CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Center for Drug Evaluation and Research
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Maternal Health Team Review

Date: September 8, 2008 **Date Consulted:** July 2, 2008

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To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: AdreView; NDA 22-290

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of AdreView labeling.

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On March 20, 2008, GE Healthcare submitted a new drug application (NDA) 22-290 to the Division of Medical Imaging and Hematology Products (DMIHP) for AdreView. AdreView is a diagnostic radiopharmaceutical containing a radioiodinated benzylguanidine. The sponsors proposed indication for AdreView is for use as an imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas.

On July 2, 2008, DMIHP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the AdreView package insert, and provide comment. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of AdreView labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of AdreView labeling.

SUMBMITTED MATERIAL

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with AdreView. [redacted] AdreView should be given to a pregnant woman only if clearly needed.

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8.3 Nursing Mothers

[redacted]

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RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

Highlights of Prescribing Information:

----------**USE IN SPECIFIC POPULATIONS**----------

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8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with AdreView. AdreView should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether AdreView is excreted into human milk. However, Iodine 123 is excreted into human milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants a decision should be made whether to interrupt nursing after administration of AdreView or not to administer AdreView, taking into account the importance of the drug to the mother. Based on the nursing women may consider interrupting nursing for 6 days after administration.

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CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for AdreView is provided on page 2 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A –

Track Changes Version of Labeling

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 7

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/s/

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CLINICAL REVIEW

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Application Type	———
Submission Number	N000
Submission Code	
Letter Date:	3/21/2008
Stamp Date:	3/21/08
PDUFA Goal Date:	9/19/08
Reviewer Name:	Robert J. Yaes, MD
Review Completion Date:	8/14/08
Established Name:	I-123-MIBG
(Proposed) Trade Name:	Adreview
Therapeutic Class:	Diagnostic Radiopharmaceutical
Applicant:	GE Healthcare
Priority Designation:	P
Formulation:	IV
Dosing Regimen:	——— b(4)
	370 MBq for planar + SPECT imaging
Indication:	Detection of neuroendocrine tumors
Intended Population:	Patients with known or suspected neuroendocrine tumors

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Appears This Way
On Original

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I-123-MIBG is safe and effective for imaging pheochromocytoma and neuroblastoma
I-123-MIBG should be approved for marketing as an imaging agent for Pheochromocytoma and neuroblastoma

Safety:
In the prospective Phase 3 clinical study of [MBG308] in 251 patients, 1 SAE and 15 mild to moderate AEs unrelated to the drug were reported. Only 2 mild to moderate AEs (0.8%) related to the drug were reported. No systematic changes in laboratory, vital sign or EKG parameters were noted after administering the drug
In the European post-marketing experience, among patients exposed to the drug only two adverse events were reported to the sponsor by medical professionals. Both were allergic reactions which resolved spontaneously

Efficacy:
The prospective efficacy target: lower limits of confidence interval for both sensitivity and specificity > 80% for 2 out of 3 readers was not achieved [Table 15] However for all three readers the confidence intervals for both sensitivity and specificity excluded 50% which would correspond to a coin toss is excluded and thus the null hypothesis that the scans provide NO diagnostic information , is excluded. Thus the imaging agent is effective but not quite as effective as originally thought. The 80% value is arbitrary and is probably based on values in the literature which may have resulted from unblinded reads. The meta-analysis [MBG304] showed lower limits of confidence intervals for sensitivity and specificity > 90%. The results were probably better than for the prospective study because of publication bias and because the readers in the published papers were probably not blinded

1.2 Recommendation on Postmarketing Actions

No post marketing actions are required

1.2.1 Risk Management Activity

No clinically significant risks were identified and therefore no risk management activity is required

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are required

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1.2.3 Other Phase 4 Requests

No other phase 4 requirements are needed

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Efficacy is assessed on the basis of data from 2 Clinical studies
1) MBG308 A prospective Phase 3 clinical study at 24 study centers of 251 subjects (179 US, 72 Europe) with neuroblastoma or pheochromocytoma imaged with I-123-MIBG
2) MBG304 A retrospective meta-analysis of published data on patients with pheochromocytoma or neuroblastoma imaged with I-123-MIBG

Safety is assessed on the basis of safety data from the prospective Phase 3 study MBG-308 and on the basis of post marketing safety reports from Europe where the drug is approved

1.3.2 Efficacy

There are two sources of Clinical data used to evaluate efficacy
1) MBG308 A prospective Phase 3 clinical study at 24 study centers of 251 subjects (179 US, 72 Europe) with neuroblastoma or pheochromocytoma imaged with I-123-MIBG
2) MBG304 A retrospective meta-analysis of published data

Study:MBG308: a Phase 3 prospective open label multicenter study
Title: An Open Label, Multicenter Phase 3 Scintigraphy Study Assessing I-123-MIBG Uptake in Subjects Being Evaluated for Pheochromocytoma or Neuroblastoma
Subjects: 251patients with known or suspected neuroblastoma or pheochromocytoma
Primary Efficacy Objective To demonstrate thatI-123-MIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnosis of neuroblastoma or pheochromocytoma
Primary safety objective To collect safety data on I-123-MIBG
Efficacy Evaluation:
Each patient received 10 mCi I-123-MIBG.For pediatric patients weighing < 70 kg dose was scaled to body weight Planar and SPECT images were obtained 24 hours after injection of I-123-MIBG if subject could tolerate SPECT imaging
Images were evaluated for the presence or absence of focal increased uptake (presence or absence of active tumor) by three independent blinded readers at a core laboratory. The standard of truth was "current" histology (histology obtained before imaging with no intervening therapy between biopsy and imaging). Where current histology was not available the truth standard was an evaluation of all clinical data other than the I-123-MIBG scan by an expert panel of two physicians expert in Neuroblastoma or in Pheochromocytoma as appropriate Efficacy was assessed in terms of sensitivity and specificity for each blinded reader, reading the planar images in determining the presence or absence of active tumor, using the gold standard defined above.

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Prospectively it was agreed that efficacy would be demonstrated if the lower limit of the confidence interval for sensitivity and specificity was > 80% for 2 of the 3 blinded readers

Table ES-1 Sensitivity and Specificity for **Planar Images** (from table 14)			
	Reader A	Reader B	Reader C
Sensitivity (pt. estimate)	0.80	0.77	0.79
95% confidence Interval	0.73-0.86	0.70-0.84	0.71-0.85
Specificity (pt. estimate)	0.77	0.73	0.69
95% confidence Interval	0.63-0.87	0.59-0.84	0.55-0.81

Reviewer's comment: Since the lower limits of the confidence intervals are below 80% for sensitivity and specificity for all three readers technically the prospectively determined demonstration of efficacy is not demonstrated. However the 80% value was arbitrary and probably based on clinical data where the readers were not blinded. .It should be noted that all of the confidence intervals exclude 50% which would be the sensitivity and specificity for a coin toss. Thus if the null hypothesis is that the images convey no diagnostic information then that null hypothesis is ruled out by the data. Thus efficacy is demonstrated but it is not as good as estimated before the study was done

Study: MBG304
Study Type: Retrospective Meta-Analysis
Study Title: A Meta-Analysis Study to Evaluate Performance of I-123-MIBG Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma
Objective: To evaluate the performance of I-123-MIBG imaging for the detection of neuroblastoma and pheochromocytoma at the subject level
Efficacy Evaluation: Articles Identified by means of a computerized literature search were reviewed by two nuclear medicine physicians. Articles where I-123-MIBG scans were used in the diagnosis of neuroblastoma, pheochromocytoma, paraganglioma MCT or carcinoid were included if there was an acceptable gold standard comparator, were included. Data from each article was collected on a case report form. A meta-analysis was performed to calculate sensitivity and specificity

Table ES-2 Meta-Analysis Results Fixed Effect Model (from table 22)					
	Sensitivity		specificity		
	Point estimate	Confidence interval	Point estimate	Confidence interval	Number of studies
pheochromocytoma	96%	93%-99%	95%	93%-97%	6
neuroblastoma	97%	95%-99%	Could not be estimated		7

Reviewer's comment: The meta-analysis shows much higher values for sensitivity and specificity than the prospective study. There are two possible explanations for this
1) Publication bias, only positive results are published

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2) the readers in the published papers used in the meta analysis may not have been blinded. Readers with all of the clinical information will always do better than readers who are blinded. Thus the meta-analysis results could even be closer to what happens in a real clinical setting than the results of MBG 308. In any event the meta-analysis results lends support to the hypothesis that I-123-MIBG is effective

1.3.3 Safety Evaluation

MBG 308

Safety was evaluated on the basis of vital signs, pulse-ox, 12 lead EKGs and Adverse Events. All subjects who received I-123-MIBG were evaluated for safety

There were 251 patients dosed and evaluable for safety in MBG308
There were no systematic changes in vital sign or EKG parameters noted
There were 16 AEs reported:
One serious adverse event, an arrhythmia that began before dosing and therefore was not drug related. 15 mild to moderate adverse events of which 2 were drug related

MBG304
There was no safety evaluation is study MBG304

Post marketing Experience
Safety was evaluated on the basis of safety reports submitted by medical professionals in countries where I-123-MIBG is approved

1.3.4 Dosing Regimen and Administration

Single dose 10 mCi IV (for pediatric patients weighing < 70 kg, dose was scaled by body weight)

1.3.5 Drug-Drug Interactions

It is known from clinical experience with I-131-MIBG which is chemically and pharmacologically identical to I-123-MIBG that drugs that interfere with norepinephrine uptake will also interfere with tumor uptake of I-123-MIBG

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Special Populations

I-123-MIBG is eliminated primarily by the kidneys. Patients with renal impairment may have a longer serum half-life and a higher whole body radiation absorbed dose

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

MIBG is an analogue of norepinephrine and is taken up in neuroendocrine tumor cells by the norepinephrine transporter system. It is also taken up by sympathetic neurons that innervate the heart. MIBG can be radiolabeled with either I-123 or I-131. I-131 emits a beta and a gamma. The gamma can be used for gamma camera imaging and I-131-MIBG is approved for that purpose for imaging neuroendocrine tumors (neuroblastoma and pheochromocytoma). [redacted]

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[redacted] The gamma ray from I-123 has a lower energy than the gamma from I-131 and can thus, in principle produce a sharper image with better resolution than the gamma from I-131. I-123-MIBG is approved in Europe for imaging Neuroendocrine tumors. In US, although I-123-MIBG is not marketed, it is compounded in individual hospital radio pharmacies for imaging neuroblastoma and pheochromocytoma.

2.2 Currently Available Treatment for IndicationsI-131-MIBG is currently approved in the US for imaging Neuroblastoma and Pheochromocytoma

[redacted]

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2.3 Availability of Proposed Active Ingredient in the United States

Both MIBG and I-123 are available in the United states

2.4 Important Issues With Pharmacologically Related Products

I-131-MIBG and I-123- MIBG are chemically and pharmacologically identical compounds. The only difference is in the isotope of iodine, its half-life and its mode of radioactive decay. Thus pharmacokinetic and biodistribution data obtained with I-131-MIBG can be used to accurately predict the pharmacokinetics and biodistribution of I-123-MIBG. Pharm-tox data for I-131-MIBG can also accurately predict the pharmacological toxicity of I-123 MIBG

2.5 Presubmission Regulatory Activity

April 18,2003 Pre IND meeting between FDA (DMIRDP) and Amersham Health (subsequently taken over by GE) to discuss Amersham Health's replacement of [redacted] as a source of I-131-MIBG [redacted] and also to discus the development of I-123-MIBG as an imaging agent CMC issues regarding I-123-MIBG were discussed in detail

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August 9, 2007 End of Phase 3 meeting between FDA and GE Healthcare. The bulk of the meeting was the sponsor's presentation and this was followed by discussion. The sponsor noted

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that I-123-MIBG had become the standard of care for imaging neuroendocrine tumors in Europe and is being used for imaging in several institutions in the US even though it is not approved in the US for that purpose. The results of the pivotal Phase 3 study, MBG308 were discussed
3/21/08 NDA submitted

2.6 Other Relevant Background Information

Neuroendocrine tumors studied in this protocol are Neuroblastoma and Pheochromocytoma. Neuroblastoma is a malignancy of infants and young children whereas Pheochromocytoma is a malignancy of adults. Thus the study population will include both adult and pediatric subjects, specifically pediatric subjects with neuroblastoma and adult subjects with pheochromocytoma

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

I-123-MIBG will be manufactured at the GE healthcare facility at Arlington I-131-MIBG and I-123-MIBG are chemically identical. The principal radiochemical impurity is

3.2--Animal Pharmacology/Toxicology

No new preclinical pharm-tox studies have been performed. The sponsor has reviewed CIS-US pharm-tox data for MIBG which is chemically and pharmacologically identical to I-123-MIBG. Repeat dose toxicity studies in the rat showed a NOAEL dose of 10 mg/kg 235 times the human mass dose of 5.8 μg/kg in a 70 kg man. Repeat dose toxicity studies in beagle dogs found a NOAEL dose of < 2.5 mg/kg

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

There are two sources of Clinical data
1) MBG308 A prospective Phase 3 clinical study at 24 study centers of 251 subjects (179 US, 72 Europe) with neuroblastoma or pheochromocytoma imaged with I-123-MIBG
2) MBG304 A retrospective meta-analysis of published data

4.2 Tables of Clinical Studies

There were two clinical studies a prospective open label Phase 3 study (MBG308) and a retrospective meta-analysis (MBG304)

Study: MBG308
Study Type: Phase 3 prospective study
Title: An Open Label, Multicenter Phase 3 Scintigraphy Study Assessing I-123-MIBG Uptake in Subjects Being Evaluated for Pheochromocytoma or Neuroblastoma
Subjects: 251 (179 US, 72 Europe) with known or suspected neuroblastoma or pheochromocytoma

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Objective
Primary: To demonstrate thatI-123-MIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnosis of neuroblastoma or pheochromocytoma
Secondary: To determine the incremental value of SPECT for improving the sensitivity and specificity of I-123-MIBG planar imaging in detecting Pheochromocytoma or Neuroblastoma
To collect safety data on I-123-MIBG
Efficacy Evaluation:
Thyroid blockage was achieved in each patient with KI or Lugol's, according to local regulations, before injection with I-123-MIBG. Planar and SPECT images were obtained 24 hours after injection of I-123-MIBG
Images were evaluated for the presence or absence of focal increased uptake (presence or absence of active tumor) by three independent blinded readers at a core laboratory. The standard of truth was current histology. Where current histology was not available the truth standard was an evaluation of all clinical data other than the I-123-MIBG scan evaluated by an expert panel of two physicians expert in Neuroblastoma or in Pheochromocytoma as appropriate
Safety Evaluation:
Safety was evaluated on the basis of vital signs, pulse-ox, 12 lead EKGs and Adverse Events. All subjects who received I-123-MIBG were evaluated for safety

Study:MBG304
Study Type: Retrospective Meta-Analysis
Study Title: A Meta-Analysis Study to Evaluate Performance of I-123-MIBG Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma
Objective: To evaluate the performance of I-123-MIBG imaging for the detection of neuroblastoma and pheochromocytoma at the subject level
Efficacy Evaluation: Articles Identified by means of a computerized literature search were reviewed by two nuclear medicine physicians. Articles where I-123-MIBG scans were used in the diagnosis of neuroblastoma, pheochromocytoma, paraganglioma MCT or carcinoid were included if there was an acceptable gold standard comparator. Data from each article was collected on a case report form. A meta-analysis was performed to calculate sensitivity and specificity

4.3 Review Strategy

This application contains two clinical studies
1) A prospective phase 3 multi-center study of safety and efficacy of I-123 MIBG in the diagnosis of pheochromocytoma and neuroblastoma
2) A retrospective meta-analysis of articles in the literature on the safety and efficacy of I-123-MIBG in the diagnosis of pheochromocytoma and neuroblastoma
It is impossible to combine data from a prospective Phase 3 study with data from a series of articles reviewed retrospectively in a meta-analysis. Therefore the two studies will be reviewed separately. The prospective Phase 3 study will be considered to be the pivotal study and the meta-analysis will be considered to be supportive

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4.4 Data Quality and Integrity

While the data quality and integrity in the retrospective study can be assessed by a careful review of the study report the same is not true for the meta-analysis. Each published article used in the meta-analysis contains much less information than a full study report. In journal articles the emphasis is usually placed on the final results with only a very brief discussion of how those results were obtained. The agency would have no access to the underlying raw data. To the extent that the quality of the data in each article can be assessed, it is likely to vary significantly from article to article. For these reasons it would be extremely difficult to attempt to assess the integrity and quality of the data used in the meta-analysis

Compliance with Good Clinical Practices

Study: MBG308 was conducted in compliance with Good Clinical Practice according to the JCH Harmonized Tripartite Guidelines

In a retrospective study, compliance with good clinical practice can be assessed by a careful review of the study report. With papers published in the literature there is usually insufficient information to make such an assessment. Compliance with good clinical practice is likely to vary significantly between the articles used in the meta-analysis.

4.6 Financial Disclosures

A financial disclosure form has been submitted and signed by the GE associate director of clinical operation, certifying that no financial arrangements have been made with any of the investigators at any of the study centers, or with any of the readers or expert panel participants at the core laboratory. A complete list of investigators, readers and panel members has been provided.

5 Clinical Pharmacology

I-123-MIBG is chemically and pharmacologically identical to I-131-MIBG MIBG is a norepinephrine analog so I-123-MIBG is taken up by adrenergic nerve endings and by neuroendocrine tumors by the norepinephrine transporter system

5.1 Pharmacokinetics

I-123 MIBG is chemically and physiologically identical to I-131-MIBG so pharmacokinetics is identical to that of I-131-MIBG

5.1.1 Human dosimetry
From data contained in report ICRP1998 for a prescribed dose of 10 mCi (370 MBq), the organ receiving the highest dose is the liver with a radiation absorbed dose of 24.8 mGy (2.48 rad) in a 70 kg man. The bladder wall would receive 17.8 mGy and the spleen 7.4 mGy. The effective

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dose is 4.8 mGy. Since dose is scaled by body weight in children organ doses should be similar in pediatric patients with neuroblastoma

,5.2 Pharmacodynamics

I-123-MIBG is taken up by neural crest tumors by the norepinephrine transporter system. I-123 emits a gamma that can be used for gamma camera imaging of these tumors. The pharmacodynamics of I-123-MIBG is thus identical to the pharmacodynamics of I-131-MIBG except for two important differences: I-123-MIBG does not emit a beta and will therefore deposit less energy in the region of uptake and I-123 emits a lower energy photon than I-131-MIBG which may affect the quality of the image

5.3 Exposure-Response Relationships

The mass dose of MIBG is sub pharmacological so no pharmacological response is expected. To obtain a usable image a minimum of activity is necessary to produce enough photons in a reasonable imaging time to produce a readable image. Image quality per se is not assessed in this study

Cancer risk from radiation is believed to vary linearly with dose. The risk is so small that it can only be assessed quantitatively in large exposed populations as at Hiroshima. The risk is minimized by keeping the dose as low as reasonably achievable (ALARA). The sponsor has performed no dose ranging studies. The sponsor is using a dose of 370 MBq (10 mCi) I-123-MIBG for patients weighing ——————————

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Dosing is based on the European experience with I-131-MIBG.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

I-123-MIBG is indicated for the detection of primary or metastatic pheochromocytomas and neuroblastomas

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Reviewer's comment. This indication does not address the ability of the scan to provide spatial information but only to provide a diagnosis. The proposed product labeling and the endpoint in the prospective clinical study also refer to diagnosis only and not to spatial information

6.1.1 Methods

There are two sources of efficacy data
1) MBG308 A prospective Phase 3 clinical study of 251 subjects with neuroblastoma or pheochromocytoma imaged with I-123-MIBG
2) MBG304 A retrospective meta-analysis of published data on imaging with I-123-MIBG.ince it is impossible to combine data from these two disparate sources the data for each study will be considered separately

The results of studies MBG308 and study MBG304 are described below. Detailed descriptions of the designs of studies MBG 308 and MBG 304 are found in section 10.1 of this review

Study MBG308

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for study MBG 308 was sensitivity and specificity of the central blinded read of the I-123 MIBG scans in detecting or ruling out active tumor. The standard of truth comparator was current histology if available. If current histology was not available, the presence or absence of active tumor was determines by an expert panel of two oncologists who reviewed all available clinical information with the exception of the I-123-MIBG scans being evaluated. There were separate expert panels for neuroblastoma and pheochromocytoma. The pre-determined statistical target was for the lower bound of the confidence interval for both sensitivity and specificity greater than 80% Efficacy was deemed to be demonstrated if this endpoint had been achieved for two out of three readers. Secondary endpoint was sensitivity and specificity for the combined reading of the planar and SPECT images in those subjects who had both planar and SPECT images

6.1.3 Study Design

This is a Phase 3 open label multicenter Phase 3 scintigraphy study to assess the ability of blinded readers of planar I-123-MIBG scans to confirm or rule out the presence of active neuroblastoma or pheochromocytoma. No assessment of the

ability of the readers to determine spatial information (tumor location, tumor size, presence or absence of metastases etc.) is made in the analysis of data from this study A detailed discussion of the study design of study MBG308 is contained in section 10.1 of this review

6.1.4 Efficacy Findings

A total of 101 patients with confirmed or suspected neuroblastoma and 154 patients with confirmed or suspected pheochromocytomas were recruited at 27 study centers. 251 patients (100 neuroblastoma and 151 pheochromocytoma) were dosed with I-123-MIBG, were imaged and were evaluable for safety. 250 patients were evaluable for efficacy Image quality was assessed for all 250 patients by the blinded readers. Images were classified as either Optimal diagnostic (O), Suboptimal Diagnostic (S) or non-diagnostic (N)

Patient Disposition

Table 1 Patient disposition MBG308			
Patient group	Total	Neuroblastoma	Pheochromocytoma
Total enrolled	255	101	154
Enrolled but not dosed	4	1	3

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Dosed and evaluable for safety	251	100	151
Completed study but ineligible for efficacy evaluation (wrong diagnosis)	1		1
Evaluable for efficacy	250	100	150
Indeterminate gold standard Diagnosis (GSD)	39	Type of tumor not specified if GSD is indeterminate	
Dosed, imaged and with Determinate (GSD)	211	Population for which sensitivity and specificity can be calculated	
GSD Active tumor present Database for Sensitivity	159	92*	57*
GSD No Active tumor present Database for specificity	52	Type of tumor not specified if GSD is no active tumor	

* for gold standard diagnosis of active tumor present type of tumor is determined by gold standard diagnosis

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\Demographics

Table 2 Demographics MBG308			
Characteristics	Total N=251	Neuroblastoma N= 100	Pheochromocytoma N = 151
AGE: Mean ± SD	31.4 ± 24.9	4.7 ± 6.9	49 ± 14.7
Range	0.08* -88	0.08 – 58	17 - 88
Male/Female	119/132	57/43	62/89
Race			
White	220	88	132
Black	12	4	8
Asian	3	0	3
Other	16	8	8
Weight (kg) range	3 -168	3 -91	47 -168
Height (cm) range	49 - 197	49 - 178	142 - 197

- 0.08 year = 1 month

Reviewer's comment: The difference in age distribution between neuroblastoma patients and pheochromocytoma patients reflects the fact that neuroblastoma is a disease of young children while pheochromocytoma is an adult disease

Image Quality

MBG308 Table 3 Blinded Reader Assessment of **Planar Image** Quality: Reader A							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	250	243	97.2%	6	2.4%	1	0.4%
Neuroblastoma	100	98	98%	1	1%	1	1%
Pheochromocytoma	150	145	96.7%	5	3.3%	0	0%

Sponsor's table 14.2.1.1

MBG308 Table 4 Blinded Reader Assessment of Planar Image Quality: Reader B							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	250	189	75.6%	61	24.4%	0	0%
Neuroblastoma	100	79	79.0%	21	21%	0	0%
Pheochromocytoma	150	110	73.3%	40	26.7%	0	0%

MBG308 Table 5 Blinded Reader Assessment of **Planar Image** Quality: Reader C							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	250	244	97.6%	5	2%	1	0.4%
Neuroblastoma	100	96	96%	3	3%	1	1.0%
Pheochromocytoma	150	148	98.7%	2	1.3%	0	0%

Reviewer's Comment: Readers A and C consistently rate more than 95% of images as optimal, whereas for reader B it is closer to 75%. The reason for this difference is not clear. Since the presumed advantage of I-123-MIBG over I-131-MIBG is better image resolution the results for readers A and C is encouraging. Of course there is no direct comparison of I-123-MIBG images ands I-131-MIBG images in this study. It is not clear whether which readers had had the majority of their clinical experience with I-131-MIBG, the currently approved product in the US, or with I-123-MIBG, which, according to the sponsor, although not yet approved, is readily available in the US. A reader's previous experience could influence his/her assessment of image quality Assessment of image quality for neuroblastoma appears to be similar to that for pheochromocytoma for all 3 readers

For assessing the image quality of SPECT images, the images of 200 patients who had had both planar and SPECT images were evaluated.

b(4)

MBG308 Table 6 **Planar + SPECT** Image Quality: Reader A							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	200	147	73.5%	38	19%	15	7.5%
Neuroblastoma	51	42	82.4%	6	11.8%	3	5.9%
Pheochromocytoma	149	105	70.5%	32	21.5%	12	8%

Sponsor's table 14.2.1.2

MBG308 Table 7 **Planar + SPECT** Image Quality: Reader B							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	200	147	73.5%	38	19%	15	7.5%
Neuroblastoma	51	45	88.2%	6	11.8%	0	0%
Pheochromocytoma	149	102	68.5%	32	21.5%	15	31.9%

MBG308 Table 8 **Planar + SPECT** Image Quality: Reader C							
		Optimal		Sub-optimal		Nondiagnostic	
Group	N	n	%	n	%	n	%
All patients	200	131	65.5%	50	25%	19	9.5%
Neuroblastoma	51	44	86.3%	5	9.8%	2	3.9%
Pheochromocytoma	149	87	58.4%	45	30.2%	17	11.4%

Reviewer's Comment: In general the Planar image sets were accorded higher quality scores than the Planar + SPECT image sets, particularly by readers A and C. This may be due to either of two causes
1) The readers set a higher quality standard for the planar + SPECT image sets than for the Planar images alone
2) Compared to what the readers were used to, the SPECT images in general were of poorer quality than the Planar images
If the term "Non-diagnostic" is taken literally to mean "not able to make a diagnosis from the scan" the results are somewhat puzzling because all three readers were unable to make a diagnosis for a larger number of patients from the Planar + SPECT image sets than from the Planar images alone. One would think that when more information is provided, a diagnosis could be made for more patients not less. The Planar + SPECT will not reflect the primary efficacy outcome of the trial since the primary efficacy outcome variable was based on the planar images alone

b(4)

Abnormalities Seen

MBG308 Table 9 Abnormality seen Planar Images							
		Reader A		Reader B		Reader C	
Group	N	yes	no	yes	no	yes	no
All patients	250	163	86	179	71	210	39
Neuroblastoma	100	66	33	75	25	78	20
Pheochromocytoma	150	97	53	104	46	132	18

Sponsor's table 14.1.2.3

MBG308 Table 10 Abnormality seen Planar + SPECT Images							
		Reader A		Reader B		Reader C	
Group	N	yes	no	yes	no	yes	no
All patients	200	138	48	141	49	154	27
Neuroblastoma	51	35	13	38	13	41	8
Pheochromocytoma	149	103	35	103	36	113	19

Sponsor's table 14.2.1.4

Reviewer's Comment: In general there were fewer abnormalities seen in the planar + SPECT image sets than in the planar images although one would imagine that metastases that could not be seen in the planar images might be detected in the SPECT images. This result is however consistent with the results for image quality

MBG308 Table 11 Change in number of abnormalities (increase or decrease) seen planar to planar +SPECT							
		Reader A		Reader B		Reader C	
Group	N	I	D	I	D	I	D
All patients	200	50	42	45	49	31	110
Neuroblastoma	51	9	13	9	12	9	19
Pheochromocytoma	149	41	29	36	37	22	91

I = increase D = Decrease Sponsor's table 14.2.1.7

Reader's Comment: It would be more clinically relevant to know how many readings went from single abnormality to multiple abnormalities (or visa versa) in going from planar to SPECT. A single abnormality could indicate primary tumor

b(4)

only while multiple abnormalities would represent primary plus metastases, a clinically significant change in diagnosis

MBG308 Table 12 Did **SPECT images** provide additional diagnostic value?										
		Reader A			Reader B			Reader C		
Group	N	yes	no	MD	yes	no	MD	yes	no	MD
All patients	200	87	100	13	92	98	10	77	104	19
Neuroblastoma	51	26	23	2	33	18	0	21	28	2
Pheochromocytoma	149	61	77	11	52	87	10	53	79	17

MD = missing data Sponsor's table 14.2.1.8

200/250 (80%) of patients had both planar and SPECT images
51/100 (51%) of patients with neuroblastoma and 149/150 (99.3%) patients with pheochromocytoma had both planar and SPECT images

Reviewer's comment: The smaller number of patients with SPECT scans in the neuroblastoma group probably reflects the difficulty in obtaining SPECT scans on very young children. In those patients who had SPECT scan, all three readers found that SPECT provided additional information over planar images in about half of the patients. Although the readers found that the SPECT images provided additional diagnostic value this did not translate into more abnormalities seen on the planar + SPECT image sets

Reviewer's comment: Note that of 150 evaluable patients with Neuroblastoma, 149 had both planar and SPECT images whereas of 100 patients with neuroblastoma, only 51 had both planar and SPECT images. These numbers are consistent with the hypothesis that the primary reason for not getting SPECT images was the difficulty in immobilizing very young children for the scan

159 patients had a gold standard diagnosis of active tumor, 52 subjects had a diagnosis of no active tumor and 39 were indeterminate. The 211 patients with a diagnosis of either active tumor or no active tumor formed the intent to diagnose patient group for planar imaging which was analyzed for efficacy. 167 of these patients had also had SPECT images and formed the intent to diagnose group for SPECT. None of the patients with a gold standard diagnosis of indeterminate had had a diagnosis by current histology. Evaluation of sensitivity was based on the

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159 patients with a gold standard diagnosis of active tumor and specificity was based on the 52 patients with a diagnosis of no active tumor as given in table 13 below

MBG308 Table 13 Gold standard diagnoses								
		Active tumor present			Type of tumor			Diagnosis Indeterminate
Gold standard type	N	yes	no		P	N	O	
All Patients	250	159	52		92	67	0	39
Histology	50	42	8		22	20	0	0
Expert panel	200	117	44		70	47	0	39

P = Pheochromocytoma, N = Neuroblastoma, O = Other table14.2.2.1

Reviewer's Comment: Of the 250 evaluable for Efficacy, 211 patients had a definitive gold standard diagnosis (159 active tumor, 52 no active tumor) and 39 had a gold standard diagnosis of indeterminate. Calculation of sensitivity and specificity could only be done for the 211 patients with a definitive gold standard diagnosis. Sensitivity was calculated for the 159 patients with a gold standard diagnosis of active tumor and Specificity was calculated for the 52 patients with a gold standard diagnosis of no active tumor

Table 14 MBG308 Primary Outcome Variable, Sensitivity and Specificity for **Planar Images**			
	Reader A	Reader B	Reader C
Sensitivity			
N	159	159	159
Point estimate	0.80	0.77	0.79
95% confidence Interval	0.73-0.86	0.70-0.84	0.71-0.85
Specificity			
N	52	52	52
Point estimate	0.77	0.73	0.69
95% confidence Interval	0.63-0.87	0.59-0.84	0.55-0.81

Sponsor's Table 14.2.5

Prospectively, the result that would demonstrate efficacy would be a lower bound of the confidence interval for both sensitivity and specificity of ≥ 80% for two out

of three readers for the planar scans. It is clear that this lower bound of 80% was not achieved for either sensitivity or specificity for any of the three readers

MBG308 Table 15 Sensitivity and Specificity for **Planar Images** for the patients with "current" histology			
	Reader A	Reader B	Reader C
Sensitivity N = 81			
Point estimate	0.88	0.85	0.84
95% confidence Interval	0.78-0.94	0.76-0.92	0.74-0.91
Specificity N = 15			
Point estimate	0.80	0.60	0.73
95% confidence Interval	0.52-0.96	0.32-0.84	0.45-0.92

Sponsor's Table 14.2.9.1

Reviewer's comment: For those patients whose gold standard diagnosis was based on current histology, the point estimates for sensitivity and specificity were higher than for the whole patient group. However because of the smaller number of patients, the lower bounds of the confidence interval did not change much for sensitivity and actually decreased for specificity. It is thus possible that if ALL of the patients in the entire study had had a histological gold standard diagnosis, the prospective condition for demonstrating efficacy might have been met.

MBG308 Table 16 Primary Outcome Variable, Sensitivity and Specificity **Planar + SPECT Images** for the Population with SPECT images			
	Reader A	Reader B	Reader C
Sensitivity			
N	125	125	125
Point estimate	0.76	0.78	0.80
95% confidence Interval	0.68-0.83	0.70-0.85	0.71-0.87
Specificity			
N	42	42	42
Point estimate	0.52	0.57	0.55
95% confidence Interval	0.36-0.68	0.41-0.72	0.39 -0.70

Sponsor's table 14.2.6

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Reviewer's comment: Comparing the results for planar and for planar + SPECT image sets, it appears that sensitivity is similar for all three readers but specificity is lower for all three readers for the Planar + SPECT images than for the planar images. These results are not consistent with the hypothesis that adding SPECT images to the planar image set would provide the reader with additional information that would result in more accurate diagnoses

Study: MBG304

Study Type: Retrospective Meta-Analysis
Study Title: A Meta-Analysis Study to Evaluate Performance of I-123-MIBG Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma
Objective: To evaluate the performance of I-123-MIBG imaging for the detection of neuroblastoma and pheochromocytoma at the subject level
Study Procedure:
A computerized literature search was performed using computerized databases of medical articles such as PUB Med. Articles sought were published between 1980 and 2004, and described clinical diagnostic imaging studies using MIBG and involved I-123 imaging of pheochromocytomas, neuroblastoma, MCT (medullary carcinoma of the thyroid), carcinoid tumors or paragangliomas. 1274 published articles were identified by the computerized search. These articles were screened by two nuclear medicine physicians using inclusion –exclusion criteria:

Inclusion criteria

1) diagnosis of neuroblastoma, pheochromocytoma, paraganglioma, MCD or carcinoid
2) Gold standard diagnosis from histology or acceptable combination clinical, laboratory and imaging data for all subjects who receivedI-123-MIBG
3) Provided sufficient data to calculate sensitivity and specificity at the subject level
4) If both I-123-MIBG and I-131-MIBG were used in the study the articled distinguished between the results of the two

Exclusion criteria

1) Less than 16 subjects in the study
2) I-123-MIBG results based on more than one scan
3) Article dealing with multiple tumor types with results not distinguishable by tumor type

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A total of 19 articles were identified as meeting all of the inclusion and exclusion criteria

Table 21 Articles Included in Meta-analysis				
Study Number	Country	# of subjects	Injected activity	Blinding
Carcinoid				
#1 (1037)	UK	24	130-185 MBq	Not mentioned
#2 (1050)	Germany	28	185 MBq	Not mentioned
Neuroblastoma				
#3 (1005)	Japan	33	111 MBq	Not mentioned
#4 (1007)	Germany	22	Not stated	Not mentioned
#5 (1020)	Switzerland	27	Not stated	Not mentioned
#6 (1041)	Japan	19	37-74 MBq	Not mentioned
#7 (1046)	Germany, Sweden, Austria	88	Not stated	Not mentioned
#8 (1057)	Spain	20	Not stated	Not mentioned
#9 (1082)	France	27	Not stated	Not mentioned
Paraganglioma				
#10 (1053)	Italy	50	185 MBq	Not mentioned
Pheochromocytoma				
#11 (1022)	France	63	Not stated	Not mentioned
#12 (1036)	USA	120	370 MBq	Not mentioned
#13 (1056)	Granada	20	Not stated	Not mentioned
#14 (1058)	France	80	Not stated	Not mentioned
#15 (1060)	USA	48	Not stated	Not mentioned
#16 (1085)	Italy	284	Not stated	Not mentioned
#17 (2014)	Denmark	30	185 MBq	Not mentioned
#18 (2044)	Spain	30	Not stated	Not mentioned
#19 (2071)	UK	31	370MBq	Not mentioned

Table 6 MBG304 Study Report

Reviewer's comment: There are several conclusions that can be made from the above table:

1) *Since blinding is not mentioned for any of these studies we should consider these studies to have had un-blinded reads. In ordinary clinical practice as opposed to controlled clinical studies, image readers are not blinded to other clinical data since the objective is to obtain an accurate diagnosis based on all available information for the purpose of patient management*
2) *To be supportive of a marketing application data should be presented on subjects who have received the recommended dose of the drug to study safety and efficacy at the recommended dose. Only in the two US studies did all subjects receive the recommended dose of 370 MBq (10 mCi) In fact in the Sponsor's table 6 in the study report the injected activity is not stated for 11 of papers probably because it was not specified in the underlying papers themselves. A dose of 370MBq (the recommended dose for Planar + SPECT) is listed for the two US studies which may mean that both planar and SPECT scans were obtained and read in these studies. The two Italian studies and the German*

study used 185 MBq, the recommended dose for planar imaging, while the doses for the three other studies where the dose was listed ranged from 37 to 185 MBq. Many of the studies were small studies with as few as 19 patients in the study

Primary Efficacy Endpoint

1) Sensitivity and specificity at the subject level for correctly identifying subjects with and without neuroblastoma
2) Sensitivity and specificity at the subject level for correctly identifying subjects with and without neuroblastoma

The numbers of true positives, true negatives, false positives were obtained for each study and sensitivity and specificity for the study were calculated. Meta-analysis was used to obtain overall estimates of sensitivity and specificity using SAS and Proc-StatXact software. Actually two separate Meta-analyses were preformed , one for neuroblastoma and the other for pheochromocytoma

Reviewer's Comment: This medical reviewer is not commenting on the quality or the applicability of the meta-analysis methods used. This issue will be addressed in the statistical review

Meta-analysis results

Table 22 Meta-Analysis Results Fixed Effect Model					
	Sensitivity		specificity		
	Point estimate	Confidence interval	Point estimate	Confidence interval	Number of studies
pheochromocytoma	96%	93%-99%	95%	93%-97%	6
neuroblastoma	97%	95%-99%	Could not be estimated		7

Table 8, MBG304 study report

Reviewer's Comment: Several points should be noted in comparing the results of MBG304 to MBG308:
1) In MBG308 the primary outcome variable was sensitivity and specificity for the entire patient group. In MBG304, sensitivity and specificity were calculated for each tumor type (neuroblastoma or pheochromocytoma) separately

2) The estimates of sensitivity and specificity in MBG304 are much higher than those of MBG308. The sponsor attributes this to "publication bias", only the most positive results are published. There may have been another important reason. The papers used in the meta-analysis do not state whether the readers were blinded. In ordinary clinical practice readers are not blinded and it is therefore likely that readers were not blinded in most of these papers. Un-blinded readers, having more information are more likely to make an accurate diagnosis that blinded readers. It is even possible that readers had access to information that was included in

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the "gold standard". Histology, other test results etc. It would be understandable that unblinded readers would have higher sensitivity and specificity than blinded readers. One would also not expect the results of a meta-analysis to be as accurate as the results from a single large well designed study

6.1.6 Efficacy Conclusions (see 9.1 Conclusion in the Overall Assessment)

7 INTEGRATED REVIEW OF SAFETY

I-123-MIBG is chemically, and pharmacologically identical to I-131-MIBG. Therefore the pharmacological toxicity profile should be identical to that of I-131-MIBG which has been approved in the US for imaging neuroendocrine tumors for almost 20 years. At diagnostic doses, no pharmacological toxicity of I-131-MIBG has been encountered in either clinical studies or in post marketing surveillance. The radiation toxicity of I-123-MIBG should be less than that of I-131-MIBG since, at the recommended dosages, the effective dose of I-123-MIBG is less. In addition, I-123-MIBG has been approved in Europe as an imaging agent for several years and is known to have a benign safety profile

7.1 Methods and Findings

Dosimetry of I-123 MIBG and I131-MIBG

The sponsor has used biodistribution data for I-131-MIBG from ICRP publication #53 to calculate dosimetry tables for I-123-MIBG. Since I-123-MIBG and I-131-MIBG are chemically and pharmacologically identical, biodistribution and pharmacokinetics for the two drugs should be identical and can be used interchangeably in dosimetry calculations.

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Table 23 Dosimetry of I-123-MIBG and I-131-MIBG at the recommended doses (adults)				
Organ	I-123 recommend dose 10 mCi		I-131 recommended dose 0.5 mCi*	
	rad/mCi	rad/10 mCi	rad/mCi	Rad/0.5 mCi
Bladder wall	.024	.24	2.8	1.4
Liver	.24	2.4	2.9	1.45
Spleen	.074	0..74	2.2	1.1
Heart wall	.066	0.66	0.3	.15
Adrenals	.059	0.59	0.8	.4
Gallbladder wall	.074	0.74	0.5	.25
Pancreas	.044	0.44	0.3	.15
Thyroid	.017	0.17	0.3	.15
Kidneys	.048	0.48	0.3	.15.
Uterus	.047	0.47	0.3	.15
Ovaries	.029	0.29	0.3	0.15
Testes	.02	0.2	0.2	0.1
Brain	.014	.14	0.2	0.1
Effective dose	.052	.52	0.7	0.35

- I-131 dosimetry taken from package insert
- I-123 dosimetry from sponsor's [redacted]

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Reviewer's comment: For the recommended injected activities, the doses to individual organs are similar for I-131-MIBG and for I-123-MIBG (the bladder wall may be an exception but the dose to the bladder wall is highly dependent on assumptions made about voiding. The Effective dose for I-123 is higher than that for I-131.

7.1.1 Deaths

There were no deaths reported

7.1.2 Other Serious Adverse Events

One serious adverse event was reported. A 50 year old male with a history of Wolff-Parkinson-White syndrome developed 2 episodes tachycardia before dosing. After dosing he was hospitalized for stabilization of the tachycardia that developed before dosing. In the investigator's opinion this SAE was unrelated to the study drug

Reviewer's comment: If the patient developed a tachycardia before dosing that was severe enough to be subsequently determined to require hospitalization for stabilization, he should have been dropped from the study and not dosed or imaged

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7.1.3 Dropouts and Other Significant Adverse Events

Of 255 patients entered 4 patients dropped out of the study before dosing for reasons unrelated to the study drug. Of the 251 subjects dosed one was not evaluated for efficacy because of an error in diagnosis. There were no other study dropouts

7.1.3.1 Overall profile of dropouts

No patients dropped out after dosing

7.1.3.2 Adverse events associated with dropouts

No patients dropped out after dosing

7.1.3.3 Other significant adverse events

In the 251 patients dosed there was one unrelated SAE.

7.1.4 Other Search Strategies

No other search strategies were applied.

7.1.5 Common Adverse Events

There were also 16 mild to moderate AEs among 13 patients (5%). 15/17 were considered by the investigators to be unrelated to the study drug There were 2 cases of injection site hemorrhage and 2 cases of dizziness. Other AEs included asthenia, pain, dysgeusia, thrombocytopenia, bradycardia, abdominal distension, peripheral edema, candidiasis, constipation, diarrhea, pruritis, macular rash, and flushing. 12 AEs were mild and 5 were moderate.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were categorized using MEDRA preferred terms

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7.1.5.3 Incidence of common adverse events

Table 24 Adverse events using MEDRA terminology, Study: MBG308		
Body system	AE	# of patients with AE
Blood and lymphatics	Thrombocytopenia	1
Cardiac	Bradycardia	1
Gastrointestinal	Abdominal distension	1
	Constipation	1
	Diarrhea	1
General	Asthenia	1
	Injection site hemorrhage	2
	Peripheral edema	1
Infections	Candidiasis	1
Nervous system	Dizziness	2
	Dysgeusia	1
Skin	Pruritis	1
	Macular rash	1
Vascular	Flushing	1

7.1.5.4 Common adverse event table

The most common adverse events were injection site hemorrhage and dizziness with 2 patients each

7.1.5.5 Identifying common and drug-related adverse events

All AEs were uncommon. Injection site hemorrhage and dizziness occurred in 2 patients each (0.8%) All other AEs occurred in one patient each (0.4%)

7.1.5.6 Additional analyses and explorations

The numbers were too small for additional explorations

7.1.6 Less Common Adverse Events

All AEs were uncommon. Injection site hemorrhage and dizziness occurred in 2 patients each (0.8%) All other AEs occurred in one patient each (0.4%)

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7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Table 25 Safety Monitoring, Study: MBG308							
	Pre-Dose			Dosing	Post dose		
	baseline	-1 hr	- 5 min		immediate	30 min	24 hr
Informed consent	x						
Pregnancy test		x					
Check Inclusion-exclusion criteria	x						
history	x						
Clinical laboratory tests (CBC Chemistries etc.)	x					x	x
Limited physical exam	x	x				x	x
Thyroid blockade		x					
I-123-MIBG				x			
Injection site monitoring			x	x	x	x	x
12 lead EKG	x		x		x	x	x
Vital signs	x		x		x	x	x
Planar Imaging ± SPECT							x
AE Monitoring	X*	X*	X*	x	x	x	x

*Pre-existing signs and symptoms would not be attributed to the drug if they also occurred after dosing

Study MBG 304 was a retrospective meta-analysis of published data. For each publication, patient safety monitoring was performed in accordance with each individual institution's practice.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

MBG308 was an open label study; there was no control group

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were only 2 patients with changes in laboratory values considered to be adverse events. There was one case of tachycardia attributed to a pre-existing arrhythmia and one case of bradycardia in a 10 month old male attributed to sedation required for imaging.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no dropouts among patients who had been dosed

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

There were 2 changes in vital signs considered to be AEs. One was the tachycardia listed above as an SAE.
The other was a 10 month old male who experienced bradycardia of 83 BPM compared to the lower limit of normal for that age of 85BPM his baseline HR was 112BPM ands at discharge his HR was 95 BPM. Tachycardia was attributed by the investigator to sedation and was considered to be unrelated to the study drug

Reviewer's comment Patients with active neuroendocrine secreting tumors would be expected to have higher than normal BP and HR and indeed patients with a gold standard diagnosis of active tumor had higher average heart rate and systolic and diastolic blood pressures. However mean values of all three parameters showed only minimal change from baseline in both active tumor and no active tumor subgroups

7.1.8.1 Overview of vital signs testing in the development program

There was 1 prospective study in the development program. Vital sign testing for study MBG308 is given in table 19 in the study report, and the review of the table has not revealed any safety signals.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

There were no controlled studies in this submission

7.1.8.3 Standard analyses and explorations of vital signs data

No systematic changes in vital signs post dosing were noted

7.1.8.3.1 Analyses focused on measures of central tendencies

No systematic changes in vital signs post dosing were seen. There were no individual clinically significant vital sign abnormalities that were attributed to the study drug

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Only 1 abnormal laboratory value was reported as an AE. An 18 month male with neuroblastoma had a platelet count of 53 which remained low throughout treatment and the followup period.

The low platelet count was attributed to the patient's neuroblastoma and was considered unrelated to the study drug.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts for vital sign abnormalities. There were two changes in vital signs considered to be AEs, one case each of tachycardia and bradycardia. Both were attributed to causes other than the study drug by the respective investigators

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Scheduling of EKGs in study MBG308 is given in table 19

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

There was no control group in study MBG308

7.1.9.3 Standard analyses and explorations of ECG data

EKGs were read by a board certified central laboratory cardiologist

7.1.9.3.1 Analyses focused on measures of central tendency
There were no systematic changes in EKG parameters

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities
There were no dropouts due to EKG abnormalities
There were two outliers considered to be AEs, one case of tachycardia and another case of bradycardia. Neither case was attributed to the study drug

7.1.9.4 Additional analyses and explorations

None

7.1.10 Immunogenicity

Two instances of allergic reactions have been reported in the European post marketing experience, one case of facial flushing (which may have been caused by the carcinoid tumor) and one case of rash on both arms. Both events were self-limiting and resolved spontaneously.

7.1.11 Human Carcinogenicity

All radioactive drugs are carcinogenic. Carcinogenicity is minimized by keeping the dose of injected activity as low as reasonably achievable (ALARA)

7.1.12 Special Safety Studies

There were no special safety studies in this submission

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no abuse potential with this drug

7.1.14 Human Reproduction and Pregnancy Data

All radioactive drugs have teratogenic potential

7.1.15 Assessment of Effect on Growth

I-123-MIBG is administered to adults with pheochromocytoma and to children with neuroblastoma. The adults are past their years of growth potential and since the neuroblastoma patients have a relatively short life expectancy the effect on growth is hard to assess. It would also be difficult to isolate the effect of the study drug from that of the disease itself and from the effect of the chemotherapy agents and/or external beam radiotherapy that are often part of these patient's treatment

7.1.16 Overdose Experience

Because radiopharmaceuticals are always assayed for radioactivity immediately before administration, there is little or no overdose experience. No overdoses were reported in study MBG308. There were no postmarketing reports of overdosing

7.1.17 Postmarketing Experience

I-123-MIBG is approved as an imaging agent in Europe. As of August 31, 2006, I-123-MIBG had marketing approval in:

The Netherlands

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Switzerland
United Kingdom
Denmark
Germany
France
Norway
And marketing applications were submitted in:

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From September 1, 2001 through August 31, 2006, —— patients were exposed to I-123-MIBG. During that period two adverse events (0.0085%) were reported to the sponsor by medical professionals. Both events were allergic reactions. A 55 F with carcinoid tumor, received 375 MBq (10 mCi) I-123-MIBG and developed, 23 minutes post injection shivering, dyspnea nausea and facial edema, which according to the investigator could have been due to carcinoid flush. A 40 M received 400 MBQ (10.8 mCi) I-123-MIBG developed a rash on the underside of both arms 3hours after injection. The rash resolved spontaneously after 24 hours

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7.2 Adequacy of Patient Exposure and Safety Assessments

In addition to the 251 patients in study MBG308, from September 1, 2001 through August 31, 2006, —— patients were exposed to I-123-MIBG, post-marketing in Europe. The retrospective meta-analysis Study MBG304 is based on the European post-marketing experience with I-123-MIBG. I-131-MIBG is approved as an imaging agent in the US. Since I-123-MIBG and I-131-MIBG have identical chemical and pharmacological properties the pharmacological toxicity of both drugs should be the same

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7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

There was a single prospective Phase 3 study with 251 exposed patients
From September 1, 2001 through August 31, 2006, ——— patients were exposed to I-123-MIBG, post-marketing in Europe.

b(4)

7.2.1.1 Study type and design/patient enumeration

There was a single prospective Phase 3 study with 251 exposed patients

7.2.1.2 Demographics

See table 2

b(4)

7.2.1.3 Extent of exposure (dose/duration)

All subjects received the same dose of 10 mCi except for patients under 55 kg whose dose was adjusted for body weight in study MBG308

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Clinical experience with I-131-MIBG, an approved product, is supportive of safety of I-123-MIBG since both products are identical chemically and pharmacologically

7.2.2.1 Other studies

There was only one prospective Phase III study submitted

7.2.2.3 Literature

A literature review has been used to provide an estimate of sensitivity and specificity by meta-analysis

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience reported included a single Phase 3 trial with 251 patients and European post-marketing experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no animal data in this submission

7.2.5 Adequacy of Routine Clinical Testing

Safety evaluations in study MBG308 were adequate

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Diagnostic radiopharmaceuticals have little potential for toxicity because of the small mass dose and the small radiation absorbed doses to individual organs

7.2.8 Assessment of Quality and Completeness of Data

Data was submitted from only a single Phase 3 clinical study

b(4)

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were only 17 adverse events among 251 exposed patients in the Phase 3 clinical trial only 2/17 were believed to be drug related

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was only one prospective phase 3 study

7.4.1.1 Pooled data vs. individual study data

Data from a prospective study and from a retrospective meta-analysis can not be pooled

7.4.1.2 Combining data

Data from the prospective study and from the meta-analysis can not be combined

7.4.2 Explorations for Predictive Factors

Because there were so few AEs related to the drug, exploration of predictive values was not possible

7.4.2.1 Explorations for dose dependency for adverse findings

All subjects received the same dose of 10 mCi except for patients under 55 kg whose dose was adjusted for body weight

7.4.2.2 Explorations for time dependency for adverse findings

Late radiation toxicity is known to take from 6 months to more than a year after treatment to appear. However it is highly unlikely that any late radiation toxicity would occur with a diagnostic dose of I-123-MIBG

7.4.2.3 Explorations for drug-demographic interactions

There were too few adverse events and too few non-white patients for such an exploration

b(4)

7.4.2.4 Explorations for drug-disease interactions

Since I-123-MIBG is excreted primarily by the kidneys, renal dysfunction could lead to delayed excretion and to a higher whole body radiation dose

7.4.2.5 Explorations for drug-drug interactions

Drugs that interfere with norepinephrine uptake could lead to decreased tumor uptake of I-123-MIBG and to suboptimal images. Patients taking such drugs were explicitly excluded from the prospective clinical study

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

van Santen HM, de Kraker J, van Eck BLF, de Vijder JJM, Vulsma T.
Improved radiation protection of the thyroid gland with thyroxine, methimazole, and potassium iodide during diagnostic and therapeutic use of radiolabeled metaiodobenzylguanidine in children with neuroblastoma. Cancer 2003;98:389-96 (reference provided by the sponsor)

During radiolabeled metaiodobenzylguanidine (MIBG) administration in children with neuroblastoma, the thyroid is protected from 123/131 I uptake by potassium iodide. Despite this protection, up to 64% of patients develop thyroid dysfunction. The authors introduce a new method of radiation protection for the thyroid gland. The results of this study indicate that the combination of thyroxine, methimazole and potassium iodide protect the thyroid more effectively against radiation damage with I-123 or I-131-MIBG administration than potassium iodide alone in children with neuroblastoma

Reviewer's comment: Usage of KI or Lugol's solution for thyroid blockage for administration of I-131-MIBG or I-123-MIBG is a virtual universal practice and id considered adequate even for therapeutic doses of I-131- MIBG It is unlikely that significant radiation damage to the thyroid would occur from a single ***diagnostic*** *dose of I-123-MIBG or I-131-MIBG. For I-123-MIBG the radiation absorbed dose to the thyroid is .0047mGy/MBq. For the prescribed dose of 10 mCi, the thyroid would receive a dose of 0.47 rad. The tolerance dose of the thyroid is 4500 rad*

8.1 Dosing Regimen and Administration

10 mCi IV slow infusion

8.2 Drug-Drug Interactions

Psychotropic drugs which inhibit norepinephrine re-uptake may inhibit tumor uptake of I-123-MIBG. In patients with pheochromocytoma such drugs have been shown to reduce sensitivity from 83% to 52% for I-131-MIBG (I-131-MIBG labeling)

b(4)

8.3 Special Populations

Patients with renal impairment may have delayed excretion of I-123-MIBG increasing the effective dose

8.4 Pediatrics

Pediatric patients with neuroblastoma were studied in MBG308

8.5 Advisory Committee Meeting

An advisory committee meeting is not required

8.6 Literature Review

A literature review was used to perform the meta-analysis in MBG304

8.7 Postmarketing Risk Management Plan

No risk management plan is necessary

8.8 Other Relevant Material

I-131-MIBG labeling

9 OVERALL ASSESSMENT

9.1 Conclusions

I-123-MIBG should be approved for marketing as an imaging agent

I-123-MIBG is safe and effective for imaging pheochromocytoma and neuroblastoma

I-123-MIBG 10mCi IV is safe. With 251 patients dosed in MBG308, only one serious adverse event occurred which was not considered drug related. In addition, there were 16 mild to moderate adverse events of which only two were attributed to the drug by the investigators. There were no systematic changes in vital signs or in EKG parameters. In the European post marketing experience, from September 1, 2001 through August 31, 2006 ——— patients were exposed to I-123-MIBG. During that period two adverse events in 2 patients (0.0085%) were reported to the sponsor by medical professionals. Both events were allergic reactions.

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I-123-MIBG 10mCi IV is effective. Although the prospective efficacy endpoint (lower limit of confidence interval for both sensitivity and specificity >80% for 2 out of 3 readers) was not

b(4)

achieved in study MBG308 (table 14), the lower limits were sufficiently larger than 50% (sensitivity and specificity achieved by pure guessing) to support the conclusion that the imaging agent is effective even though not as effective as predicted. The lower limits for specificity were lower than for sensitivity probably because of the fewer number of negative patients. However if imaging is considered to be a screening test, to be confirmed by biopsy if positive, then sensitivity is more important than specificity. The 80% value was arbitrary in the first place and was probably based on clinical data. In a clinical situation, readers are not blinded but rather are given all relevant clinical information and have access to the patient's chart. A blinded read is thus an artificial situation which might not accurately predict what would happen in an actual clinical situation. One would therefore expect that readers in a clinical situation would achieve significantly better results than blinded readers. This assumption is confirmed by the results of the meta-analysis, MBG-308 where percentage sensitivities and specificities in the high 90s were seen (table 22). It is reasonable to assume that the meta-analysis is a more reliable predictor of what would happen in the clinical situation where readers are not blinded.

Addition of SPECT images to planar images has not improved sensitivity or specificity in this study.

9.2 Recommendation on Regulatory Action

I-123-MIBG 10 mCi IV (adjusted by body weight in children) should be approved for marketing for planar imaging of pheochromocytoma and neuroblastoma.

9.3 Recommendation on Postmarketing Actions

No post marketing actions are required

9.3.1 Risk Management Activity

No risk management activity is required

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required

9.3.3 Other Phase 4 Requests

No other Phase 4 requests need be made

b(4)

9.4 Labeling Review

9.5 Comments to Applicant

b(4)

10 APPENDICES

10.1 Review of Individual Study Reports / Study design

Study: MBG308
Study Design
Study Type: Phase 3 prospective study
Title: An Open Label, Multicenter Phase 3 Scintigraphy Study Assessing I-123-MIBG Uptake in Subjects Being Evaluated for Pheochromocytoma or Neuroblastoma
Study type: Open Label, Multicenter Phase 3 Study
Subjects: 251subjects (179 US, 72 Europe) with known or suspected neuroblastoma or pheochromocytoma at 24 study centers
Objective
Primary: To demonstrate that I-123-MIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnosis of neuroblastoma or pheochromocytoma.
Reviewer's comment: The clinical information provided by a scan does not only include Confirmation/Exclusion of diagnosis, but also spatial information such as location of primary tumor, existence and location of metastases etc. With this objective, the study was not designed to assess the scan's efficacy at providing spatial information
Secondary: To determine the incremental value of SPECT for improving the sensitivity and specificity of I-123-MIBG planar imaging in detecting Pheochromocytoma or Neuroblastoma
To collect safety data on I-123-MIBG
Reviewer's Comment: The collection and evaluation of safety data should always be part of a study's primary objective
Study initiation date: August 2, 2005
Study completion date: September 27, 2006
Study Sponsor: GE Healthcare

STUDY DESIGN
Enrollment Plan
Plan was to enroll:
A minimum of 40 subjects with known or suspected pheochromocytoma
A minimum of 40 subjects with known or suspected neuroblastoma
A minimum of 40 subjects with confirmed tumor
A minimum of 40 subjects confirmed to be without tumor
A minimum of total of 90 subjects in the study
Inclusion Criteria

1) Either age $\geq$ 6 months with known or suspected neuroblastoma or age $\geq$ 18 with known or suspected pheochromocytoma
2) Referred for clinically indicated MIBG scan
3) Negative pregnancy test in females capable of reproduction

Exclusion Criteria:

1) Entry in another clinical trial within 30 days

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2) Known allergy to iodinated contrast agents
3) Other serious life-threatening illness
4) Renal insufficiency (serum creatinine ≥ 3mg/dL)
5) Any medication that would interfere with I-123-MIBG uptake

Study Procedure:

Dosing:

After it is confirmed that a subject has met the inclusion and exclusion criteria, all adult and pediatric subjects with weight ≥ 55 kg received 370 MBq (10 mCi) I-123-MIBG
For subjects with weight < 55kg the dose was scaled to body weight as proposed by the European Association of Nuclear Medicine Pediatric Task Group
The prescribed dose was diluted with 5ml NS, measured with a dose calibrator and injected IV over 30-60 sec.
One hour before I-131-MIBG injection each subject received KI, Lugol's or potassium iodate (100mg iodine, scaled by body weight in children) to block thyroid uptake of iodine

Imaging

At 24± 6 hours after dosing subjects returned to the study site for gamma camera imaging.. Anterior and posterior whole body images were obtained from the head to below the knees. Alternately for studies on children or where whole body imaging is not possible because of equipment limitations overlapping spot images from the head to the knees were obtained. Additional spot images were obtained on some subjects where the investigator ascertained that such images would help in optimal patient assessment. SPECT images of the abdomen and thorax were also obtained on each subject unless either:

1) The investigator has judged that the subject could not tolerate the procedure
2) The investigator has judged that the information that might be obtained from SPECT would be of no clinical value

Reviewer's comment: Subjects judged unable to tolerate the SPECT procedure would likely include young children with neuroblastoma. The judgment that SPECT images would provide no clinically useful information is highly subjective and speculative. The best way to have determined whether the SPECT images would have produced useful information would have been to obtain SPECT images on all subjects who could tolerate the procedures and then let the blinded readers at the core laboratory determine whether these images actually provided useful clinical information

Image Evaluation

Images were first read at the individual study sites and then digital copies were transferred the image core laboratory for blinding. Image sets were presented on a computer screen to the blinded readers in random order. At the core laboratory, images were read by three independent nuclear medicine physicians with experience in nuclear oncology. Readers answered specific questions about the images on an electronic case report form for each image set read. The readers were blinded to clinical information. Each of the three blinded readers reviewed all planar images on each subject and then filled in the Planar CRF for that subject. If that subject has had SPECT imaging, the SPECT Images were then given to the reader who then filled out the Planar + SPECT CRF for that subject. Questions to be answered by the reader on the CRFs for planar images include:

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Are findings on planar films consistent with active tumor yes or no?

Reviewer's Comment: The primary efficacy analysis was based on the reader' answer to the single question above on the planar image case report form. (Not all subjects had SPECT images)

Readers of the Neuroblastoma films were asked to choose one of the answers below:
Primary tumor no metastases
Primary tumor with metastases
Metastases no primary tumor
Readers of Pheochromocytoma films were asked to choose one of the answers below:
Primary adrenal tumor no metastases
Primary adrenal tumor with metastases
Primary extra-adrenal tumor no metastases
Primary extra adrenal tumor no metastases
The same questions were answered on the planar + SPECT CRF when both image sets were read together. The readers were also asked if the SPECT images clarified the tumor location or diagnosis

Reviewer's comment: Spatial information was collected on the case report forms but not used in the primary efficacy analysis. It should be noted that the possibility of metastases without a visible primary tumor is allowed for neuroblastoma but not for pheochromocytoma

Readers were also asked to assess the quality of both the planar and the planar + SPECT image sets as Optimal, Sub-Optimal or Non-Diagnostic, to determine the number of abnormalities seen in each image set and to determine whether the SPECT images assed useful clinical information to the planar image sets.

Efficacy Analysis:

The primary objective of the study was to demonstrate that I-123-MIBG planar scintigraphy was sensitive and specific for confirming or excluding the diagnosis of neuroblastoma and pheochromocytoma

To determine sensitivity and specificity, the reader's answer to the question on the planar image case report form "Are findings on the planar film consistent with active tumor yes or no" was compared to the truth standard for the presence or absence of active tumor. If histology was obtained before imaging and the patient received no therapy between the time of obtaining tissue and the time of imaging then the patient is said to have "current histology" For patients who have "current histology", the histological diagnosis is the truth standard diagnosis

Reviewer's comment: An exception should be made for the case where histology is obtained by gross total excision because in that the surgery may be both diagnostic and therapeutic and the patient may have no gross residual tumor at the time of imaging.

Gold Standard Diagnosis

Expert panel of two oncologists with expertise in one or two tumor types (pheochromocytoma or neuroblastoma) was formed. For patients without current histology the appropriate expert panel reviewed all of the available clinical data on each patient and determined from that data whether active tumor was present. For that patient, the panel's determination wasthe truth standard. Using this gold standard, sensitivity and specificity were calculated for the intent to diagnose population (all subjects who received MIBG and who had a standard of truth diagnosis).

The prospective statistical endpoint that would demonstrate efficacy was a lower bound of the confidence interval for both sensitivity and specificity of greater than 80%

b(4)

Patient Safety monitoring included limited physical exams, injection site monitoring, 12 lead EKGs, vital signs and monitoring for adverse events

Table 20 Safety Monitoring, Study: MBG308							
	Pre-Dose			Dosing	Post dose		
	baseline	-1 hr	- 5 min		immediate	30 min	24 hr
Informed consent	x						
Pregnancy test		x					
Check Inclusion-exclusion criteria	x						
history	x						
Limited physical exam	x	x				x	x
Thyroid blockade		x					
I-123-MIBG				x			
Injection site monitoring			x	x	x	x	x
12 lead EKG	x		x		x	x	x
Vital signs	x		x		x	x	x
Planar Imaging ± SPECT							x
AE Monitoring	X*	X*	X*	x	x	x	x

*Pre-existing symptoms would not be attributed to the drug

Reviewer's Comment: Pregnancy test where appropriate should have been done at baseline to eliminate pregnant patients early. If negative it should be repeated 1 hour before planned dosing

Safety analysis
Adverse events
All AEs reported by the subject or observed by study personnel were recorded on th CRF using MEDRA terminology AEs were classified as serious or non-serious. Non-serious AEs were classified as mild, moderate or severe.

EKGs
12 Lead EKG data was transmitted to an EKG core laboratory where it was interpreted by cardiologist who prepared a written report. For each EKG tracing he report included PR, QRS, QT and RR intervals, wave changes and calculated QTc values

Physical Examination
Physical examinations were performed by qualified physicians. The physician recorded any abnormalities found in general appearance, lungs, cardiovascular system, abdomen , skin and extremities

Study:MBG304
Study Type: Retrospective Meta-Analysis
Study Title: A Meta-Analysis Study to Evaluate Performance of I-123-MIBG Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma

b(4)

Objective: To evaluate the performance of I-123-MIBG imaging for the detection of neuroblastoma and pheochromocytoma at the subject level

Study Procedure:

A computerized literature search was performed using computerized databases of medical articles such as PUB Med. Articles sought were published between 1980 and 2004, and described clinical diagnostic imaging studies using MIBG and involved I-123 imaging of pheochromocytomas, neuroblastoma, MCT (medullary carcinoma of the thyroid), carcinoid tumors or paragangliomas. 1274 published articles identified by the computerized search. These articles were screened by two nuclear medicine physicians using inclusion –exclusion criteria:

Inclusion criteria

1) diagnosis of neuroblastoma, pheochromocytoma, paraganglioma, MCD or carcinoid
2) Gold standard diagnosis from histology or acceptable combination clinical, laboratory and imaging data for all subjects who receivedI-123-MIBG
3) Provided sufficient data to calculate sensitivity and specificity at the subject level
4) If both I-123-MIBG and I-131-MIBG were used in the study the articled distinguished between the results of the two

Exclusion criteria

1) Less than 16 subjects in the study
2) I-123-MIBG results based on more than one scan
3) Article dealing with multiple tumor types with results not distinguishable by tumor type

b(4)

A total of 19 articles were identified as meeting all of the inclusion and exclusion criteria

Table 21 Articles Included in Meta-analysis				
Study Number	Country	# of subjects	Injected activity	Blinding
Carcinoid				
#1 (1037)	UK	24	130-185 MBq	Not mentioned
#2 (1050)	Germany	28	185 MBq	Not mentioned
Neuroblastoma				
#3 (1005)	Japan	33	111 MBq	Not mentioned
#4 (1007)	Germany	22	Not stated	Not mentioned
#5 (1020)	Switzerland	27	Not stated	Not mentioned
#6 (1041)	Japan	19	37-74 MBq	Not mentioned
#7 (1046)	Germany, Sweden, Austria	88	Not stated	Not mentioned
#8 (1057)	Spain	20	Not stated	Not mentioned
#9 (1082)	France	27	Not stated	Not mentioned
Paraganglioma				
#10 (1053)	Italy	50	185 MBq	Not mentioned
Pheochromocytoma				
#11 (1022)	France	63	Not stated	Not mentioned
#12 (1036)	USA	120	370 MBq	Not mentioned
#13 (1056)	Granada	20	Not stated	Not mentioned
#14 (1058)	France	80	Not stated	Not mentioned
#15 (1060)	USA	48	Not stated	Not mentioned
#16 (1085)	Italy	284	Not stated	Not mentioned
#17 (1053)	Italy	50	185 MBq	Not mentioned
#18 (1022)	France	63	Not stated	Not mentioned
#19	USA	120	370MBq	Not mentioned

Sponsor's table 6 (MBG304 Study Report)

Reviewer's comment: The following conclusions can be made from the above table:

1) *Since blinding is not mentioned for any of these studies we should consider these studies to have had un-blinded reads*
2) *To be supportive of a marketing application data should be presented on subjects who have received the recommended dose of the drug to study safety and efficacy at the recommended dose. Only in the two US studies did all subjects receive the recommended dose of 370 MBq (10 mCi)*

b(4)

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REFERENCES

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DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Secondary Clinical Review Memorandum

Date: September 5, 2008

NDA: 22-290 (Letter date 03-21-08; PDUFA goal date 09-19-08)

Product: AdreView (I-123 MIBG)

Drug Class: Radioactive diagnostic agent for gamma-scintigraphy

Sponsor: GE Healthcare

Investigated Use: Detection of neuroendocrine tumors

Primary Clinical Reviewer: Robert Yaes, M.D.

Clinical Team Leader: Alexander Gorovets, M.D.

Recommendation

The team leader concurs with the primary clinical reviewer's overall assessment of the sponsor's application and recommends the approval of AdreView as a radioactive diagnostic agent for the use with gamma-scintigraphy in detection of pheochromocytoma and neuroblastoma.

Review Methods

This review is based on the critical appraisal of the primary clinical review, on the sponsor's Overview and on other excerpts from the application.

Regulatory Background and Product Information

The cold compound in AdreView, MIBG (meta-Iodobenzylguanidine, or Iobenguane), is a false neurotransmitter analogue and can be taken up in neuroendocrine tumor cells by the norepinephrine transporter system. MIBG can be radiolabeled with either I-123 or I-131. I-131-MIBG is approved in US for imaging neuroendocrine tumors (neuroblastoma and pheochromocytoma). I-123-MIBG is approved in Europe. In US, there is no standardized, FDA approved production of I-123-MIBG. It is compounded in individual radio-pharmacies. Based on the accumulated clinical experience and on certain theoretical advantages, the use of I-123-MIBG is thought to result in better images, with

greater resolution. (Of note, there are no known extensive studies of the head-to-head comparison between the two compounds).

Chemically, I-123-MIBG and I-131-MIBG are identical compounds except for the iodine isotope. The two isotopes differ in their half-lives and mode of radioactive decay. I-123 has a relatively short half-life of 13.2 hours; the half-life of I -131 is 8.04 days. I-123 is a pure gamma emitter; I-131 emits both gamma and beta. Pharmacokinetic and biodistribution data obtained with I-131-MIBG can be used to accurately predict the pharmacokinetics and biodistribution of I-123-MIBG. Toxicology data for I-131-MIBG can also accurately predict the pharmacological toxicity of I-123 MIBG.

With the I-131-MIBG serving as a reference compound and with its European production experience, the sponsor, GE Healthcare, has submitted the NDA for I-123-MIBG (AdreView) as a 505(b)(2) application. The application has been designated for a Priority review due to the CMC considerations in that there is a public health advantage in having available across the US a standardized product manufactured according to the FDA guidelines.

The following indication statement has been proposed by the sponsor:
AdreView — a diagnostic radiopharmaceutical ——————————————— *the detection of primary or metastatic pheochromocytoma — neuroblastoma.*

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Neuroblastoma is a malignant solid extra-cranial tumor in children. Pheochromocytoma is a catecholamine-producing tumor most commonly identified in the fourth and fifth decades of life.

Sources of Clinical Data

The application contains two sources of clinical data:

1. MBG308 - A prospective Phase 3 clinical study of subjects with neuroblastoma or pheochromocytoma imaged with I-123-MIBG.
2. MBG304 - A retrospective meta-analysis of published data.

Study Design and Conduct

Study MBG308

This was a prospective study entitled "An Open Label, Multicenter Phase 3 Scintigraphy Study Assessing I-123-MIBG Uptake in Subjects Being Evaluated for Pheochromocytoma or Neuroblastoma". It was conducted at 24 centers across US and Europe, involving 251 subjects (179 from US and 72 from Europe).

The primary objective was to demonstrate that I-123-MIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnosis of neuroblastoma or pheochromocytoma. The secondary objective was to determine the incremental value of SPECT in improving the sensitivity and specificity of I-123-MIBG planar imaging.

Following a thyroid blockade, the subjects were administered 10 mCi of I-123-MIBG, and images were obtained 24 hours later. Dosing was adjusted by body weight for pediatric patients weighing < 70 kg. Images were evaluated for the presence or absence of active tumor by three independent blinded readers at a core laboratory. The standard of truth (SOT) was current histology (histology obtained before imaging with no intervening therapy between biopsy and imaging). Where current histology was not available the truth standard was an evaluation of all clinical data and all available imaging data, other than the I-123-MIBG scan, provided by a clinical panel consisting of two physicians with the expertise either in Neuroblastoma or in Pheochromocytoma.

All 251 subjects who received I-123-MIBG were evaluated for safety. The population dosed in this study included 154 adults (> 16 years of age) and 97 pediatric subjects. The adult subjects (63 males and 91 females) had a mean age of 48.7 years (range 17 to 88 years). The pediatric subjects (56 males and 41 females) consisted of 32 infants (1 month up to 2 years of age), 62 children (2 years up to 12 years), and three adolescents (12 years up to 16 years).

The efficacy population was comprised of 211 subjects who received I-123-MIBG and had a Standard of Truth diagnosis available for analysis. It consisted of 127 subjects with Pheochromocytoma and 84 subjects with Neuroblastoma. Within this efficacy population, 93 subjects had the SOT defined by the current histopathology (absence of curative therapy in the time period between I-123-MIBG imaging and tissue sampling). Whereas all subjects were imaged with planar scintigraphy, only 167 subjects in the efficacy population had SPECT in addition to planar imaging.

Study MBG304

This was a retrospective study entitled "A Meta-Analysis Study to Evaluate Performance of I-123-MIBG Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma". A computerized literature search was performed to identify the articles that were then reviewed by two nuclear medicine physicians. Articles where I-123-MIBG scans were used in the diagnosis of neuroblastoma, pheochromocytoma, paraganglioma, medullary carcinoma of the thyroid or carcinoid were included if there was an acceptable Standard of Truth comparator. Data from each article were collected on a Case Report Form. A meta-analysis was performed to calculate the subject level sensitivity and specificity. This study did not involve any Safety analyses.

Efficacy Data Analyses

Study MBG308

The pre-specified primary endpoint consisted of demonstrating that Sensitivity and Specificity of I-123-MIBG planar scintigraphy each measured as greater than 0.80 by the lower bound of the 95% Confidence Interval (CI) for two out of three readers.

Out of 211 subjects in the efficacy population, measurement of Sensitivity was based on the 159 subjects with a SOT diagnosis of active tumor and measurement of Specificity was based on the 52 subjects with a diagnosis of no active tumor. The following measurements of the diagnostic performance of I-123-MIBG planar imaging were obtained: Sensitivity among three readers ranged from 0.77 [95% CI: (0.70; 0.84)] to

0.80 [95% CI: (0.73; 0.86)], and Specificity ranged from 0.69 [95% CI: (0.55; 0.81)] to 0.77 [95% CI: (0.63; 0.87)].

The by-reader data are presented in the Table below:

AdreView Planar Imaging: Sensitivity and Specificity			
	Reader A	Reader B	Reader C
Sensitivity (N=159)			
Point estimate	0.80	0.77	0.79
95% confidence Interval	0.73-0.86	0.70-0.84	0.71-0.85
Specificity (N=52)			
Point estimate	0.77	0.73	0.69
95% confidence Interval	0.63-0.87	0.59-0.84	0.55-0.81

From these data, the primary endpoint does not appear to have been met according to the pre-specified criteria for success in this trial. However, the pre-specified threshold for success was arbitrarily chosen, most likely on the basis of the retrospective analysis of the European and literature-derived data which were not necessarily obtained in the same clinical circumstances that operated in this prospective trial. Most importantly, it is known that the blinded readers, while unbiased, frequently under-perform in comparison to readers like those in clinical practice who are provided with clinical data. Thus the threshold of 0.80 might have been set up too high for the blinded reads. In any event, the lower bounds for all readers in this prospective trial for both sensitivity and specificity exceed 0.50, which is clearly consistent with the demonstration of effectiveness, and the point estimates are clinically meaningful and reasonable.

Furthermore, the data analyses based on the subgroup of 93 subjects who had definitive histopathology as part of their standard of truth diagnosis demonstrated the point estimates for sensitivity ranging from 0.81 to 0.86, and for specificity from 0.71 to 0.86. The lower bounds remained similar to the ones obtained for the full efficacy population due to the small sample size of the subgroup and the consequently wide confidence intervals. Nevertheless, it is conceivable that had the sponsor ensured that all I-123-MIBG imaging diagnoses were compared against a more robust, histology based, standard of truth diagnosis, the trial might have been much closer to achieving success in accordance with the pre-specified criteria.

In reference to the relative performance of I-123-MIBG planar imaging in subjects with pheochromocytoma vs. the performance in those with neuroblastoma, the appropriate subgroup analyses demonstrated that the performance characteristics (sensitivity and specificity, respectively) of planar imaging in patients with known or suspected pheochromocytoma were similar to those in patients with known or suspected neuroblastoma.

In reference to SPECT imaging, no improvement in the performance characteristics was demonstrated when SPECT plus planar imaging was compared to planar imaging alone.

Study MBG304

A total of 19 articles were identified as meeting the pre-specified inclusion and exclusion criteria. All of the studies cited in the articles appear to have involved the un-blinded reads, i.e. the readers were provided with the clinical information for each patient as it is commonly done in clinical practice.

Sensitivity and specificity for each study were calculated, and Meta-analysis was used to obtain overall estimates of sensitivity and specificity with the pre-defined software. Two separate Meta-analyses were preformed, one for neuroblastoma and the other for pheochromocytoma.

The results of meta-analyses showed that, for pheochromocytoma, sensitivity was measured as 0.96 [95% CI: (0.93 – 0.99)] and specificity as 0.95 [95% CI: (0.93 – 0.97)]. For neuroblastoma, sensitivity was measured as 0.97 [95% CI: (0.95 – 0.99)], and specificity could not be estimated because of lack of data.

These performance characteristics clearly exceed those obtained in the prospective trial MBG308. The sponsor cites the "publication bias" in an attempt to explain this discrepancy in that only good results tend to be published. In addition to this type of bias, the difference could also be attributed to a different degree of blinding among the retrospectively analyzed studies on one hand and the prospective study on the other. The

difference in patient characteristics might also have played a role: the retrospectively analyzed studies appear to have been mostly the studies of patients in whom the tumor diagnoses were in the process of just being established, whereas the prospective trial consisted of many patients in whom a possibility of recurrence was being evaluated.

Overall, the data obtained in the meta-analysis study support the conclusion that I-123-MIBG imaging is effective in the detection of neuroendocrine tumors.

Safety Analyses

The pharmacological toxicity profile of I-123-MIBG is expected be identical to that of I-131-MIBG which has been approved in US for imaging neuroendocrine tumors since 1999. No pharmacological toxicity of I-131-MIBG has been observed in the clinical studies as well as in post marketing surveillance. The radiation toxicity of I-123-MIBG should be less than that of I-131-MIBG since at the recommended dose the effective dose of I-123-MIBG is less. It is known to have been safe since its approval in Europe several years ago.

Since I-123-MIBG and I-131-MIBG are chemically and pharmacologically identical, biodistribution and pharmacokinetics data for the two drugs are considered to be identical and can be used interchangeably in dosimetry calculations. The review of the dosimetry information for I-123-MIBG provided by the sponsor confirms that the doses to individual organs are similar for I-131-MIBG and for I-123-MIBG, each respectively at the recommended injected doses, and do not represent significant safety signals.

In terms of the overall patient exposure, in addition to 251 subjects comprising safety population in the clinical study MBG308, the sponsor reports safety experience with ——— patients exposed to I-123-MIBG in Europe. In the clinical study, there were no deaths and the only reported Serious Adverse Event did not appear to have been treatment-related. There were no significant changes in vital signs, laboratory values or EKG parameters. Two treatment-related adverse reactions were reported in the clinical

b(4)

study: mild dysguesia and mild asthenia, one in each of two subjects. During the postmarketing experience in Europe, rarely occurring hypersensitivity reactions have been reported.

Of note, the I-123-MIBG drug product proposed for manufacturing in US contains benzyl alcohol and, generally, should not used in infants under one month of age or weighing less than 3 kg.

Conclusion

The reviewer concurs with the primary reviewer's conclusion that I-123-MIBG is safe and effective for imaging pheochromocytoma and neuroblastoma. The overall assessment of risks and benefits of I-123-MIBG scintigraphy favors the approval of AdreView as a radiodiagnostic agent for use in detection of these tumors in adults and in pediatric patients of one month of age or older and weighing 3 kg or more.

In reference to the indication statement, the submitted data did not specifically address the issue of primary vs. metastatic tumors and utilizing the wording consistent with this drug's pharmacologic class should be limited to the following: b(4)

The reviewer further notes that the Clinical Studies section of the labeling proposed by the sponsor contains a table and other references in relation to the use of histopathology in deriving various standards of truth for measuring the diagnostic performance of the test agent (AdreView). It appears confusing, clinically uninformative and potentially misleading. Therefore, a draft of the Clinical Studies section is being appended to this review. The efficacy table from this review (see above) can also be incorporated in this section to replace the table proposed by the sponsor.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Alexander Gorovets
9/9/2008 08:19:45 PM
MEDICAL OFFICER