CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

SUMMARY REVIEW

DIVISION DIRECTOR'S REVIEW MEMORANDUM

NDA:	22-290
DRUG:	Iobenguane I-123 injection
TRADENAME:	AdreView®
FORMULATION:	Single use vials that contain 5 mL solution that contains , within each mL, 74 mBq (2 mCi) of I-123 as iobenguane sulfate I-123 along with specified excipients that include 1% benzyl alcohol
ROUTE:	Intravenous administration as an injection administered at over 1 to 2 minutes
DOSE:	10 mCi (370 MBq) for adults; dose for pediatric patients ——————— is specified within a package insert table that adjusts the dose based on weight
SPONSOR:	GE Healthcare
SUBMITTED:	March 20, 2008
PDUFA DUE DATE:	September 19, 2008
DD MEMO COMPLETED:	September 17, 2008
DD MEMO PREPARERS:	Dwaine Rieves, MD, Director Division of Medical Imaging and Hematology Products

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SPONSOR'S PROPOSED INDICATION:

"AdreView is a radiopharmaceutical indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests."

RELATED DRUGS:

The only other "related" drug is:

Iobenguane Sulfate I-131, manufactured and marketed by CIS-US; this product is the I-131 form of iobenguane and is indicated "as an adjunctive diagnostic agent in the localization of primary or metastatic pheochromocytomas and neuroblastomas." The I-131 in this product is both a beta particle and a gamma ray emitter. In contrast, I-123 is only a gamma ray emitter.

Of note, the I-123 form of iobenguane sulfate is thought to be relatively widely used in the US because of the perceived "improved image quality" of this radio-imaging agent, compared to the I-131 marketed product. The I-123 iobenguane used in current clinical practice is manufactured in compounding pharmacies or at local facilities.

RELATED REVIEWS:

Clinical:	Robert Yaes, M.D.; Alex Gorovets, M.D.
Statistics:	Xiaoping (Janet) Jiang, PhD, Jyoti Zalkikar, Ph.D.
Chemistry:	Eldon Leuzinger, Ph.D.
Microbiology:	Robert Mello, Ph.D.
Pharm-toxicology:	Siham Biade, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Christy John, Ph.D, Young Moon Choi, Ph.D.
Project Manager:	James Moore, Pharm.D.

DSI (inspection): Robert Young, MD and Tejashri Purohit-Sheth, MD
OSE/DMEPA: Cathy Miller, MPH, BSN
Advisory Committee: None

RECOMMENDED REGULATORY ACTIONS:

1) Approval of AdreView for the proposed indication:

AdreView is an I-123 version of iobenguane sulfate, a molecule somewhat similar to norepinephrine and which has been shown in model systems to be taken up by cells of neuroectodermal origin (cells that contain intracellular adrenergic storage granules).

The I-131 form of iobenguane sulfate has been marketed for many years and is well accepted as an important diagnostic tool to assist in the diagnosis of neuroblastoma or pheochromocytoma. Over the last few years, the I-123 form of iobenguane sulfate has also been clinically used in place of I-131 because the I-123 form is thought to be safer (no beta particle emission) and also because the image quality is generally recognized as better. Indeed, some publications suggest that the I-123 form of iobenguane has largely supplanted the use of I-131 iobenguane in the US. The I-123 in clinical use is manufactured by compounding pharmacies or local/on-site nuclear pharmacies. The market availability of a cGMP-compliant, well specified manufacturing process for I-123 is an advance over the less well controlled manufacturing processes for I-123.

Some professionals within the medical imaging community questioned the need for any additional systematic collection of clinical data to support the safety and efficacy of I-123 iobenguane sulfate since the mechanism of action/imaging/diagnostic consequences are largely the same as those for the I-131 form of iobenguane sulfate. Nevertheless, GE Healthcare performed a prospective clinical study that provided definitive performance characteristics for AdreView.

The AdreView performance characteristics (sensitivity and specificity) did not meet the statistically-predefined limits for success. However, the predefined statistical criteria were relatively arbitrary choices, based upon published literature. The published literature is heavily biased toward over estimation of the performance characteristics of I-123 iobenguane sulfate because the image interpretations are almost uniformly performed with knowledge of clinical data. In contrast, the study conducted by GE Healthcare excluded all clinical data from image interpretation. The sensitivity from the study of AdreView was approximately 80% and the specificity was 75%; these outcomes are clinically solid evidence of acceptable diagnostic performance since the study used extremely rigorous methods in image interpretation. Too, these performance characteristics are similar to those for the I-131 form of iobenguane sulfate; additionally, the confidence intervals on these performance characteristics exceed 50%, indicating that, in the extreme, AdreView information exceeds chance diagnostic value.

AdreView presents no new safety findings beyond those typical for a radionuclide and, in comparison to the I-131 version of iobenguane sulfate, may offer safety advantages. Hence, no post-marketing committments or requirements are needed.

2) Approval of the trade name, AdreView®

This recommendation is consistent with that of the FDA Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis. The name, "AdreView," was regarded as acceptable.

3) Pediatric Research Equity Act (PREA) of 2003 expectations:

The sponsor had previously obtained Orphan Drugs designation for I-123 iobenguane sulfate. Hence, PREA expectations do not apply. Nevertheless, the main clinical study supporting approval of the product included 97 pediatric patients. The pediatric patients (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).

REVIEW COMPONENTS:

Background

As noted above, medically compounded I-123 iobenguane sulfate has been widely used in the US for many years as an alternative to the I-131 form of iobenguane sulfate. The extent of information regarding the mechanism of action, diagnostic utility and limitations is remarkable and the value of radiolabeled iobenguane sulfate as diagnostic tool is indisputable.

The I-123 version of iobenguane sulfate raises no new safety or efficacy concerns, compared to the currently marketed I-131 version of the product. This conclusion is verified by the findings from the one clinical study performed by GE Healthcare. This study firmly defined I-123 iobenguane sulfate performance characteristics under stringent diagnostic conditions. In clinical practice, the performance characteristics are likely to exceed those shown in the clinical study.

Brief Regulatory Timeline

- March 20, 2008 - NDA submission
- May 20, 2008 - Filing meeting, NDA was assigned a priority review
- August 19, 2008 Mid-cycle meeting
- September 19, 2008 PDUFA due date

Clinical Review

The clinical review was performed by Dr. Robert Yaes. Dr. Alex Gorovets provided Team Leader expertise to the review and a secondary review. I have examined the clinical review and I concur with the findings, comments and recommendations.

AdreView —— was evaluated in a single clinical study that enrolled patients with known or suspected neuroblastoma or pheochromocytoma. Very rigorous diagnostic methods were used in the assessment of AdreView performance characteristics, including use of a predefined "standard of truth" as well as determination of image findings by three readers who were completely masked to clinical information. The predefined primary endpoint was a co-primary endpoint that defined success as a 95% confidence interval on sensitivity and specificity that exceeded 80%. This expection was, in retrospect, a very high threshold, especially considering the average

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performance characteristics for the currently marketed form of iobenguane sulfate are generally in the 80% range (ie., the confidence interval boundary is lower than 80%).

Diagnostic efficacy for the detection of metabolically active neuroblastoma or pheochromocytoma was determined by comparison of focal increased radionuclide uptake on planar scintigraphy at 24 ± 6 hours post-administration of AdreView against the definitive diagnosis (standard of truth). Anterior and posterior planar whole-body images, or alternatively whole-body overlapping spot images, were acquired from the head to below the knees. Additional spot images were performed as deemed appropriate at the discretion of the clinical image reviewer. Single photon-emission computerized tomography (SPECT) imaging of the thorax and abdomen was then obtained when possible.

Of the 251 subjects dosed with AdreView, 100 had known or suspected neuroblastoma and 151 had known or suspected pheochromocytoma. The population included 154 adults and 97 pediatric patients; the majority of adults were female (59%), the majority of pediatric subjects were male (58%). The adult subjects had a mean age of 49 years (range 17 to 88 years). The pediatric patients (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 definitive diagnosis (standard of truth) for the presence or absence of metabolically active pheochromocytoma or neuroblastoma was determined by histopathology or, when histopathology was unavailable, a composite of imaging (i.e., CT, MRI, [^{131}I]-*m*IBG scintigraphy), plasma/urine catecholamine and/or catecholamine metabolite measurements, and clinical follow-up.

A standard of truth was available for 211 subjects (127 with pheochromocytoma, 84 with neuroblastoma) and this group comprised the diagnostic efficacy population. For 93 of these subjects, the standard of truth was based solely upon histopathology. Of 211 subjects in the efficacy population, all had planar scintigraphy and 167 subjects had SPECT in addition to planar imaging. All images were assessed independently by three readers blinded to all clinical data. Table 1 summarizes the AdreView performance characteristics, by reader.

Table 1. AdreView Planar Imaging: Sensitivity and Specificity

Outcome	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

Performance characteristics (sensitivity and specificity) of AdreView planar imaging in patients with known or suspected neuroblastoma were similar to those in patients with known or suspected pheochromocytoma. Among the selected patients who also underwent SPECT imaging, no meaningful difference in the performance characteristics of AdreView scintigraphy was observed when SPECT plus planar imaging was compared to planar imaging alone.

Safety outcomes were assessed over a 24 hour period following AdreView administration. The adverse event reports were remarkably few. Indeed, any single adverse reaction was reported by no more than two patients and the most common adverse reactions were isolated occurrences of one of the following dizziness, rash, pruritus, flushing or injection site hemorrhage. No serious adverse reactions were reported. These safety findings are consistent with the experience for the I-131 form of iobenguane sulfate.

Statistical Review:

The statistical review was performed by Dr. Janet Jiang, lead statistician for the NDA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Jiang's statistical review report and I concur with her statistical analyses, findings and comments that the prespecified primary endpoint was not achieved.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Christy John. The findings from the review were secondarily reviewed by Young Moon Choi, Team Leader. The reviewers determined that the supplied data are sufficient to support approval. The OCPB team importantly contributed to the development of the label, particularly with respect to information pertaining to the limitations of diagnostic use among patients with severe renal insufficiency. Since iobenguane sulfate is excreted renally, severe renal insufficiency may importantly alter diagnostic performance and may increase patient exposure to the radionuclide.

I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments.

Chemistry and Microbiology

The Chemistry review was performed mainly by Dr. Eldon Leutziner. The microbiology review was performed by Dr. Robert Mello. The review team verified that facilities inspections were completed and the facilities were compliant with FDA expectations.

I have read the summary of the chemistry review findings and concur with the results. Dr. Leutziner observed that the supplied chemistry and manufacturing information was sufficient to support the product's approval and had no requests for post-marketing commitments.

I have examined Dr. Mello's summary findings, including inspectional considerations, and concur with the findings.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. Siham Biade and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations. The reviewers provided important information regarding the labeling aspects related to benzyl alcohol. Since AdreView contains benzyl alcohol in a concentration similar to many other products, the label contains statements similar to other labels--specifically noting the risks for toxicity in low birth weight and premature infants.

Pediatric Safety and Efficacy

The clinical study included reasonable numbers of pediatric patients > one month of age. The label indicates that safety and efficacy have not been established in pediatric patients under one month of age.

Proposed Labeling

During the review cycle, FDA and the sponsor developed multiple revisions of the AdreView product label. These revisions largely related to the description of the clinical studies and the safety information. I have reviewed the final product label and concur with the text.

Office of Surveillance and Epidemiology

The Division of Medication Error Prevention provided the main review contribution for OSE. As previously mentioned, AdreView presents no unique safety findings, when compared to the currently marketed I-131 form of the product.

Division of Scientific Investigation (DSI)

As described in a detailed memorandum from Dr. Robert Young, the core imaging laboratory was inspected and the integrity of the clinical study data was assessed as reasonable. No 483 form was issued.

Financial Disclosure

As noted in Dr. Yaes's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

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/s/

Rafel Rieves
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MEDICAL OFFICER