBG308 study design which included a review of the methodology, standard of truth, and statistical hypothesis. Dr. Gorovets requested clarification of the definition for "current" histopathology. Dr. Jacobson responded by stating that per the protocol histopathology was considered "current" if it was obtained within 30 days after the ^{123}I-*m*IBG scan or if obtained prior to the scan without any intervening therapy or surgery.

Dr. Jacobson proceeded to explain that the statistical assumptions were determined prior to study initiation based on a review of the literature. An overview of the study results followed. In response to one of the questions contained in the Division's August 7th fax, Dr. Jacobson stated

that out of the 50 patients with current histology serving as the standard of truth, 39 subjects were from the US and 11 were from Europe. During review of the demographics, Dr. Jacobson pointed out that the key message was that the minority of patients enrolled into the study did not have a diagnosis prior to imaging therefore the majority of subjects were not treatment naive. After a brief review of the safety results, Dr. Jacobson presented the primary efficacy results including a breakdown of the primary efficacy by tumor type which showed remarkable consistency with the overall results.

A secondary analysis of the sensitivity and specificity of subjects with current histopathology as the standard of truth was then presented. Dr. Jacobson remarked that the sensitivity and specificity results were better but pointed out that this is still on the backdrop of a totally blinded uninformed read. Next an overview of the false positives and false negatives was presented. Dr. Jacobson noted that the largest group of false negatives represented either tumors with low or no NET expression or previously treated disease with minimal residual tumor that was below the resolution limits of the imaging method. During discussion of the false positive and false negative cases Dr. Jacobson stated that there are several categories which would likely be corrected in an informed read. If the blinded reviewers had been provided clinical information in adrenal hyperplasia cases, for example, these probably would have been correctly identified.

A review of the data from the CIS-US NDA 20-084 was presented next. Dr. Jacobson pointed out that there was a substantial number of indeterminates in the CIS trials due to an inadequate standard of truth. Dr. Jacobson proceeded to highlight the major differences between GEHC study MBG308 and the clinical trials contained in NDA 20-084. The most relevant comparison between the two pertained to the sensitivity and specificity results of the cases in which histology was the standard of truth. Derived consensus values for ^{123}I-*m*IBG are higher than the ^{131}I-*m*IBG results.

———————————————— led the next section of the presentation. ———— began by introducing himself and stated that ^{123}I-*m*IBG is the second most common nuclear imaging agent used at his institution. ———— presented a comparison of ^{123}I-*m*IBG and ^{131}I-*m*IBG images and detailed the advantages of ^{123}I-*m*IBG over ^{131}I-*m*IBG. Next ————commented on a few of the cases which had resulted in a mismatch between the standard of truth diagnosis and the diagnosis made by the blinded readers. Provision of appropriate information, e.g. biochemical results, to the blinded readers may have resulted in a match.———— commented that in clinical practice images are not reviewed in a vacuum; rather the physician evaluates the ^{123}I-*m*IBG images together with all of the available clinical information, e.g. patient history, cross-sectional imaging such as CT and MRI scans, to arrive at a decision.————concluded by stating that clinicians would like to see a FDA regulated product widely available. Finally, Dr. Jacobson presented GEHC proposal to conduct a partially informed re-read of selected MBG308 images.

b(4)

In conclusion Mr. Longenecker stated that GEHC had shown the level of comparability of ^{123}I-*m*IBG to ^{131}I-*m*IBG and the clinical experts had described how they regularly use the product and that it is considered standard of care. Although ^{123}I-*m*IBG is currently available under pharmacy practice, a readily available FDA approved product would assure clinicians a highly consistent, GMP product.

Dr. Yaes opened the discussion by stating that the number of ^{131}I-*m*IBG subjects in the NDA 20-084 study with histological confirmation of disease was much larger than in MBG308. Assuming

that histology is better than an expert panel diagnosis, Dr. Yaes speculated that MBG308 may have been underpowered. Dr. Rieves commented that this is simply a case where there is a need to be able to describe the performance characteristics, e.g. planar vs. SPECT. Dr. Rieves believed that if the diagnosis was based on the EP determination rather than histopathology then this may be a concern to physicians. Dr. Rieves inquired if additional follow-up could be obtained for the EP assessed patients. Dr. Rieves also commented that the 80% threshold values for sensitivity and specificity and the definition of current histopathology sounded arbitrary. He further stated that the FDA statisticians would not accept a selective re-read and that the FDA was more concerned about being able to describe the performance characteristics of the product.

Dr. Bell responded by stating that GEHC would work with the Division and the plan for partially informed re-read of select images was our first proposal. Dr. Bell asked the clinical experts to comment. Dr. Jacobson stated that the proportion of subjects with histopathology was similar in MBG308 and the CIS data. Dr. Jacobson clarified that all but 1 of the 159 subjects positive for active tumor had histopathology results at some point in their diagnosis; about 100 subjects had histopathology within 3 months of ^{123}I-*m*IBG scanning. He commented some of these cases were neuroblastoma subjects who had a biopsy diagnosis followed by 1 cycle of chemotherapy prior to the ^{123}I-*m*IBG scan. ——— indicated that this sequence of events was not unusual for newly diagnosed neuroblastoma patients. b(4)

Dr. Bell confirmed the 80/80 statistical measures and the 30 day definition for "current" histology were arbitrary and that GEHC is confident that in speaking with the clinical experts their confidence in the product has not been shaken by the study results. ——— added that in terms of clinical practice it is common for patients with a neuroblastoma diagnosis to begin treatment prior to performance of the ^{123}I-*m*IBG scan and that the MBG308 clinical protocol had very rigid criteria. ——— added that a ^{123}I-*m*IBG scan is the international standard for staging these types of tumors and that she sees it only as a positive to have the product available commercially. Dr. Gorovets inquired if the ——— based their recommendation on image quality or some other data of which the FDA is not aware. ———replied that the recommendation is based on clinical experience and image quality. In response to an inquiry from Dr. Gorovets,———replied that she currently obtains ^{123}I-*m*IBG from a local pharmacy. ——— also stated that the proposed neuroblastoma staging system no longer includes the previously required criteria of a bone scan if the ^{123}I-*m*IBG study is positive for bone/marrow metastases. Dr. Gorovets inquired if this decision was based on data or just better images with clinical experience. ———replied clinical experience. She further added that clinicians are beginning to incorporate results of the ^{123}I-*m*IBG scan into treatment approaches for patients with refractory disease. b(4)

Dr. Bell requested ——— to provide his thoughts as he was one of the members of the expert panel. ——— stated that the CIS label has an adjunctive indication and that the images from MBG308 were read in a blinded fashion and that is not how clinicians use ^{123}I-*m*IBG in clinical practice. He also explained that there has been a change in patient demographics due to advances in therapy. Neuroblastoma patients are seen over and over again and there is no need to obtain further histology. The problem encountered by the expert panel was that they did not have the ^{123}I-*m*IBG scan and that the ^{123}I-*m*IBG scan was especially important in assessing patients with abnormal catecholamine levels but uncertain anatomic abnormalities. ——— further commented that the product made by a commercial pharmacy fails approximately once every 6 months resulting in a cascade of events inconveniencing patients and staff due to the cancelling of b(4)

scans, anesthesia, etc. This also results in a delay of patient care and management.

Dr. Yaes stated that the Division understands the image quality aspects but the problem is that the clinical study did not look at staging for example. If the study had been designed with only current histopathology as the standard of truth then chances are that the study objectives would have been achieved. Dr. Rieves interjected by stating that together we need to come up with an action plan as all want the product on the market with an accurate label. Dr. Rieves recommended GEHC should make a proposal to FDA to better describe the characteristics and that the problem here is with the standard of truth. FDA needs clarity on the truth standard and the submission would be viewed more favorably if the truth standard were better defined. Dr. Jacobson stated that there was an onsite diagnosis for every patient. When Dr. Rieves inquired if the onsite investigators saw the ^{123}I-*m*IBG images, Dr. Jacobson replied in the affirmative.

Dr. Rieves inquired if some of the patients would be watched for a longer follow-up. ——— explained that if there was a negative scan and the clinical suspicion was not high then a pheochromocytoma would be ruled out and the patient would no longer be followed. Dr. Bell commented that the fundamental challenge is the dichotomy of the local standard of truth (diagnosis) vs. the EP standard of truth and the blinded read. When all of those factors are thrown together it becomes exceedingly challenging to have a successful study. Dr. Bell stated that he hoped that we could come to a resolution and that where we can tease out like-to-like then we are spot on. Dr. Rieves replied by stating that the label shouldn't say "we believe" (inferring that the label needs to be based on hard data). Dr. Rieves inquired if additional follow-up data could be obtained. Dr. Bell agreed that the label has to be data driven but it is a challenge to standardize the information. b(4)

Dr. Campion added that what was found to be challenging was the number of cases that were mis-classified simply because the blinded readers did not know basic information such as a patient's previous history. In order to correctly diagnose the false positives it would be useful to apply adjunctive diagnostic information to the background.

Dr. Jacobson inquired whether if GEHC were able to solidify the diagnosis of patients would we be able to re-incorporate the indeterminates back into the intent-to-diagnose population? Dr. Rieves replied that this would be a reasonable proposal instead of the selective re-read which would introduce too much bias. Dr. Bell agreed and stated that the selective re-read was off the table. Dr. Bell stated that GEHC would have to work with our clinical experts and provide a proposal to the Division regarding definitive diagnosis. The proposal would be submitted to FDA for review. Dr. Rieves encouraged GEHC to try and follow-up the patients, especially the neuroblastoma patients.

When Dr. Gorovets inquired if GEHC was still pursuing a 505(b)(2) application, Mr. Longenecker replied affirmatively, especially regarding the preclinical data. Ms. Kacuba summarized by stating that GEHC should solidify the EP standard of truth and could submit a proposal for a re-read for all subjects. Dr. Rieves stated that a re-read per say was not needed but GEHC needs to firm up the standard of truth diagnosis. Dr. Yaes inquired if it would be possible to establish a true negative. Dr. Rieves suggested that he anticipated that at a minimum the on-site diagnosis of cancer should be followed to confirm that a patient definitely had cancer not just a presumption of cancer. Dr. Rieves added that there are ways to confirm this e.g., if a patient receives chemotherapy then that would be considered cancer. Dr. Bell stated that GEHC would work with

the consultants to come up with a plan. Dr. Zalkikar added that if GEHC wants the indication to include text regarding adjunctive use of ^{123}I-*m*IBG then a re-read would have to be performed. At this point the meeting ended.

III. Sponsor questions in July 11, 2007 BGP and FDA responses in August 8, 2007 facsimile. Questions and responses were not discussed at the meeting.

IV. Summary/Action Items

A. The sponsor will consider the discussion today.
B. The sponsor will submit proposal for re-reads of the images.

Minutes Preparer: Alice Kacuba

Chair Concurrence: Alex Gorovets, M.D.

Attachments

27 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 7

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/s/

Alice Kacuba
8/30/2007 03:33:16 PM