CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA	22-290	*Submission Date(s)*	March 20, 2008
Brand Name		ADREVIEW®	
Generic Name		[I-123]Iobenguane; [I-123]MIBG	
Reviewer		Christy S. John, Ph.D	
Team Leader		Young Moon Choi, Ph.D.	
OCP Division		V	
ORM Division		Division of Medical Imaging and Hematology Drug Products	
Sponsor		General Electric Healthcare, Inc.	
Relevant IND(s)		IND 62,669	
Submission Type; Code		S	1
Dose and Route of administration		10 mCi Intravenous Injection for adults, weight based for pediatrics	
Indication		Adreview is indicated for the detection of primary or metastatic pheochromo-cytomas and neuroblastomas.	

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1 Executive Summary

AdreView® (Iobenguane I-123 Injection, also known as [I-123]MIBG (metaiodobenzylguanidine)), a diagnostic radiopharmaceutical, is proposed to be used as an imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas.

The sponsor submitted the NDA 22-290 as a 505 b(2) application by cross referencing chemistry, pre-clinical, clinical pharmacology and clinical safety data from NDA 20-084 ([I-131]MIBG), as well as from existing literature. A meta-analysis was performed by the sponsor to establish clinical efficacy. In addition, one prospective clinical trial was conducted to establish the efficacy of AdreView®.

1.1.1 Recommendations:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V, has reviewed the application submitted to NDA 22-290 and found that the application is acceptable from a clinical pharmacology perspective.

1.2 Phase IV Commitments: N/A

1.3 Summary of Clinical Pharmacology Findings:

Background: [I-123]MIBG was approved in the European Union (EU) in 1995. It is indicated for the diagnostic localization of tumors originating in tissues that embryologically stem from the neural crest. In 1994 [I-131]MIBG (NDA 20-084) was approved by Food and Drug Administration (FDA). However there are a number of disadvantages to the [I-131] isotope, i.e. lack of spatial resolution, poor image quality etc. I-123 (physical $t_{1/2}$ = 13.2 hours) is a gamma emitter, the energy of photon is 159 KeV and it can be easily imaged. I-131 (physical $t_{1/2}$ = 8 days) and it emits beta and high energy gamma (364 KeV), which is difficult to image due to scatter. For this reason I-123 is preferred for diagnostic imaging over I-131.

Both products, [I-123]MIBG and [I-131]MIBG, have been used all over the world for the last 25 years. The pharmacokinetics is well documented in the scientific literature. Both products have identical pharmacokinetic profiles as the change of radionuclide (I-131 to I-123) does not affect distribution, metabolism, and elimination. No formal clinical pharmacology studies have been conducted for the approval of AdreView®. Following is the important clinical pharmacology information of [I-123]MIBG:

Clinical pharmacology: The majority of the MIBG dose is excreted unaltered in the urine. Less than one percent of the injected dose is eliminated in the feces. A rapid initial clearance of circulating MIBG is observed, followed by a slow clearance as MIBG is released from other compartments. In patients with normal renal function 40 to 55% of the administered activity was excreted in the urine in 24 hours and 70-90% in 96 hours. Based upon HPLC analyses, the primary component of the activity in the urine was unaltered MIBG (>85%). The primary metabolite of MIBG identified was meta-iodohippuric acid (typically 10% of recovered activity), with trace amounts (<1%) of parahydroxy meta-iodobenzylguanidine and meta-iodobenzoic acid seen in some patients.

The clearance of MIBG from the blood over 72 hours was measured in four patients with normal renal function, two with reduced function, and one anephric patient. In the two groups, the mean half-lives were 33.86 hours and 62.23 hours, while there was essentially no clearance in the anephric patient. In addition, MIBG was not cleared by dialysis. It is therefore, recommended that caution should be exercised when administering [I-123]MIBG to patients with reduced renal function.

Drug-Drug Interactions: Based upon literature reports in patients and in-vitro systems and the known same mechanism of uptake of MIBG as norepinephrine, the following drugs have potential to interact with MIBG:

a) antihypertensives that deplete norepinephrine stores or reuptake (reserpine, labetalol),

b) antidepressants that inhibit norepinephrine transporter function (amitryptyline and derivatives, imipramine and derivatives,
c) selective serotonin reuptake inhibitors, sympathomimetic amines (phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine), and cocaine.

It is therefore, recommended that these drugs should not be taken at least 14 days prior to undergoing MIBG scan.

Dose: For adults (> _____of age) an intravenous dose of 10 mCi (370 MBq) is recommended. The pediatric dose calculation is based on the methods and rationale reported in the literature using body weight. Children <18 years of age (with a weight of 8-70 kg) received an activity of [I-123]MIBG calculated on the basis of the 370 MBq (10 mCi) activity used for adult subjects, scaled to body weight according to the schedule published by the European Association of Nuclear Medicine (EANM) Pediatric Task Group. For children weighing <8 kg, the investigator had the option to employ the same scaling formula or to use a fixed minimum activity of 80 ±10% MBq (72 to 88 MBq [1.9 to 2.2 mCi]). Administration of [I-123]MIBG to pediatric subjects was also limited to 0.1 ml/kg (based on quantity of benzyl alcohol) due to genotoxicity of benzyl alcohol.

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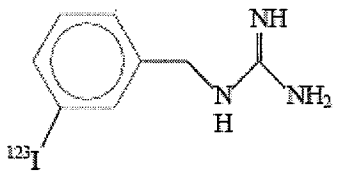
Dosimetry: The radiation dosimetry has been evaluated using OLINDA software approved by the Agency. The target organs are kidneys and liver. The radiation absorbed dose for 10 mCi of [I-123]MIBG is acceptable and the values are similar for various organs as compared to the approved 0.5 mCi of [I-131]MIBG.

2 Question Based Review

2.1 General Attributes of Drug

2.1.1 What are the general attributes of the drug AdreView®?

AdreView® is a sterile solution for intravenous injection (2 mCi/mL at the time of calibration).



Structure of [I-123]MIBG

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2.1.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of [I-123]MIBG?

[I-123]MIBG was studied under an IND 62,669 for the detection of primary or metastatic pheochromocytomas and neuroblastomas. The clinical protocol was initiated in August 2005. [I-123]MIBG (Iobenguane [^{123}I] (meta-iodobenzyl guanidine)) has been approved in the European

Union (EU) since 1995, where it is indicated for the diagnostic localization of tumors originating in tissues that embryologically stem from the neural crest. MIBG labeled either by I-123 or I-131 began to be used as a clinical diagnostic imaging agent in the United States (U.S.) in the 1980s. In 1994, [I-131]MIBG was approved by Food and Drug Administration (FDA) and became generally available. However, there are a number of disadvantages to the [I-131] isotope. These disadvantages include the high energy of emitted photons (364 KeV). As a result, the spatial resolution of [I-131] images is not good. For comparable clinical radioactivity administered to adults, [I-123]MIBG provides images with better spatial resolution and up to 40% less radiation dose to the patients. The [I-123] isotope provides superior image quality and allows identification of more lesions.

UNMET MEDICAL NEED:

In the U.S. a number of clinical sites, especially large academic medical centers and pediatric hospitals with large oncology practices have active Investigational New Drug Applications (INDs) for [I-123]MIBG and use this agent for clinical studies. In addition, commercial radiopharmacies in many larger cities compound [I-123]MIBG under "practice of pharmacy" regulations for clinical use (on a named-patient basis) per order of a physician. This current situation makes [I-123]MIBG available only to selected minority of patients, and individuals who live in smaller cities or more rural locations might have to travel hundreds of miles to reach a facility where [I-123]MIBG can be obtained. However, even traveling a long distance does not guarantee access, since the unapproved status of the product may result in an insurance coverage rejection that will cause the procedure to be cancelled. Even in locations where [I-123]MIBG is available, it is not manufactured under Good Manufacturing Practices (GMP) standards, and numerous factors (especially failure or delay in receipt of [I-123] or failure to pass required quality control (QC) tests) can result in product not being available for scheduled patient procedures. This in turn can result in major inconvenience to the patients and in some cases may result in delay in initiation of important therapies.

Some important advice and regulatory history is shown below:

Interaction date and type	Key discussions and conclusions	Follow-up actions
06 August 2002 10 October 2002 Teleconferences		GE Healthcare submitted a formal meeting request to present pre-clinical, clinical, and CMC proposal in support ——— paper NDA ~ for — [^{123}I]*m*IBG injection ——— ——— to evaluate the safety and efficacy of the drug product — as 505 (b)(2) application —
17-18 April 2003 Face-to-face Pre-NDA meeting		
12 July 2004 FDA faxed comments to background materials for 15 July 2004 pre-IND meeting.	The Division was in principle willing to consider the evidence presented from a single adequate and well-controlled trial, alone with literature data, to demonstrate that [^{123}I]*m*IBG is safe and effective for the proposed indication. As the FDA comments were clear and straightforward, GE Healthcare requested the pre-IND meeting be cancelled.	Clinical protocol, MBG308, and CMC data were submitted to the Division in original IND 62, 669. The IND included a request for Special Protocol Assessment of the MBG308 protocol
02 December 2004 Submission of original IND 62, 669	After provision of comments by the Division followed by responses from GE Healthcare the Division and GE Healthcare reached agreement on the design and analysis of clinical protocol MBG308 via the Special Protocol Assessment process. This agreement was documented in a written acceptance of the protocol design by the Division dated 20 May 2005.	Clinical protocol MBG308 was initiated; first patient first visit occurred in August 2005

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20 December 2007 Face-to-face meeting	GE Healthcare and the Division discussed FDA concerns about the rigor of the standard of truth and both parties agreed that the data for inclusion in the NDA should stay within the context of the existing locked clinical database and trial master file and not bring in new data obtained after study closure. GE Healthcare better clarified that this database contained histology as part of patient diagnosis in almost 90% of the 211 subjects. The GE Healthcare proposal to reanalyze the data in the MBG308 database to strengthen the standard of truth was accepted. Additionally, a review of the NDA submission components was acceptable to FDA; it was verified that the NDA would contain one pivotal confirmatory study (MBG308) and the meta-analysis (MBG304) along with cross-reference to NDA 20-084, primarily for non-clinical safety data.	Compilation of NDA

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product as they relate to the clinical pharmacology of the drug?

The drug product comprises an aqueous, phosphate ——— solution of Iobenguane [I-123] Injection at a concentration of 74 MBq (2 mCi) of [I-123] per ml in a volume of 5 ml at a reference. b(4)

The product is supplied in 10 ml ——— glass vials sealed with a closure and ——— The sealed vials are ———

The desired patient dose, in MBq, is withdrawn from the vial prior to injection using a disposable syringe and needle. As ^{123}I has a radioactive half-life of 13.2 hours, the volume to be withdrawn and injected must be calculated from the desired patient dose (in MBq), the radioactive concentration of the product at reference, and the time of injection. Each 1 ml of solution contains ——mg of MIBG as the free base. The product is formulated in a phosphate —— ($NaH_2PO_4 \cdot 2H_2O$ and $Na_2HPO_4 \cdot 2H_2O$) which also contains benzyl alcohol (1% v/v)) as a ——— The solution has pH of 5.0-6.5. Weight composition of Iobenguane I-123 Injection final solution, ——— is shown in Table 1. b(4)

Table 1. Chemical composition of [I-123]MIBG kits

Name of Ingredient	Amount	Function	Standard
Active Ingredient			
[^{123}I]*m*IBG		Active ingredient	Own monograph See [3.2.P.5.3]
Other Ingredients			
			Own monograph See [3.2.S.4.3]
$NaH_2PO_4 \cdot 2H_2O$			USP/NF
$Na_2HPO_4 \cdot 2H_2O$			USP/NF
Benzyl alcohol			USP/NF
			USP/NF
Total Weight			

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2.1.2 What are the proposed dosage(s) and route of administration?

For adults (>16 years of age) an intravenous dose of 10 mCi (370 MBq) is recommended. [I-123]MIBG undergoes some in-vivo dehalogenation resulting in liberation of free I-123 that is taken up by thyroid gland. Therefore, before administration of AdreView the patient's thyroid gland should be blocked with Potassium Iodide Oral Solution or Lugol's Solution (equivalent to 100 mg iodide for adults, body-weight adjusted for children) or potassium perchlorate (400 mg for adults, body-weight adjusted for children). At a minimum, the blocking agent should be administered at least one hour before the dose of AdreView.

2.1.3 What is the proposed dose for the pediatric patients?

The pediatric dose calculation is based on body weight. Children [redacted] years of age (with a weight of [redacted]) received an activity of [I-123]MIBG calculated on the basis of the 370 MBq activity used for adult subjects, scaled to body weight according to the schedule published by the European Association of Nuclear Medicine (EANM) Pediatric Task Group. [redacted]

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2.1.4 What is the proposed mechanism(s) of action?

MIBG (iobenguane) is similar in structure to the antihypertensive drug guanethedine and to the neurotransmitter norephinephrine (NE). Like NE, MIBG is taken up by the NE transporter in adrenergic nerve terminals and stored in the presynaptic storage vesicles. MIBG accumulates in adrenergically innervated tissues such as the adrenal medulla, salivary glands, heart, liver, spleen, and lungs. By labeling iobenguane with the isotope I-123, it is possible to obtain scintigraphic images of the desired organs and structures in which it accumulates. MIBG is taken up by the norepinephrine transporter (NET) with a higher affinity than norepinephrine (NE) (Km=0.31 μM and 1.8 μM, respectively), but with a similar capacity as NE. MIBG uptake is also sensitive to the vesicular monoamine transporter (VMAT) inhibitor reserpine, and radiolabeled mIBG has been observed in vesicles using electron spectroscopic imaging, indicating vesicular uptake. MIBG is not metabolized by either monoamine oxidase (MAO) or catechol-O-methyl transferase (COMT), therefore, the majority of mIBG taken up by the NET is available for VMAT uptake into vesicles. NE and MIBG can compete for uptake by the NET, MIBG having a slightly higher IC50 for uptake than NE. Specific uptake of MIBG, by either extraneuronal monoamine transporter (EMT) or organic cation transporters 1 and 2 (OCT1 and 2), has not yet been studied, however MIBG is known to enter cells via non-NET dependent uptake-2 activity.

2.2 General Clinical Pharmacology:

2.2.1 What are the design features of clinical pharmacology?

There were no formal clinical pharmacology studies conducted for the support of this NDA. The sponsor has used the literature data and NDA 20-084 for [I-131]MIBG for the support of clinical pharmacology. The uptake of radiolabeled MIBG in different organs depends on catecholamine excretion and/or adrenergic innervation. After intravenous injection approximately 50% of the administered radioactivity appears in the urine by 24 hours, and 70-90% of the residual activity is recovered within 48 hours. Since MIBG is excreted in the urine, the bladder and urinary tract show intense activity. MIBG is normally taken up mainly by the liver; smaller uptake is described in spleen, lungs, salivary glands, thyroid, skeletal muscles and myocardium. Normal adrenal glands are usually not seen, but faint uptake may be visible 48-72 hours after injection in up to 15% of cases. MIBG may accumulate to a variable degree in nasal mucosa, lungs, gallbladder, colon, and uterus. Free iodine in the bloodstream may cause some uptake in the digestive system and also in the thyroid (if not properly blocked). Bone is not seen after MIBG administration; this is important as increased uptake in the skeleton (focal or diffuse) is indicative of bone marrow involvement and/or skeletal metastases.

2.2.2 What is the basis for selecting the response endpoints, i.e, clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The diagnostic utility of [I-123]MIBG was established based upon sensitivity and specificity of detection.

2.2.3 Exposure-response Evaluation

2.2.3.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The sponsor conducted an open label multicenter Phase 3 clinical trial (MBG308) to demonstrate that [I-123]MIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnoses of neuroblastoma and pheochromocytoma. A total of 251 subjects were evaluated for known or suspected pheochromocytoma or neuroblastoma and received a dose of [I-123]MIBG. Of these 251, a total of 163 subjects entered the study with a confirmed history of neuroblastoma or pheochromocytoma. Eighty-eight subjects entered the study with suspected neuroblastoma or pheochromocytoma based upon signs, symptoms, abnormal imaging findings and elevated urine/plasma catecholamines or catecholamine metabolite measurements. Each eligible subject received an injection of [I-123]MIBG: for adults 370 MBq (10 mCi±10%); for children <18 years of age an amount scaled to the adult reference activity. At 24 ±6 hours post-administration of [I-123]MIBG, scintigraphic imaging was done.

Anterior and posterior planar whole-body images, or alternatively whole-body overlapping spot images, were acquired from head to below the knees. Additional spot images were performed as deemed appropriate by the investigator for optimal subject assessment. Single photon emission computed tomography (SPECT) imaging of the thorax and abdomen were then obtained when possible. All images were reviewed by three independent nuclear imaging specialists, who each provided a final interpretation of the planar images alone as being positive or negative for active pheochromocytoma or neuroblastoma. A similar interpretation was provided for a subsequent combined reading of planar plus SPECT images (available for 200 subjects).

Decisions concerning procedures employed to establish the diagnosis for each subject were made by the on-site clinician as per current standards of practice. The presence or absence of active pheochromocytoma or neuroblastoma (standard of truth) was established in one of two ways. If there were "current" histopathological results, i.e. results from tissue obtained prior to study imaging procedures with no interval therapy or from tissue obtained within 30 days after study imaging procedures, again without intervening therapy, these data were considered to establish the diagnosis. If there were no "current" histopathology results, all available data provided by the site, including other histology results (outside the "current" 30 day time window), reports of radiological studies (e.g. CT, MR imaging, [I-123]MIBG scintigraphy), biochemistry data (eg plasma/urine catecholamines and/or metabolites), and clinical follow-up information were provided for independent review by either a pheochromocytoma or neuroblastoma Expert Panel, which rendered a decision concerning disease status. If the Expert Panel review was unable to establish a definitive diagnosis because of insufficient or incomplete data, the subject was designated as indeterminate for the standard of truth. The standard of truth for all patients are shown in Table 2.
The primary efficacy population, also known as the intent-to-diagnose (ITD) population, consisted of subjects injected with [I-123]MIBG, who had a standard of truth diagnosis based upon "current" histopathology or a definitive decision (positive or negative) from an Expert Panel. Sensitivity and specificity of [I-123]MIBG planar scintigraphy in confirming or excluding the diagnoses of neuroblastoma and pheochromocytoma were estimated for the ITD population for each reader. The trial null hypothesis was that the sensitivity and specificity were each 80%. In order to reject this hypothesis, the sensitivity (or specificity) for a reader had to be sufficiently higher than 80% such that the lower confidence interval (CI) for this estimate would also be higher than 80%. For the trial to achieve statistical success, the null hypothesis for both sensitivity and specificity needed to be rejected by at least two readers.

Table 2. Standard of Truth for all patients:

		Active Tumor Present?			If Yes, Type of Tumor	
		Yes	No	Indeterminate	Pheochro-mocytoma	Neuroblastoma
	N	n (%)	n (%)	n (%)	n (%)	n (%)
Total	250	159 (63.6)	52 (20.8)	39 (15.6)	92 (57.9)	67 (42.1)
Current Histopathology*	50	42 (84.0)	8 (16.0)	0	22 (52.4)	20 (47.6)
Expert Panel	200	117 (58.5)	44 (22.0)	39 (19.5)	70 (59.8)	47 (40.2)

The sensitivity and specificity for confirming/excluding the diagnosis of pheochromocytoma or neuroblastoma in intent to treat population is shown in Table 3.

Table 3. Sensitivity and specificity for detection of tumors by three independent readers.

	Reader A	Reader B	Reader C
Sensitivity			
N	159	159	159
Estimate	0.80	0.77	0.79
95% CI	0.73, 0.86	0.70, 0.84	0.71, 0.85
P-Value[a]	0.48	0.77	0.64
Specificity			
N	52	52	52
Estimate	0.77	0.73	0.69
95% CI	0.63, 0.87	0.59, 0.84	0.55, 0.81
P-Value[a]	0.66	0.86	0.96

CI = confidence interval

a: P-value presented only for primary efficacy analyses of sensitivity and specificity for both tumors combined. Each statistic was tested under the null hypothesis H_0: $p_s=0.80$ vs. H_1: $p_s \geq 0.80$ at the 0.05 Type I error rate. P-values for estimates that were less than 0.80 were not calculated.

The results of prospectively designed trial showed that:

- The lower bounds of the 95% confidence intervals (CI) for sensitivity and specificity for all readers were <80%. The null hypothesis was not rejected by any reader. The primary statistical objective of the trial was not met.
- Sensitivity and specificity for the two tumor subpopulations were similar: neuroblastoma: sensitivity 78% to 81%, specificity 71% to 76%; pheochromocytoma: sensitivity 77% to 79%, specificity 66% to 80%.
- Sensitivity and specificity for the "current" histopathology subgroup were higher than for the no "current" histopathology subgroup: "current" histopathology: sensitivity 83%.

However, the results of meta-analysis of efficacy of data from the literature published data showed a sensitivity and specificity of greater than 95%. The reason for this higher sensitivity and specificity may be the fact that the most published clinical research was performed as an open-label and that the readers of film had additional information such as clinical history, X-ray, CT and other laboratory test results etc. The blinded readers in the sponsor's prospectively designed clinical trial did not have this information available to them.

2.2.3.2 What are characteristics of the exposure-response relationship (dose-response, concentration-response) for safety?

See above.

2.2.3.3 Does this drug prolong QT or QTc interval?

No clinical pharmacology studies for QTc prolongation were performed. The in vitro HERG-1 channel inhibition with MIBG was only at clinically irrelevant doses (about 1000 multiples of Cmax).

At the nominal concentrations of 8 and 80 μM MIBG(16.6 and 166 multiples of Cmax respectively), MIBG hemisulphate had no significant effect on the HERG-1 tail current when compared with the vehicle recordings. Under the conditions of the test as described, at the nominal concentrations of 200, 400 and 800 μM MIBG significantly reduced the HERG-1 tall current amplitude by 26, 45 and 77 %, respectively, when normalized by the vehicle group results. The IC50-value estimated for the HERG current inhibition by MIBG was 487 μM (equal to 1008 multiples of Cmax).

2.2.3.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose selected by the sponsor for pediatric study was based upon the dose reported used in pediatric studies in the literature. There are no unresolved issues with the dosing or administration.

2.2.4 Pharmacokinetic Characteristics

2.2.4.1 What are the PK characteristics of the drug and its major metabolite?

Several literature articles have been cited including Lashford LS, Moyes J, Ott R, Fielding S, Babich J, Mellors S, Gordon I, Evans K, Kemshead JT. The biodistribution and pharmacokinetics of meta-iodobenzylguanidine in childhood neuroblastoma. Eur. J. Nucl. Med. 1988; 13: 574-577.

A brief description of pharmacokinetics from this article is given below: "Following a bolus intravenous injection of radiolabeled MIBG, activity cleared from the blood following biexponential clearance kinetics. The first clearance component was very rapid with 1.5 % and 10% of the injected dose remaining in blood at 60 min. Subsequent loss of isotope was mono-exponential over the assay period of 48 h. The biological half

life of this clearance component was variable between patients and lay between 9 and 130 h. The early biodistribution of the compound was followed using the dynamic acquisition series. Within the first 30 min radiolabel was observed to be excreted by the kidney and isotope was demonstrated to accumulate rapidly in the bladder. This phase of renal filtration was of short duration and after 15 – 20 min no further increase in bladder activity was seen. The magnitude of this early loss was small, and did not account for the vascular loss. Direct measurement of urine activity at 3 h indicates only 13% of the injected dose excreted by this mechanism (range 11% – 26%). Additional loss occurs due to selective organ uptake. Accumulation of counts within the liver occurred rapidly over the first 5 min. During the following 25 min observation period the activity or counts remained constant. Scintigrams performed after the dynamic aquisition study consistently demonstrated a high concentration of isotope in salivary tissue, myocardium, and liver".

According to Jacobsson et. al. (Jacobsson L. Matlsson S, Johansson L. Lindberg S, Fjalling M. Biokinetics and dosimetry of I-metaiodo benzylguanidine. Proceedings of 4th Int. Radiopharmaceutical Dosimetry Symposium. Oak Ridge, Tennessee 1985:389-398) about 1/3rd of the injected dose reaches liver within 15 minutes. The distribution of the activity within the body is quite constant during the whole measurement period (0-14 days) indicating approximately the same half- life in all organs with a significant uptake. Most of the radioactivity which leaves the body is excreted via the urine. In the first 15 minutes after the injection about 10% of the activity is excreted and after 5 days between 66 and 91% of the activity has been excreted via the urine. Analysis of blood samples shows that 1.5% of the injected activity is present in the total-blood volume. The retention in whole blood up to 14 days after injection is described by a single exponential function corresponding to an effective half-life of 32 hours as a mean for 6 patients. Half of the activity is found in plasma and the other half in the blood cells.

The urinary excretion was the major route of elimination. Less than 1% of radioactivity was detected in feces after 4 days post-injection. The majority of the MIBG dose is excreted in the urine, with a rapid initial

clearance of circulating MIBG, followed by a slow clearance as MIBG is released from other compartments. In patients with normal renal function, 40 to 55% of the administered activity was excreted in the urine in 24 hours and 70-90% in 96 hours. Based upon HPLC analyses, the primary component of the activity in the urine was unaltered [I-131]MIBG (>85%), with the next largest component being [I-131] (2 to 5%). The primary metabolite of [I-131]MIBG identified was meta-iodohippuric acid (typically =10% of recovered activity), with trace amounts (<1%) of parahydroxy meta-iodobenzylguanidine and meta-iodobenzoic acid seen in some patients. Less than one percent of the injected dose is eliminated via the feces [Mangner T.J. et al. Journal of Nuclear Medicine 1986, 27(1); 127-129].

2.2.4.2 What is the radiation absorbed dose for various organs for [I-123]MIBG?

Based upon the recommendation of Oncology Committee of European Society of Nuclear Medicine, the estimated absorbed radiation dose to various organs in healthy subjects following administration of [I-123]MIBG is given in the Table IV. The data for [I-123]MIBG are quoted from ICRP 80.

Table IV. Estimated Radiation absorbed doses for [I-123]MIBG

Organ	Absorbed dose per unit activity administered(rads/mCi)			
	Adult	15 years	5 years	1 yr
Adrenals	**0.059**	**0.078**	**0.155**	**0.248**
Bladder	**0.244**	**0.311**	**0.407**	**0.748**
Brain	**0.014**	**0.018**	**0.048**	**0.089**
Gall Bladder	**0.074**	**0.089**	**0.126**	**0.352**
Heart Wall	**0.067**	**0.085**	**0.196**	**0.348**
Kidneys	**0.048**	**0.059**	**0.089**	**0.218**
Liver	**0.248**	**0.322**	**0.666**	**1.221**
Lungs	**0.059**	**0.085**	**0.178**	**0.329**
Thyroid	**0.017**	**0.023**	**0.059**	**0.111**
Effective Dose (mSv/mCi)	**0.507**	**0.670**	**1.39**	**2.52**

The estimated absorbed radiation doses to adults and children from intravenous administration of [I-123]MIBG are shown in Tables below. The Agency had asked the sponsor on August 9, 2007 to re-calculated the radiation absorbed doses to various organs using FDA approved OLINDA software package. The biodistribution data was selected from a literature reference (Swanson et al) for the calculations. The radiation absorbed doses for kids for various age groups is shown in the table below:

ORGAN / TISSUE		ABSORBED DOSE PER UNIT ADMINISTERED ACTIVITY											
		ADULT		15-YEAR OLD		10-YEAR OLD		5-YEAR OLD		1-YEAR OLD		NEONATES	
		µGy / MBq	rad/mCi	µGy / MBq	rad/mCi	µGy / MBq	rad/mCi	µGy / MBq	rad/mCi	µGy / MBq	rad/mCi	µGy / MBq	rad/mCi
Adrenals		16	0.059	21	0.078	31	0.115	42	0.155	67	0.248	111	0.411
Brain		3.9	0.014	4.9	0.018	8.1	0.030	13	0.048	24	0.089	55.9	0.207
Breast		4.7	0.017	5.9	0.022	9.4	0.035	15	0.056	28	0.104	65.3	0.242
Gallbladder		20	0.074	24	0.089	34	0.126	51	0.189	95	0.352	200	0.740
GI Tract	Stomach Wall	7.6	0.028	10	0.037	17	0.063	27	0.100	51	0.189	114	0.422
	Small Intestine Wall	7.7	0.028	9.8	0.036	16	0.059	25	0.093	46	0.170	104	0.385
	Colon Wall	8.1	0.030	10	0.037	16	0.059	26	0.096	46	0.170	104.3	0.386
	Upper Large Intestine Wall	8.4	0.031	11	0.041	18	0.067	30	0.111	53	0.196	119	0.440
	Lower Large Intestine Wall	7.7	0.028	9.6	0.036	15	0.056	21	0.078	38	0.141	84.9	0.314
Heart Wall		18	0.067	23	0.085	35	0.130	53	0.196	94	0.348	182	0.673
Kidneys		13	0.048	16	0.059	24	0.089	35	0.130	59	0.218	132	0.488
Liver		67	0.248	87	0.322	130	0.481	180	0.666	330	1.221	720	2.664

Lungs		16	0.059	23	0.085	32	0.118	48	0.178	89	0.329	215	0.796
Muscles		6	0.022	7.6	0.028	12	0.044	17	0.063	33	0.122	75.1	0.278
Esophagus		6	0.022	7.6	0.028	11	0.041	18	0.067	32	0.118	72.2	0.267
Osteogenic Cells		16	0.059	21	0.078	31	0.115	47	0.174	100	0.370	254	0.940
Ovaries		7.9	0.029	10	0.037	15	0.056	22	0.081	41	0.152	92.3	0.342
Pancreas		12	0.044	15	0.056	25	0.093	39	0.144	68	0.252	143	0.529
Red marrow		5.6	0.021	6.8	0.025	10	0.037	15	0.056	30	0.111	89.5	0.331
Skin		3.7	0.014	4.4	0.016	7.1	0.026	11	0.041	21	0.078	53.1	0.196
Spleen		20	0.074	27	0.100	42	0.155	64	0.237	110	0.407	282	1.043
Testes		5.4	0.020	7.1	0.026	11	0.041	16	0.059	30	0.111	69.9	0.259
Thymus		6	0.022	7.6	0.028	11	0.041	18	0.067	32	0.118	72.2	0.267
Thyroid		4.7	0.017	6.1	0.023	9.9	0.037	16	0.059	30	0.111	69.4	0.257
Urinary Bladder Wall		66	0.244	84	0.311	110	0.407	110	0.407	200	0.740	478.0	1.769
Uterus		11	0.041	14	0.052	21	0.078	28	0.104	51	0.189	110.0	0.407
Whole Body		8.1	0.030	10	0.037	16	0.059	24	0.089	44	0.163	104.0	0.385
EFFECTIVE DOSE	µSv/MBq	13.7		18.1		26.7		37.6		68		162	
	mSv/mCi	0.507		0.670		0.988		1.39		2.52		6	

*OLINDA/EXM calculation based on biodistribution data from Swanson et al and Publication 53 of the ICRP (International Commission on Radiological Protection)

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2.3 Intrinsic Factors

2.3.1 What intrinsic factors (such as renal and hepatic dysfunction) influence pharmacokinetics (exposure)?

The sponsor has not formally studied influence of any intrinsic factors on pharmacokinetics of [I-123]MIBG. [I-123]MIBG is known to be cleared renally by glomerular filteration and is not dialyzable. The radiation dose to the kidneys would be much higher if the kidneys are not working normally as the biological half-life of the drug would be considerably reduced. It is therefore, recommended in the labeling section that the use of [I-123]MIBG in patients with reduced renal function should be carefully considered. Also, because of reduced of clearance of [I-123]MIBG in renally impaired subjects the target to non-target ratios would be much lower and the efficacy of drug may be compromised.

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2.4 Extrinsic factors:

2.4.1 What extrinsic factors such as smoking etc. influence pharmacokinetics of MIBG?

Extrinsic factors, including use of herbal products, diet, smoking, and alcohol, are not known to affect results of administration of [I123]MIBG injection.

2.4.2 What drug-drug interaction can possibly effect [I-123]MIBG imaging?

No formal drug interaction studies have been carried out in humans for this particular application. However, a number of categories of medications are known or suspected to interfere with neuronal uptake of [I-123]MIBG. The two most important mechanisms by which drugs affect [I-123]MIBG uptake are through inhibition or blocking of the NE transporter and enhancement of release of NE from intracellular storage vesicles. Interference with the mechanisms of [I-123]MIBG uptake and neuronal retention can result in false-negative imaging studies.

Based upon the known mechanism of uptake of [I-123]MIBG, the following drugs have potential to decrease the uptake of [I-123]MIBG;

a) antihypertensives that deplete norepinephrine stores or reuptake (reserpine, labetalol),

b) antidepressants that inhibit norepinephrine transporter function (amitriptyline and derivatives, imipramine and derivatives,

c) serotonin selective reuptake inhibitors, sympathomimetic amines (phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine), and cocaine. The clinical studies were not designed to show which drugs would cause false negative results.

It is unknown if drugs in the same classes have the same potential to inhibit the uptake of [I-123]MIBG. Increasing the dose of [I-123]MIBG will not overcome any potential uptake limiting effect of these drugs. Drugs known or expected to reduce the uptake of [I-123]MIBG should be stopped before treatment (usually five biological half-lives) as shown in the Table below.

Drugs	**Mode of interference**	**Suggested time of withdrawal**
Opioids Cocaine	Uptake inhibition	7-14 days
Tricyclic antidepressants Amitryptyline, imipramine etc.	Uptake inhibition	7-21 days
Antihypertensive Labotalol, metoprolol, calcium channel blockers	Inhibition uptake	14-21 days
Ace Inhibitors Captopril, enalapril	Increased uptake and retention	14 days

2.5 General Biopharmaceutics:

AdreView is intended for use via intravenous injection. The bioavailability and biopharmaceutics issues are not relevant.

2.6 Analytical Section:

2.6.1 How are the active moieties identified and measured?

As indicated earlier, no PK studies were performed for this application. Howevere, for product development and characterization HPLC was used.

MIBG was analysed by a ——— HPLC method, with ——— and UV detection at 240 nm. The analytical method was validated with respect to the following parameters: Accuracy (as recovery), precision (as repeatability), specificity, detection limit, quantitation limit, linearity and range. The validation was performed to GLP level according to Standard Operating Procedure (SOP), and the study design followed the recommendation for Level 1, Biological documentation studies (GLP and non-GLP) in this SOP. The accuracy, determined as total average recovery on three control standards, was ——— The precision, determined as repeatability by 6 injections of the same sample, gave an RSD of ——— The detection limit was found to be ——— free base mIBG, and the quantification limits were found to be ——— free base mIBG. Satisfactory linearity was proven within the range tested, and the correlation factor (r^2) found was ——— for the range ——— free base MIBG. Range of the method has been evaluated from linearity, and acceptable results have been confirmed in the concentration range ——— free base MIBG. Based on these results, the method is considered suitable for its intended use.

b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

4. Appendices: None

4.1 PROPOSED PACKAGE INSERT:

13 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 2

4.2 Individual Study Review: N/A

4.3 Consult Reviews: N/A

4.4 Cover Sheet and OCP Filing Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-290	Brand Name	Adreview
OCPB Division (I, II, III, IV, V)	V	Generic Name	[I-123]mIBG
Medical Division	DMIHP	Drug Class	
OCPB Reviewer	Christy S. John, Ph.D.	Indication(s)	Imaging agent to detect primary or metastatic neuroblastoma or pheochromocytomas
OCPB Team Leader	Young Moon Choi, Ph.D	Dosage Form	2 mCi/mL
		Dosing Regimen	
Date of Submission	March 20, 2008	Route of Administration	IV
Estimated Due Date of OCPB Review	October 2008	Sponsor	GE Healthcare, Inc
PDUFA Due Date	January 19, 2008	Priority Classification	
Division Due Date	October 2008		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	N/A	N/A		
Tabular Listing of All Human Studies	N/A			
HPK Summary	N/A			
Labeling				
Reference Bioanalytical and Analytical Methods	N/A			
I. Clinical Pharmacology	N/A			
Mass balance:	N/A			
Isozyme characterization:	N/A			
Blood/plasma ratio:	N/A			
Plasma protein binding:	N/A			
Pharmacokinetics (e.g., Phase I) -	N/A			
Healthy Volunteers-				
single dose:	N/A			
multiple dose:				
Patients-				
single dose:				
multiple dose:				

Dose proportionality -	N/A			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	N/A			
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	N/A			
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	N/A			
Phase 2:				
Phase 3:				
PK/PD:	N/A			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	N/A			
Data rich:				
Data sparse:				
II. Biopharmaceutics	N/A			
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	N/A			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	N/A			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	12			
Total Number of Studies				
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	**X**	**This application is based on the literature data survey and a clinical trial to determine the efficacy of [I-123]mIBG to detect primary and metastatic neuroblastoma and pheochromocytomas. The application is filabale from clinical pharmacology perspective. The clinical pharmacology section of the label has been revised.**
Comments sent to firm ?		N/A
QBR questions (key issues to be considered)	**N/A**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Christy S. John, PhD**	
Secondary reviewer Signature and Date	**Young Moon Choi, PhD**	

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

/s/

Christy John
9/11/2008 05:36:47 PM
BIOPHARMACEUTICS

Young-Moon Choi
9/11/2008 05:44:38 PM
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