

# PRODUCT MONOGRAPH

AdreView™

Iobenguane (<sup>123</sup>I) Injection

Solution for Intravenous Injection

74 MBq/mL at calibration

Diagnostic Radiopharmaceutical

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# AdreView™

## Iobenguane (<sup>123</sup>I) Injection

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Table 1: Summary Product Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medical Ingredients
Intravenous	Solution for Intravenous Injection 74 MBq/mL at calibration	Benzyl alcohol 1% v/v For a complete listing see <a href="#">Dosage Forms, Composition and Packaging section</a> .

#### DESCRIPTION

##### Physical Characteristics

Iodine-123 (<sup>123</sup>I) is a cyclotron-produced radionuclide that decays to <sup>123</sup>Te by electron capture with a physical half-life of 13.2 hours.

Table 2: Principal Radiation Emission Data <sup>123</sup>I

Radiation	Energy level (keV)	Abundance (%)
Gamma	159	83

##### External Radiation

The air kerma-rate constant for <sup>123</sup>I is  $10.0 \times 10^{-18} \frac{\text{Gy m}^2}{\text{Bq s}}$ .<sup>a, b</sup> The first half value thickness of lead (Pb) for <sup>123</sup>I is 0.04 cm. The relative transmission of radiation emitted by the radionuclide that results from interposition of various thicknesses of Pb is shown in Table 3 (e.g., the use of 2.16 cm Pb will decrease the external radiation exposure by a factor of about 1,000).

**Table 3: Reduction in In-air Collision Kerma Caused by Lead Shielding\***

Shield Thickness cm of lead (Pb)	Reduction in In-air Collision Kerma
0.04	0.5
0.13	10 <sup>-1</sup>
0.77	10 <sup>-2</sup>
2.16	10 <sup>-3</sup>
3.67	10 <sup>-4</sup>

\*Calculation based on attenuation and energy-transfer coefficients obtained from National Institute of Standards & Technology Report NISTIR 5632

## INDICATIONS AND CLINICAL USE

### **Oncology**

AdreView™ [Iobenguane (<sup>123</sup>I) Injection], a radiopharmaceutical agent for gamma-scintigraphy, is indicated for use in the detection of primary or metastatic pheochromocytoma and neuroblastoma as an adjunct to other radiological and nuclear medicine diagnostic tests.

### **Cardiology**

AdreView is indicated for scintigraphic assessment of sympathetic innervation of the myocardium. In patients with New York Heart Association (NYHA) class II or class III heart failure and left ventricular ejection fraction (LVEF) ≤ 35%, AdreView may be used as an adjunct test to other established tools to further assess the risk of mortality, using the measurement of the heart to mediastinum (H/M) ratio.

## CONTRAINDICATIONS

AdreView™ [Iobenguane (<sup>123</sup>I) Injection] is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of ingredients and of packaging components, see [Dosage Forms, Composition and Packaging](#).

## WARNINGS AND PRECAUTIONS

### **Serious Warnings and Precautions**

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

Hypersensitivity reactions have been reported following AdreView administration. Anaphylactic and hypersensitivity treatment measures should be available prior to AdreView administration.

AdreView contains benzyl alcohol. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, severe metabolic acidosis,

neurologic deterioration, and gasping respirations), particularly in premature infants and infants of low birth weight. Observe infants for signs or symptoms of benzyl alcohol toxicity following AdreView administration.

### **General**

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients and occupational workers, consistent with ALARA (As Low As Reasonably Achievable) principle.

### **Hypersensitivity Reactions**

Hypersensitivity reactions have been reported following AdreView administration. Prior to administration, the patient should be questioned for a history of reactions to iodine, an iodine-containing contrast agent or other products containing iodine. If the patient is known or strongly suspected to have hypersensitivity to any of the above, the decision to administer AdreView should be based upon an assessment of the expected benefits compared to the potential hypersensitivity risks. Anaphylactic and hypersensitivity treatment measures should be available prior to AdreView administration.

### **Risks for Benzyl Alcohol Toxicity in Infants**

AdreView contains benzyl alcohol at a concentration of 10.3 mg/mL. Benzyl alcohol has been associated with a fatal “Gaspings Syndrome” in premature infants and infants of low birth weight. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, severe metabolic acidosis, neurologic deterioration and gasping respirations), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol, which are not usually associated with a diagnostic radiopharmaceutical such as AdreView.

Observe infants for signs or symptoms of benzyl alcohol toxicity following AdreView administration. AdreView safety and effectiveness have not been established in neonates (pediatric patients below the age of 1 month).

### **Severe Renal Impairment: Increased Radiation Exposure**

AdreView is cleared by glomerular filtration and is not dialyzable. The radiation dose to patients with severe renal impairment will be increased due to the delayed elimination of the drug. Delayed AdreView clearance may also reduce the target to background ratios and decrease the quality of scintigraphic images. These risks may limit the role of AdreView in the diagnostic evaluation of patients with severe renal impairment. AdreView safety and efficacy have not been established in these patients. If the AdreView study is deemed to be necessary in oncology patients with severe impaired renal function, further delayed images at 48 hours should be considered to improve the image quality. Data are not available to establish the validity of quantitative measurements of cardiac activity (H/M ratio) in patients with severe renal impairment. As a result, obtaining cardiac images after a longer delay than 4 hours cannot be recommended.

### **Thyroid Accumulation**

Failure to block thyroid uptake of  $^{123}\text{I}$  may result in an increased long term risk for thyroid neoplasia. Administer thyroid blocking medications before AdreView administration (see [Dosage and Administration](#)).

### **Risks with Concomitant Medication Withdrawal**

Many medications have the potential to interfere with AdreView imaging and review of the patient's medications is required prior to AdreView dosing due to the risk for unreliable imaging results. If the AdreView imaging information is essential for clinical care, consider the withdrawal of the following categories of medications if the withdrawal can be accomplished safely: antihypertensives that deplete norepinephrine stores or inhibit reuptake (e.g., reserpine, labetalol), antidepressants that inhibit norepinephrine transporter function (e.g., amitriptyline and derivatives, imipramine and derivatives, selective serotonin reuptake inhibitors), and sympathomimetic amines (e.g., phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine). The period of time necessary to discontinue any specific medication prior to AdreView dosing has not been established. (See *Drug Interactions*).

### **Oncology**

Drugs which interfere with norepinephrine uptake or retention may decrease the uptake of AdreView in neuroendocrine tumors and lead to false negative imaging results. When medically feasible, stop these drugs before AdreView administration and monitor patients for the occurrence of clinically significant withdrawal symptoms, especially patients with elevated levels of circulating catecholamines and their metabolites (see [Drug Interactions](#)).

### **Cardiology**

Certain cardiovascular, pulmonary, and neuropsychiatric medications interfere with AdreView imaging (see above). AdreView imaging should not be performed if discontinuation of these medications would involve risks which outweigh the value of AdreView imaging. In clinical trials, patients were not eligible for AdreView imaging if they were receiving medications in the above categories and the risks for medication withdrawal were unacceptable or if they were

not clinically stable (e.g., experiencing continuing chest pain, hemodynamic instability, or clinically significant arrhythmia).

### **Imaging Errors due to Conditions that Affect the Sympathetic Nervous System**

Individuals with conditions that affect the sympathetic nervous system, e.g., Parkinsonian syndromes such as Parkinson's disease or multiple system atrophy, may show decreased cardiac uptake of AdreView independent of heart disease.

### **Hypertension**

Assess the patient's pulse and blood pressure before and intermittently for 30 minutes after AdreView administration. Rapid administration of AdreView may increase release of norepinephrine from chromaffin granules and produce a transient episode of hypertension. Prior to AdreView administration, ensure emergency cardiac and anti-hypertensive treatments are readily available.

### **Carcinogenesis and Mutagenesis**

Iobenguane hemisulfate was not mutagenic *in vitro* in the Ames bacterial mutation assay and in the *in vitro* mouse lymphoma test, and was negative in the *in vivo* micronucleus test in rats.

Long-term animal studies and studies in humans have not been conducted to evaluate AdreView's carcinogenic potential or potential effects on fertility.

### **Special Populations**

**Pregnant Women:** All female patients of reproductive age should be questioned on the possibility of being pregnant. A pregnancy test should be considered if clinically indicated. Ideally examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability should be performed during the first ten days following the onset of menses.

Any radiopharmaceutical, including AdreView, has a potential to cause fetal harm. It is not known whether AdreView can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with AdreView.

AdreView should be given to a pregnant woman only if clearly needed.

**Nursing Women:** It is not known whether AdreView is excreted into human milk. If AdreView is considered necessary in a nursing woman, breast-feeding should be interrupted for six days and the expressed feeds discarded. Breast-feeding can be restarted when the total radioactivity level in the milk will not result in a radiation dose to a nursing infant of greater than 1 mSv.

**Pediatrics:** The safety and effectiveness of AdreView have been established in the age groups 1 month to 16 years in patients with known or suspected neuroblastoma (see [Clinical Trials](#)). Safety and effectiveness in pediatric patients below the age of 1 month or in any pediatric patient with congestive heart failure have not been established.

**Geriatrics:**

Oncology

The AdreView clinical study did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly population should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Cardiology

In clinical studies of AdreView in heart disease, 27% of subjects were 65-74 years of age and 17% of subjects were 75 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

AdreView is excreted by the kidneys, and the risks of adverse reactions, increased radiation dose, and occurrence of inaccurate imaging results may be greater in patients with severely impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and image interpretation. Consider assessment of renal function in elderly patients prior to AdreView administration.

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

Anaphylactic and hypersensitivity reactions have been reported. Treatment measures should be available prior to AdreView administration (See [WARNINGS and PRECAUTIONS - Hypersensitivity Reactions](#)).

**Clinical Trial Adverse Drug Reactions**

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug.

During clinical development 1346 patients were exposed to AdreView, 251 patients with known or suspected pheochromocytoma or neuroblastoma, 985 patients with heart failure, and

110 control patients. All patients were monitored for adverse reactions over a 24 hour period following AdreView administration.

### **Oncology**

Serious adverse reactions were not observed in the AdreView clinical study. The average ages were 49 years (range 17 - 88 years) for adults and, for pediatric patients, 4 years (range 1 month - 16 years). Slightly less than half the patients were male. Adverse reactions were all mild to moderate in severity and were predominantly isolated occurrences ( $\leq 2$  patients) of one of the following reactions: dizziness, rash, pruritus, flushing or injection site hemorrhage.

### **Cardiology**

No serious adverse reactions to AdreView were observed in clinical studies. Adverse reactions that occurred with a frequency  $> 1\%$  were associated with the injection site (1.3%) including hematoma, erythema, edema and pain. The other most common reactions were flushing (0.3%), chest pain (0.3%) and headache (0.4%). The adverse reactions were predominantly of mild to moderate intensity.

### **Post-Market Adverse Drug Reactions**

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions have uncommonly been reported during the postmarketing use of AdreView. (See [\*WARNINGS and PRECAUTIONS - Hypersensitivity Reactions\*](#)).

### **DRUG INTERACTIONS**

The following drugs have the potential to interfere with AdreView imaging results: antihypertensives that deplete norepinephrine stores or inhibit reuptake (e.g., reserpine, labetalol), antidepressants that inhibit norepinephrine transporter function (e.g., amitriptyline and derivatives, imipramine and derivatives, selective serotonin reuptake inhibitors), sympathomimetic amines (e.g., phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine), and cocaine. Clinical studies have not determined which specific drugs may cause inaccurate imaging results nor whether all drugs in any specific pharmacologic class have the same potential to produce the inaccurate imaging results. Increasing the dose of AdreView will not overcome any potential uptake limiting effect of these drugs. Before AdreView administration, discontinue (for at least 5 biological half-lives) drugs known or expected to interfere with uptake of this agent, as clinically tolerated. (See *WARNINGS and PRECAUTIONS - Risks with Concomitant Medication Withdrawal*)

Interactions with food, herbs, and laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Thyroid Blockade

Before administration of AdreView to patients at risk for thyroid accumulation of unbound I123, administer appropriate blocking agents such as 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) to block uptake of <sup>123</sup>I by the patient's thyroid. Administer the blocking agent at least one hour before the dose of AdreView. Thyroid blockade may not be necessary for all patients; for example, those who have undergone thyroidectomy or those with a very limited life expectancy.

### Patient Preparation

Prior to administration, question the patient for a history of prior reactions to iodine, an iodine-containing contrast agent or other products containing iodine.

Patients should be encouraged to drink large volumes of fluids to facilitate excretion of AdreView.

Patients should be encouraged to void prior to imaging.

Patients should have discontinued all medications that could interfere with uptake of AdreView (See [Drug Interactions](#)).

### Dosing Considerations

The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

### Dosage

**Adults:** the recommended dose is 370 MBq

**Pediatric Patients:** the dose should be scaled according to patient body weight as shown in Table 4.

**Table 4: AdreView Dose Preparation for Pediatric Patients\***

Weight (kg)	Fraction of adult activity	AdreView (mCi) pediatric dose	AdreView (MBq) pediatric dose
3	0.1	1	37
4	0.14	1.4	52
6	0.19	1.9	70
8	0.23	2.3	85.1
10	0.27	2.7	99.9
12	0.32	3.2	118.4
14	0.36	3.6	133.2
16	0.4	4	148

18	0.44	4.4	162.8
20	0.46	4.6	170.2
22	0.5	5	185
24	0.53	5.3	196.1
26	0.56	5.6	207.2
28	0.58	5.8	214.6
30	0.62	6.2	229.4
32	0.65	6.5	240.5
34	0.68	6.8	251.6
36	0.71	7.1	262.7
38	0.73	7.3	270.1
40	0.76	7.6	281.2
42	0.78	7.8	288.6
44	0.8	8	296
46	0.82	8.2	303.4
48	0.85	8.5	314.5
50	0.88	8.8	325.6
52	0.9	9	333
54	0.9	9	333
56	0.92	9.2	340.4
58	0.92	9.2	340.4
60	0.96	9.6	355.2
62	0.96	9.6	355.2
64	0.98	9.8	362.6
66	0.98	9.8	362.6
68	0.99	9.9	366.3

\*Based on a reference activity for an adult scaled to body weight according to the schedule proposed by the European Association of Nuclear Medicine Paediatric Task Group.

### **Administration**

AdreView should be administered by slow intravenous injection into a peripheral vein, over 1 to 2 minutes.

### **Image Acquisition and Interpretation - Oncology**

**Image Acquisition:** Begin whole body planar scintigraphy imaging  $24 \pm 6$  hours following administration of AdreView. Single photon emission computed tomography (SPECT) and SPECT/CT if available may be performed following planar scintigraphy, as appropriate.

### **Image Acquisition and Interpretation – Cardiology**

Begin anterior planar imaging of the chest at 4 hours ( $\pm 10$  minutes) following administration of AdreView. The recommended collimator for all imaging is a low-energy high-resolution. The recommended matrix for planar images is 128x128. The camera should be positioned to include the entire heart and as much of the upper chest as possible within the field of view.

A clinical dose of 10 mCi (370 MBq) also allows single photon emission computed tomography (SPECT) if required.

### **Estimation of the Heart/Mediastinum (H/M) Ratio**

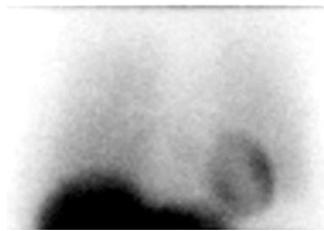
Initial evaluation of cardiac AdreView images involves visual examination of the location, pattern and intensity of cardiac radioactivity uptake to guide quantitative assessment (see Step 1 below). Perform quantitative assessment of radioactivity uptake in terms of the heart/mediastinum ratio (H/M) on anterior planar images of the chest (see Step 2 below).

### **Step 1. Visual Guidelines for AdreView Cardiac Uptake on Anterior Planar Chest Images**

#### **a. Normal:**

Distinct visualization of the left ventricular myocardium in the left lower chest, with greater uptake in the heart than in the adjacent lungs and mediastinum (Figure 1).

**Figure 1. Normal anterior planar AdreView image of the chest**

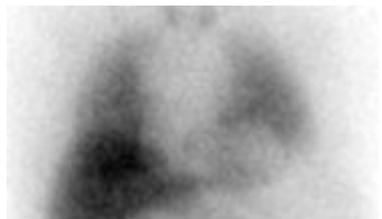


#### **b. Abnormal:**

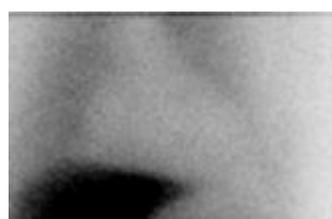
Homogeneously or heterogeneously decreased cardiac uptake, with indistinct or absent visualization of the left ventricular myocardium. Cardiac activity is usually less than or equal to that of the adjacent left lung (Figure 2a). In extreme cases, little or no AdreView uptake is seen in the left lower chest (Figure 2b).

**Figure 2. Abnormal anterior planar AdreView images of the chest: a) Heterogeneously reduced cardiac uptake; b) Absent cardiac uptake**

**Figure 2a**



**Figure 2b**

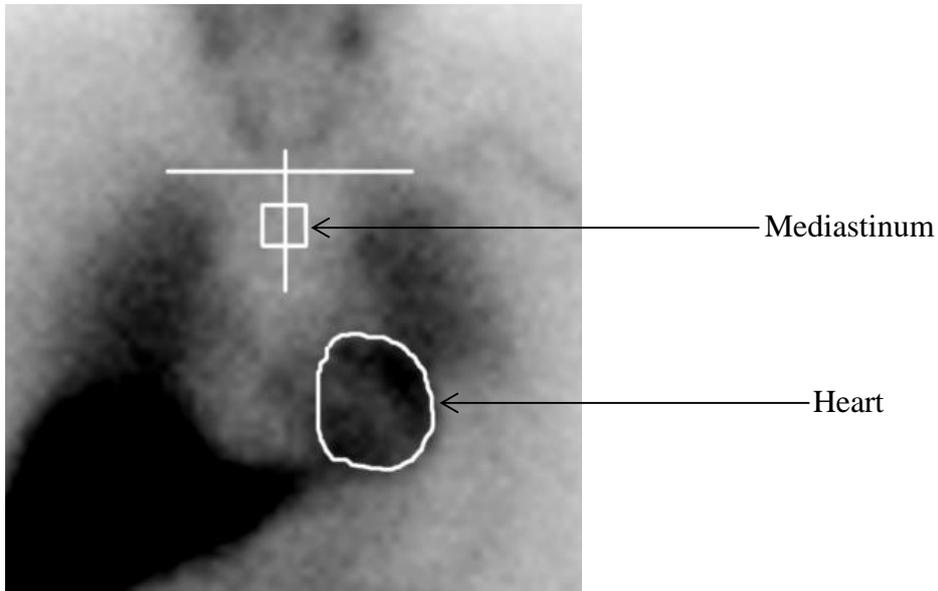


## **Step 2. Quantitate AdreView Cardiac Uptake**

The AdreView H/M ratio is determined from the activity in heart (H) and mediastinum (M) regions of interest (ROIs) drawn on the anterior planar chest image (Figure 3) using the following procedure:

- (1) Draw an irregular ROI defining the epicardial border of the heart. If the epicardial border cannot be defined because all or the majority of the myocardium is not visualized, draw the ROI based upon the presumed location of the heart, using the medial aspects of the left and right lower lung for anatomical guidance.
- (2) Draw a horizontal line to mark the estimated location of the lung apices. If the most superior aspect of the image does not include the lung apices (because of limited field of view for a small gamma camera), draw this line at the top of the image display.
- (3) Draw a vertical line approximately equidistant from the medial aspects of the right and left lung.
- (4) Examine the counts for the 12 pixels along the vertical line starting 4 pixels below the intersection point with the horizontal line determined in step 2, and identify the pixel with the lowest counts. If more than one pixel has this same number of counts, choose the most superiorly located pixel.
- (5) Using the pixel defined in step 4 as the center, draw a square ROI of 7x7 dimensions.
- (6) Calculate the H/M ratio by dividing the counts/pixel in the total myocardium ROI determined in step 1 by the counts/pixel in the 7x7 pixel mediastinal ROI determined in step 5.

**Figure 3. Illustration of creation of regions of interest for determination of the H/M ratio**



**Step 3. Interpretation of AdreView H/M Ratio**

The expected range for AdreView H/M ratio is 1.0 to 2.4 [see *Clinical Studies (14.2)*].

**Figure 4. Examples of AdreView Images in Subjects with low and high H/M ratios**



H/M=1.38



H/M=2.03

### **Instructions for Preparation and Use**

AdreView is supplied as a ready-to-use intravenous solution.

Aseptic conditions must be observed during withdrawal of a patient dose from the vial, including microbial decontamination of the rubber stopper with a suitable disinfectant before removal of a dose.

This product contains no preservatives. After removal of a dose from the vial, store at 2°C - 8°C and use within one working day.

## RADIATION DOSIMETRY

For all age groups, the critical organ is the liver, followed by the urinary bladder. The absorbed radiation dose to the bladder can be reduced by ensuring adequate hydration to promote frequent voiding.

The adult effective dose is 1.3E-02 mSv/MBq, resulting in an effective dose of 4.8 mSv after an administered activity of 370 MBq.

**Table 5: ICRP 80 Dosimetry<sup>d</sup>**

	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	1.7E-02	2.2E-02	3.2E-02	4.5E-02	7.1E-02
Bladder	4.8E-02	6.1E-02	7.8E-02	8.4E-02	1.5E-01
Bone surfaces	1.1E-02	1.4E-02	2.2E-02	3.4E-02	6.8E-02
Brain	4.7E-03	6.0E-03	9.9E-03	1.6E-02	2.9E-02
Breast	5.3E-03	6.8E-03	1.1E-02	1.7E-02	3.2E-02
Gallbladder	2.1E-02	2.5E-02	3.6E-02	5.4E-02	1.0E-01
Stomach	8.4E-03	1.1E-02	1.9E-02	3.0E-02	5.6E-02
SI	8.4E-03	1.1E-02	1.8E-02	2.8E-02	5.1E-02
Colon	8.6E-03	1.1E-02	1.8E-02	2.9E-02	5.2E-02
(ULI	9.1E-03	1.2E-02	2.0E-02	3.3E-02	5.8E-02)
(LLI	7.9E-03	1.0E-02	1.6E-02	2.3E-02	4.3E-02)
Heart	1.8E-02	2.4E-02	3.6E-02	5.5E-02	9.7E-02
Kidneys	1.4E-02	1.7E-02	2.5E-02	3.6E-02	6.1E-02
Liver	6.7E-02	8.7E-02	1.3E-01	1.8E-01	3.3E-01
Lungs	1.6E-02	2.3E-02	3.3E-02	4.9E-02	9.2E-02
Muscles	6.6E-03	8.4E-03	1.3E-02	2.0E-02	3.7E-02
Oesophagus	6.8E-03	8.8E-03	1.3E-02	2.1E-02	3.7E-02
Ovaries	8.2E-03	1.1E-02	1.6E-02	2.5E-02	4.6E-02
Pancreas	1.3E-02	1.7E-02	2.6E-02	4.2E-02	7.4E-02
Red marrow	6.4E-03	7.9E-03	1.2E-02	1.8E-02	3.2E-02
Skin	4.2E-03	5.1E-03	8.2E-03	1.3E-02	2.5E-02
Spleen	2.0E-02	2.8E-02	4.3E-02	6.6E-02	1.2E-01
Testes	5.7E-03	7.5E-03	1.2E-02	1.8E-02	3.3E-02
Thymus	6.8E-03	8.8E-03	1.3E-02	2.1E-02	3.7E-02
Thyroid	5.6E-03	7.3E-03	1.2E-02	1.9E-02	3.6E-02
Uterus	1.0E-02	1.3E-02	2.0E-02	2.9E-02	5.3E-02
Remaining organs	6.7E-03	8.5E-03	1.3E-02	2.0E-02	3.7E-02
<b>Effective dose (mSv/MBq)</b>	<b>1.3E-02</b>	<b>1.7E-02</b>	<b>2.6E-02</b>	<b>3.7E-02</b>	<b>6.8E-02</b>

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The major manifestations of overdose relate predominantly to increased radiation exposure, with the long term risks for neoplasia.

The primary effects of an overdose of iobenguane are due to the release of norepinephrine. This effect is of short duration and requires supportive measures aimed at lowering the blood pressure. Depending on the severity of overdose, prompt injection of a short acting alpha-adrenergic blocking agent (phentolamine) followed by a beta-blocker (propranolol) may be needed.

The patient should be well hydrated to promote a high urine flow and encouraged to void frequently to reduce the absorbed radiation dose to the bladder.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Iobenguane is similar in structure to the antihypertensive drug guanethidine and to the neurotransmitter norepinephrine (NE). Iobenguane is, therefore, largely subject to the same uptake and accumulation pathways as NE. Iobenguane is taken up by the NE transporter in adrenergic nerve terminals and stored in the presynaptic storage vesicles. Iobenguane accumulates in adrenergically innervated tissues such as the adrenal medulla, salivary glands, heart, liver, spleen and lungs as well as tumors derived from the neural crest. By labeling iobenguane with  $^{123}\text{I}$ , it is possible to obtain scintigraphic images of the organs and tissues in which the radiopharmaceutical accumulates.

### Pharmacodynamics

AdreView contains microgram quantities of iobenguane and is not expected to produce a significant pharmacodynamic effect. Although a structural and functional analogue of norepinephrine (NE), iobenguane possesses only weak sympathomimetic properties and is a poor ligand for adrenergic receptors. However a rapid administration of AdreView may cause a rapid displacement of norepinephrine from intraneuronal storage granules causing sympathomimetic effects such as palpitations, transient hypertension, dyspnea and flushing.

### Pharmacokinetics

AdreView is rapidly cleared from the blood and accumulates in adrenergically innervated tissues. Uptake is greatest in organs with high levels of sympathetic innervation, including the liver, spleen, heart, lungs, adrenal and salivary glands.

The majority of the AdreView dose is excreted unaltered by glomerular filtration. A rapid initial clearance is followed by a slow phase as iobenguane is released from other compartments. In patients with normal renal function, 70 to 90% of the administered dose is recovered unaltered in urine within 4 days. Most of the remaining radioactivity recovered in the urine is in the form of the radioiodinated metabolite *m*-iodohippuric acid (MIHA) (typically  $\leq 10\%$ ) and free radioiodide (typically  $\leq 6\%$ ). The enzymatic process responsible for metabolism has not been well characterized and the pharmacologic activity of these metabolites has not been studied. Only a small amount ( $< 1\%$ ) of the injected dose is eliminated via the feces.

**Renal Insufficiency:** The elimination of iobenguane ( $^{123}\text{I}$ ) is decreased with decreasing renal function. There is essentially no clearance in the anephric patient. Hemodialysis does not effectively remove iobenguane ( $^{123}\text{I}$ ) from the circulation.

## STORAGE AND STABILITY

AdreView may be stored at 20 to 25 °C. Do not freeze.

This product contains no preservatives. After removal of a dose from the vial, store at 2° to 8°C and use within one working day.

Radiochemical purity is maintained for 36 hours from the time of calibration.

The 13.2-hour half-life of  $^{123}\text{I}$  is the limiting factor in the useful clinical-life of AdreView. Beyond the date and time of calibration, it is not possible to obtain a full adult dose (370 MBq). If a dose of AdreView is administered to an adult patient after the calibration time, adjustment in imaging parameters (e.g. acquisition time and image duration) may be necessary to ensure that images of adequate quality for diagnostic interpretation are obtained. Beyond 36 hours after calibration, it is unlikely that sufficient radioactivity remains to acquire a diagnostic image.

## SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

AdreView is a sterile, pyrogen-free solution for intravenous injection containing 74 MBq/mL of iobenguane ( $^{123}\text{I}$ ) in 5 mL for a total activity at calibration of 370 MBq.

The final drug product also contains iobenguane sulfate, a phosphate buffer, and (1% v/v) benzyl alcohol as a radiostabilizer.

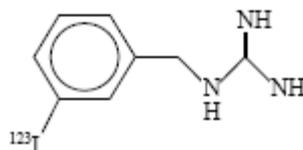
The product is supplied in 10 ml USP Type 1 glass vials sealed with a rubber closure and oversealed with an aluminum seal. The sealed vials are terminally sterilized by autoclave and shipped in lead containers.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Common names:	Iobenguane ( $^{123}\text{I}$ ) Metaiodobenzyl guanidine ( $^{123}\text{I}$ ) injection $^{123}\text{I}$ -mIBG
Chemical names (2:1)	1-(3- $^{123}\text{I}$ iodobenzyl)guanidine sulfate
(2:1)	(( <i>m</i> -Iodo- $^{123}\text{I}$ )-benzyl)guanidine sulfate
U.S. Adopted Name (USAN)	Iobenguane sulfate $^{123}\text{I}$
International Non-Proprietary Name (INN)	Iobenguane ( $^{123}\text{I}$ )
Molecular formula / mass:	$\text{C}_8\text{H}_{10}^{123}\text{IN}_3 / 271$
Structural formula:	



#### Product Characteristics

Iobenguane ( $^{123}\text{I}$ ) injection is a clear, colourless aqueous solution with a pH of 5.0 to 6.5.

Not less than 97% of the total radioactivity in AdreView is from  $^{123}\text{I}$ . Not less than 95% of the total radioactivity is in the chemical form of iobenguane ( $^{123}\text{I}$ ).

$^{123}\text{I}$ -(free Iodide) and others are not more than 5.0 % of total chromatographic peak area for the radiochemical impurities. All other radionuclidic impurities ( $^{121}\text{Te}$ ,  $^{121}\text{I}$  and others) are not more than 3.0% of the total radioactivity.

AdreView is carrier-added.

## CLINICAL TRIALS

### *Oncology*

The safety and efficacy of AdreView were assessed in an open-label, multicenter, multinational trial of 251 subjects with known or suspected neuroblastoma or pheochromocytoma.

Diagnostic efficacy for the detection of metabolically active neuroblastoma or pheochromocytoma was determined by comparison of focal increased radionuclide uptake on planar scintigraphy at  $24 \pm 6$  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. 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, iobenguane ( $^{131}\text{I}$ ) scintigraphy], plasma/urine catecholamine and/or catecholamine metabolite measurements, and clinical follow-up. Of the 250 subjects included in the total evaluable efficacy population (1 dosed subject was withdrawn for a protocol violation), 159 were classified as having active tumour, 52 subjects were classified as not having active tumour, and 39 were classified as indeterminate (see Table 6).

**Table 6: Standard of Truth (All-Dosed Efficacy Population)**

		Active Tumour Present?			If Yes, Type of Tumour	
		Yes	No	Indeterminate	Pheochromocytoma	Neuroblastoma
	N	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Total</b>	<b>250</b>	159 (63.6)	52 (20.8)	39 (15.6)	92 (57.9)	67 (42.1)
<b>Histology*</b>	<b>50</b>	42 (84.0)	8 (16.0)	0	22 (52.4)	20 (47.6)
<b>Expert Panel</b>	<b>200</b>	117 (58.5)	44 (22.0)	39 (19.5)	70 (59.8)	47 (40.2)

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. In the calculations of sensitivity and specificity for the trial, the results for one subject with non-diagnostic images per Reader A and C were excluded. Table 7 summarizes the AdreView performance characteristics, by tumour type and by reader.

**Table 7. AdreView Diagnostic Accuracy (Planar Imaging)**

	Neuroblastoma			Pheochromocytoma		
	Reader A	Reader B	Reader C	Reader A	Reader B	Reader C
<b>Sensitivity</b>						
N	67	67	67	92	92	92
Estimate	0.81	0.78	0.79	0.79	0.77	0.78
95% CI	0.69, 0.89	0.66, 0.87	0.67, 0.88	0.70, 0.87	0.67, 0.85	0.68, 0.86
<b>Specificity</b>						
N	17	17	17	35	35	35
Estimate	0.71	0.71	0.76	0.80	0.74	0.66
95% CI	0.44, 0.90	0.44, 0.90	0.50, 0.93	0.63, 0.92	0.57, 0.88	0.48, 0.81

Based on the analysis from the same data in the publications<sup>r,s</sup>, the sensitivity and the specificity were 82% and 82% for the pheochromocytoma and 88% and 83% for the neuroblastoma patient groups.

Among the selected patients who also underwent SPECT imaging and based on a combined analysis of neuroblastoma and pheochromocytoma, sensitivity for all readers for the SPECT plus planar imaging population was comparable to the corresponding sensitivity for the planar imaging population alone, while the specificity was lower.

Additional analyses stratifying results by presence or absence of “current” histology are presented in Table 8. Histopathology was considered “current” if the tissue was obtained prior to study imaging procedures and no interval therapy was received, or if the tissue was obtained within 30 days of the imaging procedure. In cases where current histology was not available, the standard of truth was determined by an expert panel.

**Table 8. Estimates of Sensitivity and Specificity by Presence of Current Histopathology**

	YES			NO		
	Reader A	Reader B	Reader C	Reader A	Reader B	Reader C
<b>Sensitivity</b>						
N	42	42	42	117	117	117
Estimate	0.86	0.83	0.83	0.78	0.75	0.77
95% CI	0.71, 0.95	0.69, 0.93	0.69, 0.93	0.69, 0.85	0.66, 0.83	0.68, 0.84
<b>Specificity</b>						
N	8	8	8	44	44	44
Estimate	1.00	0.75	1.00	0.73	0.73	0.64
95% CI	0.63, 1.00	0.35, 0.97	0.63, 1.00	0.57, 0.85	0.57, 0.85	0.48, 0.78

### **Cardiology**

The safety and efficacy of AdreView were evaluated in two open label, multicenter trials in patients with New York Heart Association (NYHA) class II or III heart failure and left ventricular ejection fraction  $\leq 35\%$ . The trials excluded subjects with an acute myocardial infarction within the prior thirty days, subjects with a functioning ventricular pacemaker as well as subjects who had received defibrillation to treat a previous arrhythmic event. Subjects underwent AdreView myocardial imaging (planar and SPECT) and continued standard clinical care; AdreView results were not used in a patient’s clinical care. AdreView images in each trial were processed by a central technologist and reviewed by three independent readers who assessed the H/M ratio on 3 hour 50 minute post-injection planar scintigraphy. Readers were masked to clinical information and the majority read value was used in analyses. The prognostic performance of the H/M ratio in estimating mortality was analyzed using the pre-specified 1.6 ratio cut-point to distinguish patients with higher risk from those with lower risk; other cut-points were also analyzed.

A subsequent Phase 3 clinical trial was designed and conducted to obtain additional follow-up data on HF subjects enrolled in previous pivotal trials, extending the observational period to 24 months. Additionally, the data was re-evaluated to focus on all-cause mortality as the primary endpoint rather than adverse cardiac events (defined as HF progression, potentially fatal arrhythmic events and cardiac death). The strength of the AdreView test as a significant predictor of all-cause mortality was then evaluated using a multivariate Cox proportional hazards regression model.

Within the two trials, 964 patients were enrolled; 80% were men, 83% were categorized as NYHA class II and 17% as class III. The average age was 62 years (range 20 - 90 years of age). Most patients had ischemic heart disease (66%) and a history of smoking (74%). The patients were on a stable regimen of cardiovascular medications, including angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) (93%) and beta-blockers (92%). The range of AdreView H/M ratios in these subjects was 1.0-2.4 [mean 1.4 ( $\pm 0.2$  standard deviation)].

Within the two trials, 94 age-matched control subjects without heart disease were enrolled, 64% were men, average age was 59 years (range 29 - 82 years of age). The range of AdreView H/M ratios in these subjects was 1.1-2.4 [mean 1.8 ( $\pm$  0.2 standard deviation)].

*One Year Results:* By 12 months following enrollment, 50 (5%) patients had died, 61 (6%) had missing follow-up information and three patients had missing H/M ratios.

*Two Year Results:* By 23 months following enrollment (the requirement for designation of two-year follow-up), 96 (10%) patients had died, 201 (21%) patients had missing follow-up information and three patients had missing H/M ratio data.

*H/M Ratio Prognostic Performance Characteristics:*

Mortality results were used to estimate the baseline H/M ratio prognostic performance characteristics. In these estimates, various H/M ratio “cut points” were used to group patients into those with higher versus lower H/M values,. The group of patients who died was examined to determine the probability of these patients having had a lower baseline H/M ratio. The group of patients who survived was examined to determine the probability of these patients having had a higher baseline H/M ratio. Based upon these results, the prognostic usefulness of any given H/M ratio in a patient was estimated by the positive predictive value (PPV) and the negative predictive value (NPV). The PPV is the probability of death given a lower H/M ratio; the NPV is the probability of survival given a higher H/M ratio.

Table 9 summarizes the performance characteristics by various H/M ratio categories for one year, the time point with the most complete data.

**Table 9 One Year Mortality Outcomes and AdreView Prognostic Performance Characteristics**

H/M Group*	Subjects (n = 961)	Death	Survival**	PPV (%)	NPV (%)
< 1.2	92	12	80	13	96
≥ 1.2	869	38	831		
< 1.4	429	33	396	8	97
≥ 1.4	532	17	515		
< 1.6	760	48	712	6	99
≥ 1.6	201	2	199		
< 1.8	914	50	864	5	100
≥ 1.8	47	0	47		

\*subjects grouped by H/M ratio cut-off values; \*\*6% discontinued patients are counted as survived (non-events)

*Cox Proportional Hazards Analyses:*

The association of potential risk factors with mortality for up to two years was analyzed in Cox multivariate proportional hazard modeling that included such variables as demographics, hypertension, dyslipidemia, diabetes, cardiovascular medications, smoking, NYHA classification, LVEF and B-type natriuretic peptide (BNP). At the time of the analyses, there were 101 events (11%) and a total of 890 patients (89%) were censored. The initial model included all pre-specified variables except for H/M ratio and used backward selection of variables found to be significant risk factors of all-cause mortality ( $p < 0.05$ ) for inclusion in the final model. The final model consisted of the significant variables from the initial model plus the H/M ratio. In addition to age and BNP, in the final model, the H/M ratio was found to be a significant risk factor for mortality (Hazard Ratio= 0.23 (95% CI: 0.07, 0.76),  $p = 0.016$ ).

## DETAILED PHARMACOLOGY

See also [ACTION AND CLINICAL PHARMACOLOGY](#)

Iobenguane is a structural and functional analogue of norepinephrine (NE). Iobenguane possesses only weak sympathomimetic properties and is a poor ligand for adrenergic receptors.<sup>e,f</sup> As chemical entities, iobenguane (<sup>131</sup>I) and iobenguane (<sup>123</sup>I) are identical, and therefore data on the biodistribution, metabolism, and toxicology of iobenguane (<sup>131</sup>I) can be used to describe the behaviour of the (<sup>123</sup>I)-labelled product as well.

Iobenguane is taken up by the norepinephrine transporter (NET) with a higher affinity than NE ( $K_m=0.31 \mu\text{M}$  and  $1.8 \mu\text{M}$ , respectively), but with a similar capacity as NE. Iobenguane uptake is also sensitive to the vesicular monoamine transporter (VMAT) inhibitor reserpine.<sup>g</sup> Radiolabelled iobenguane has been observed in vesicles using electron spectroscopic imaging, indicating vesicular uptake. Iobenguane is not metabolized by either monoamine oxidase (MAO) or catechol-O-methyl transferase (COMT)<sup>h,i</sup>, therefore, the majority of iobenguane taken up by the NET is available for VMAT uptake into vesicles. NE and iobenguane can compete for uptake by the NET,<sup>j</sup> iobenguane having a slightly higher  $IC_{50}$  for uptake than NE. Specific uptake of iobenguane, by either extraneuronal monoamine transporter (EMT) or organic cation transporters 1 and 2 (OCT1 and 2), has not yet been studied, however iobenguane is known to enter cells via non-NET dependent uptake<sub>2</sub> activity.<sup>k,l</sup> Iobenguane is therefore subject to the same uptake and accumulation pathways as NE, but does not share the same catabolic pathways or pharmacodynamic effects. After every cycle of vesicular exocytosis and reuptake, NE is subject to MAO catabolism in the cytoplasm, prior to VMAT uptake into the vesicles, whereas iobenguane is not. This favours iobenguane vesicular storage over that of NE, particularly over repeated cycles of uptake and release.<sup>m</sup>

Neural crest tumours usually exhibit very high levels of both NE production and NET activity, and accumulate iobenguane to a much higher degree than that observed in normal tissues. Cell lines derived from these tumours have been used extensively to study the uptake of iobenguane. As a marker of adrenergic neuronal activity, most non-clinical work has concentrated on the uptake and efflux of iobenguane in animal models of both neural crest tumours and diseases that affect the adrenergic innervation of various tissues.

Iobenguane is rapidly cleared from the blood and accumulates in adrenergically innervated tissues including the adrenal medulla, salivary glands, heart, spleen and lungs. Between 1.5% and 10% of the injected activity remained within the vascular space at 60 minutes<sup>n</sup>. Uptake of iobenguane in the adrenal medulla and most other tissues is mediated by the mechanisms that govern intracellular localization of norepinephrine (NE), the energy-dependent NE transporter system (often referred to as uptake<sub>1</sub>) and the non-neuronal system commonly identified as uptake<sub>2</sub>. Non-neuronal accumulation is poorly retained (2 to 4 hours), whereas neuronal accumulation is retained over much longer time scales (over 24 hours). Retention is especially prolonged in highly adrenergically innervated tissues, such as adrenal medulla, heart, and salivary glands.

The majority of the iobenguane dose is excreted in the urine, with a rapid initial clearance of circulating iobenguane, followed by a slow clearance as iobenguane 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 to 90% in 96 hours. The primary component of the activity in the urine was unaltered iobenguane ( $^{131}\text{I}$ ) (>85%), with the next largest component being free  $^{131}\text{I}$  (2 to 5%). The primary metabolite of iobenguane ( $^{131}\text{I}$ ) identified was meta-iodohippuric acid (typically  $\leq 10\%$  of recovered activity), with trace amounts (<1%) of parahydroxy meta-iodobenzylguanidine and metaiodobenzoic acid seen in some patients. Less than one percent of the injected dose is eliminated via the faeces.<sup>o,p</sup>

Clearance of iobenguane ( $^{131}\text{I}$ ) 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 34 hours and 62 hours, while there was essentially no clearance in the anephric patient. In addition, iobenguane ( $^{131}\text{I}$ ) was not cleared by dialysis.<sup>q</sup>

## TOXICOLOGY

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg)	Dose Multiples – allometrically scaled based on Body Surface Area	Results
		M	F					
Single Dose	Mouse (OF1)	25 (5)	25 (5)	iv	1	30, 40, 45, 50 & 70	436, 581, 726, 1016	<p>LD<sub>50</sub> in males and females was 36 mg/kg.</p> <p>At high dose, animals died during convulsions during the injection. Other animals that died had convulsions, pallor, and apnea prior to death 3 minutes after injection. The maximum non-lethal dose was less than 30 mg/kg. The LD<sub>100</sub> was between 50 and 70 mg/kg.</p> <p>Surviving animals displayed subdued behavior and hyperpnea (following dyspnea ) for 2 hours. At 45 mg/kg subdued behavior and palpebral ptosis lasted 24 hours in 2 animals and 5 days in 1 other. No changes in body weight and gross pathology were found.</p>
Single Dose	Rat (Sprague-Dawley)	30 (5)	30 (5)	iv	1	40, 55, 60, 62, 65 & 70	1152, 1584, 1728, 1786, 1872, 2016	<p>The LD<sub>50</sub> combined for both sexes was 61 mg/kg. The maximum non-lethal dose was 40 mg/kg and the LD<sub>100</sub> was about 70 mg/kg.</p> <p>Symptoms in dying animals were subdued behavior, spasm, pallor, and prolonged apnea; the cause of death appeared to be respiratory failure.</p> <p>The injection rate had no effect on mortality at higher doses.</p> <p>Survivors exhibited subdued behavior, spasms, dyspnea and piloerection lasting up to 2 hours in higher dose animals.</p> <p>No body weight changes or gross pathological abnormalities were found.</p>

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg)	Dose Multiples – allometrically scaled based on Body Surface Area	Results
		M	F					
<b>Maximum Tolerated Dose</b>	Dog (Beagle)	4	2	iv	Varied	2.5, 5, 10, 14, & 20	248, 496, 992, 1389, 1984	<p>20 mg/kg was a lethal dose. 14 mg/kg caused transient clinical signs of toxicity (licking, salivation, nasal discharge, vomiting, loss of balance, piloerection, dyspnea, inactivation of the nictating membrane and blanching of the mucous membranes) of a short duration that generally disappeared within 30 minutes. Transitory cardiovascular effects were also seen. Additionally:</p> <ul style="list-style-type: none"> <li>• Food consumption irregular for all dose groups</li> <li>• Bodyweight loss observed in animals receiving multiple doses of 10 to 20 mg/kg <i>mIBG</i> for 7 days</li> <li>• no effects on gross pathology in the 4 multiple dose animals examined and only one animal (treated with 10 mg/kg/day for 14 days) showed congestive abnormalities of the spleen, liver and kidneys on histopathology.</li> </ul> <p>No effect levels for most clinical signs and cardiovascular measurements was 2.5 mg/kg.</p>
<b>7 Day Repeat Dose Toxicity</b>	Rat (Sprague-Dawley)	17	16	iv	7	10, 20, 30, 40	288, 576, 864, 1152	<p>Maximum non-lethal dose 10 mg/kg.</p> <p>Repeated intravenous administration at 20 to 40 mg/kg induced signs of serious clinical toxicity: polypnea, dyspnea, apnea and ataxia lasting no more than a few minutes; and subdued behavior lasting up to 1 hour. Deaths which occurred were due to irreversible apnea.</p> <p>No local adverse reactions at the injection site. No overt treatment related effects on food consumption or body weight. The only gross pathologic finding was haemorrhagic lungs due to respiratory effort.</p>

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg)	Dose Multiples – allometrically scaled based on Body Surface Area	Results
		M	F					
<b>14 Day Repeat Dose Toxicity</b>	Rat (Sprague-Dawley)	40 (10)	40 (10)	iv	14	0, 5, 10, 20	0, 144, 288, 576	<p>Maximum non-lethal dose and no effect level was 10 mg/kg/day.</p> <p>High dose animals showed subdued behavior (reflexes, co-ordination) and respiratory difficulty (polypnea, dyspnea and apnea) lasting a few minutes after each injection.</p> <p>Three deaths due to apnea occurred at 20 mg/kg.</p> <p>No local adverse reactions at injection site.</p> <p>No major or dose related changes in bodyweight, food consumption, haematology, clinical chemistry and urinalysis measurements except for dramatic elevations in urinary glucose without changes in blood glucose in about 50% of the high dose animals.</p> <p>Liver weights were greater in high dose males, and heart weights were greater in high dose females. These effects were not observed at 10 mg/kg/day.</p> <p>Histopathology showed no macroscopic or microscopic changes in any organs at any dose.</p>
<b>14 Day Repeat Dose Toxicity</b>	Dog (Beagle)	16 (4)	16 (4)	iv	14	0, 2.5, 5, 10	0, 248, 496, 992	<p>No animals died during the study.</p> <p>Clinical signs frequently observed at 5 and 10 mg/kg throughout the study were dyspnea, pale buccal mucosa, prolapse of the nictitating membrane and ptialism. The latter two were observed less frequently at 2.5 mg/kg. Piloerection, agitation, chewing movements, loss of balance, and head shaking were also occasionally seen at 5 and 10 mg/kg</p> <p>No local reactions at the injection sites.</p>

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg)	Dose Multiples – allometrically scaled based on Body Surface Area	Results
		M	F					
								<p>Body weighted gain decreased in a dose dependent manner</p> <p>On Day 1, mean blood pressure (both diastolic and systolic) rose in all animals treated with <i>mIBG</i> but not in controls but there was no clear dose relationship. On Day 14, there were also mean blood pressure increases but these were less pronounced and of shorter duration.</p> <p>In addition on Day 1, mean heart rate at the end of the injection was slowed compared to controls and was persistent in most animals in the 2 highest dose groups throughout the 20 to 80 minute observation period. However findings were inconsistent on Day 14 with transient decreased heart rate at 2.5 mg/kg, <i>mIBG</i> but increased heart rate at 5 and 10 mg/kg which fell to below baseline by the end of the observation period.</p> <p>Changes in ECG were also noted but again these were inconsistent. T wave amplitude was increased and persistent at all doses on Day 1 and in the two highest dose groups on Day 14. The PR interval also shortened persistently in response to <i>mIBG</i> administration at all doses on Day 1 but again on Day 14, the effect was only observed at the end of the injection in the 5 and 10 mg/kg groups, but not afterwards.</p> <p><i>mIBG</i> did not affect the duration of the QRS wave or QT interval.</p> <p>Other ECG findings (specifically increased incidences of junctional premature beats and ventricular premature beats, abnormal shape of the QRS wave) indicated problems in ventricular conduction caused by <i>mIBG</i>. These ECG abnormalities appeared in all dose groups and not the controls, but did not exhibit a dose/response relationship. The incidence of these ECG findings was</p>

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg)	Dose Multiples – allometrically scaled based on Body Surface Area	Results
		M	F					
								<p>lower on Day 14 than on Day 1.</p> <p>No effect level for the cardiac abnormalities was not determined as the observations occurred at all doses.</p> <p>No treatment related ophthalmic effects were seen .</p> <p>All haematology tests were negative except for:</p> <ul style="list-style-type: none"> <li>- dose related increase in platelet counts in females ; but, the count at the 2.5 mg/kg was within the normal range and was considered to be the no effect level.</li> <li>- Activated partial thromboplastin time was elevated in females dosed with 10 mg/kg. The no effect level was 5 mg/kg in this study.</li> </ul> <p>No dose-related effects on any of the clinical chemistry or urinalysis values .</p> <p>Mean prostate weights were reduced in males treated with 5 or 10 mg/kg. The no effect level on the mean prostate weight was 2.5 mg/kg.</p> <p><i>m</i>IBG administration did not produce macroscopic or microscopic changes in organs/tissues at any dose</p>

**Reverse Mutation in 5 Histidine-Requiring Strains of *Salmonella typhimurium* (Ames Test)**

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (µg/plate)	Dose Multiples based on Body Surface Area Conversions	Results
		M	F					
Genetic Toxicology: m-Iodobenzylguanidine hemisulphate (mIBG): Reverse mutation in five histidine-requiring strains of <i>Salmonella typhimurium</i> (GLP)	<i>In Vitro Salmonella typhimurium</i>  TA98 TA100 TA1535 TA1537 TA102	NA	NA	NA	Incubation for 3 days in agar plates with and without S9	Range Finder (TA100) 0 (negative solvent control) 1.6, 8, 40, 200, 1000, 5000  Experiment 1: 0 (negative solvent control) 1.6, 8, 40, 200, 1000, 5000  Experiment 2: 0 (negative solvent control) 8.192, 20.48, 51.2, 128, 320, 800, 2000, 4000, 5000	NA	Did not induce mutation in the absence or in the presence of a rat liver metabolic activation system (S9).

### Mutation at the Thymidine Kinase Locus of the Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre® Fluctuation Technique

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (µg/ml)	Dose Multiples based on Body Surface Area Conversions	Results
		M	F					
Genetic Toxicology: m-Iodobenzylguanidine hemisulphate (mIBG): Mutation at the thymidine kinase locus of the mouse lymphoma L5178Y cells (MLA) using the Microtitre® fluctuation technique (GLP)	<i>In Vitro</i> cell culture: L5187Y TK <sup>(+/-)</sup> mouse lymphoma cells.	NA	NA	NA	3 hours treatment with and without S9  24 hours treatment without S9	Range Finder (3 hours): 0 (negative solvent control) 67.19, 134.4, 268.8, 537.5, 1075, 2150  Range Finder (24 hours): 0 (negative solvent control), 0.625, 1.25, 2.5, 5, 10, 20, 40, 80, 160, 320  Experiment 1 (3 hours): 0 (negative solvent control), 25, 40, 55, 70, 85, 100, 115, 130  Experiment 2 (3 hours): 0 (negative solvent control), 25, 40, 55, 70, 85, 100, 115, 130, 145, 160  Experiment 2 (24 hours): 0 (negative solvent control), 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, 30	NA	Did not induce a reproducible and unequivocal increase in mutant frequency in the absence or presence of S-9 and is therefore not considered to be positive in this <i>in vitro</i> assay.

### Induction of Micronuclei in the Bone Marrow of Treated Rats

Study Type	Animals Species (Strain)	Total No. of Animals (no. animals per dose group)		Route	No. of Dosings	Dose (mg/kg/day)	Dose Multiples based on Body Surface Area Conversions	Results
		M	F					
m-Iodobenzylguanidine hemisulphate (mIBG): Induction of micronuclei in the bone marrow of treated rats (GLP)	Sprague Dawley CrI:CD (SD) IGS BR rats	9	35	Iv	Each rat was administered doses of vehicle, mIBG or positive control solution baed on a dose volume of 10 mL/kg. Animals were dosed once daily for two consecutive days with vehicle or mIBG via slow bolus injection over approximately 1 minute into the tail vein.	Range finding: 5, 7, 10, 25.6  Main study: 0 (vehicle control) 2.5, 5, 10  Dosing preparations were made by dissolving m-Iodobenzylguanidine hemisulphate (mIBG) in 20% (v/v) PEG 400 in phosphate buffered saline, pH 7.4	Range finding: 144, 202, 288, 737	Did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats treated with up to MTD of 10 mg/kg/day

Long-term animal studies have not been conducted to evaluate AdreView's carcinogenic potential or potential effects on fertility.

Iobenguane sulfate testing in dogs revealed electrocardiographic (ECG) changes after administration of 202 times the  $\text{mg}/\text{m}^2$  conversion of the maximum human dose for a 60 kg adult; the no observable effect level (NOEL) was not determined. When iobenguane was tested in a cell system stably expressing hERG-1 potassium channels, inhibition of potassium channels was not observed at an 80  $\mu\text{M}$  iobenguane concentration; the  $\text{IC}_{50}$  was 487  $\mu\text{M}$ .

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## PART III: CONSUMER INFORMATION

For a full listing of non-medicinal ingredients see Part 1 of the product monograph.

### AdreView™ (Add-rah-view)

Iobenguane (<sup>123</sup>I) injection

This leaflet is part III of a three-part "Product Monograph" published when AdreView was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AdreView. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

AdreView is a radioactive diagnostic product used to:

- look for a certain type of tumour, or
- examine the function of the heart muscle in patients who have been diagnosed with moderate heart failure.

#### What it does:

AdreView attaches to certain types of tumors (called neuroendocrine tumors) and to certain types of nerves (called sympathetic neurons). After you get the injection, pictures will be taken with a special machine (a Gamma Camera). These pictures may be taken on the same day or within 2 days following radiotracer injection. If the test is being done to look for tumours, the specialist will be able to see if AdreView accumulates in tissues or organs suspected of having a tumour. This will help your doctor make a diagnosis of your disease. If the test is being done to look at the heart, the specialist will be able to see how well the nerves to the heart muscle are functioning. The results of this test in addition to results of other tests will help your doctor determine your risk of dying.

#### When it should not be used:

AdreView should not be used in patients that are allergic (hypersensitive) to iobenguane or one of the other ingredients.

#### What the medicinal ingredient is:

The medicinal ingredient is iobenguane which is tagged with radioactive iodine (<sup>123</sup>I). Iobenguane is a man-made chemical similar to guanethidine which is a drug for treating high blood pressure. Iodine (<sup>123</sup>I) is a radioactive form of iodine. We consume iodine every day in our diet, but it is not radioactive.

The iobenguane takes the iodine (<sup>123</sup>I) to the target. The gamma camera sees only the iodine (<sup>123</sup>I).

#### What the important non-medicinal ingredients are:

AdreView contains benzyl alcohol. Benzyl alcohol is safe for most people but has been associated with a fatal "Gaspings Syndrome" in premature infants and infants of low birth weight.

### WARNINGS AND PRECAUTIONS

#### **Serious Warnings and Precautions**

Anaphylactic and hypersensitivity reactions have been reported. Tell your doctor if you have had allergic reactions to other diagnostic agents or iodine-containing products. AdreView contains a small amount of a non-medicinal ingredient known as benzyl alcohol (10.3 mg/ml) which may cause serious reactions in premature or low birth-weight infants under certain circumstances. If you have concerns in this regard, discuss this matter with the Doctor.

BEFORE you receive AdreView tell your doctor:

- if you have had an allergic reaction to other diagnostic agents or other iodine-containing products;
- if you are or could be pregnant. Nuclear medicine tests carried out on pregnant women also involve radiation doses to the foetus;
- if you are breastfeeding. Small amounts of radioactivity may pass into the mother's milk and you should stop breastfeeding temporarily for a few days. The doctor will let you know when you can start breast feeding again;
- what medications you are taking. Some medications can interfere with AdreView (*see below*);
- if you have reduced kidney function please tell your doctor. For people with reduced kidney function, this means a delay in taking the pictures may be needed (perhaps 2 days after the injection), and therefore you may have to return to the clinic at that time. You will be informed at the time of injection as when the pictures will be taken.

### INTERACTIONS WITH THIS MEDICATION

A large number of drugs are known or suspected to interfere with AdreView. These include antidepressants, antipsychotics, decongestants, some antihypertensives, some bronchodilators, some bladder medications, amphetamines, and cocaine.

Make sure your doctor knows what medications you are taking.

### PROPER USE OF THIS MEDICATION

AdreView will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

You should drink large glasses of water before and after you get your injection of AdreView, and urinate frequently in the hours after your injection to reduce the amount of radioactivity in your bladder.

## **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

An allergic reaction could cause one or more of the following: flushing, itching, rash, swelling around the throat or tongue, difficulty swallowing, and difficulty breathing. Report any of these effects immediately to the doctor or other medical staff at the Facility where you receive the injection and test.

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at**  
[www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: **Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, GE Healthcare Canada Inc at: 1-800-387-7146  
This leaflet was prepared by GE Healthcare

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