1. NAME OF THE MEDICINAL PRODUCT

AdreView, Iobenguane (^{123}I) Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Iobenguane (^{123}I), 37 – 740 MBq/vial (74 MBq/ml at calibration date and hour)

Iodine-123 is a cyclotron product with a physical half-life of 13.21 h.
Iodine-123 decays emitting pure gamma radiation with predominant energies of 159 keV and 27 keV.

Excipients with known effect:
Benzyl alcohol: 10.4 mg/ml
Sodium: 4.23 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

4.1.1 Oncology: Detection and staging of neural crest tumours

- Diagnostic scintigraphic localisation of tumours originating in tissue that embryologically stems from the neural crest. These are pheochromocytomas, paragangliomas, chemodectomas and ganglioneuromas.
- Detection, staging and follow-up on therapy of neuroblastomas.
- Evaluation of the uptake of iobenguane. The sensitivity to diagnostic visualisation is different for the listed pathological entities.
  The sensitivity is approximately 90% for the detection of pheochromocytoma and neuroblastoma, 70% in case of carcinoid and only 35% in case of medullary thyroid carcinoma (MTC).
- Functional studies of the adrenal medulla (hyperplasia).

4.1.2 Cardiology: Imaging of sympathetic myocardial innervation

- AdreView is a radiopharmaceutical indicated for assessment of sympathetic innervation of the myocardium as a prognostic indicator of risk for progression of symptomatic heart failure, potentially fatal arrhythmic events, or cardiac death in patients with NYHA class II or class III heart failure and LV dysfunction.

4.2 Posology and method of administration

4.2.1 Oncology

Posology

Adults
The recommended dosage in oncology studies is 80-200 MBq, higher activities may be justifiable.

Elderly population
No special dosage scheme is required for the elderly patient.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and to adolescents may be calculated according to the following dosage scheme:

- Children under 6 months (see section 4.3): 4 MBq per kg body weight (max. 40 MBq)
- Children between 6 months and 2 years: 4 MBq per kg body weight (min. 40 MBq).
- Children over 2 years: a fraction of the adult dosage should be chosen, dependent on body weight. The recommended dosages are as follows:

Weight	activity amount	weight	activity amount	weight	activity amount
3 kg	20 MBq	15 kg	76 MBq	40 kg	152 MBq
4 kg	28 MBq	20 kg	92 MBq	45 kg	162 MBq
6 kg	38 MBq	25 kg	110 MBq	50 kg	176 MBq
8 kg	46 MBq	30 kg	124 MBq		
10 kg	54 MBq	35 kg	140 Mbq		

Method of administration
Iobenguane (^{123}I) is administered by slow intravenous injection or infusion over several minutes. If desired, the administration volume can be increased by dilution.

For instructions on preparation of the medicinal product before administration, see section 12.

Image acquisition
Imaging neural crest tumors
Whole body anterior and posterior scintigraphic images and/or relevant spot images and/or SPECT images are obtained 24 hours after the iobenguane (^{123}I) administration. These views are eventually repeated at 48 hours.

4.2.2 Cardiology

Posology

Adults
The recommended dosage in imaging studies of the sympathetic myocardial innervation is 370 MBq.

Elderly population
No special dosage scheme is required for the elderly patient.

Paediatric population
For children see 4.2.1 Oncology

Method of administration
See 4.2.1 Oncology

Image acquisition
Imaging of myocardial sympathetic innervation
Anterior planar imaging of the chest should be performed at 4 hours (± 10 minutes) following administration of AdreView. The camera should be positioned to include the entire heart and as much of the upper chest as possible within the field of view. Recommended image acquisition time is 10 minutes and recommended image matrix is 128x128. Single photon emission computed tomography (SPECT) may be considered as appropriate after completion of planar imaging. Additional earlier imaging (anterior planar and SPECT) beginning at 15 minutes post AdreView administration may be performed as appropriate.

Myocardial uptake of AdreView is quantified in terms of the Heart/Mediastinum ratio (H/M ratio), measured from the planar chest image as the counts per imaging pixel in the heart divided by the same measurement in a region without specific uptake of AdreView, i.e. the upper mediastinum. The H/M ratio should be determined by dividing the counts/pixel in a whole heart region of interest (ROI) by the counts per pixel in a 7x7 pixel square ROI centered on the lowest count pixel in the midline upper chest.

In clinical trials of AdreView in heart failure patients with reduced left ventricular (LV) function (LV ejection fraction ≤ 35%), patients with H/M ratio <1.60 on 4-hour imaging were twice as likely to have heart failure progression and arrhythmic events (20% (154/760) vs. 11% (22/201) and 8% (58/760) vs. 3% (6/201) respectively) as those with H/M ratio ≥ 1.6. Cardiac death was almost seven times more likely in subjects with H/M ratio < 1.60 (7% (51/760) vs 1% (2/201)). Risk for adverse outcomes increased with decreasing H/M ratio; 2-year cardiac death rate was ten times higher in patients with H/M ratio < 1.20 compared with H/M ratio ≥ 1.60 (19.1% vs 1.8%).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Potential for hypersensitivity or anaphylactic reactions

The possibility of hypersensitivity including anaphylactic/anaphylactoid reactions should always be considered.

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal impairment and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in paediatric population, see section 4.2.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Precautions with respect to benzyl alcohol, see subsection *Specific warnings*.

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Before administration of AdreView, administer 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 iodine-123 by the patient's thyroid. Administer the blocking agent at least one hour before the dose of AdreView.

The uptake of iobenguane (^{123}I) in the chromaffinic granules might, in theory, cause rapid noradrenalin secretion which can induce a hypertensive crisis although the likelihood of such an occurrence is believed to be extremely low. This necessitates constant monitoring of the patient during administration. Iobenguane (^{123}I) must be administered slowly (take at least one minute for the administration of a patient dose). Prior to AdreView administration, ensure emergency cardiac and anti-hypertensive treatments are readily available. Consideration should be given to assessing the patient's pulse and blood pressure before and shortly after AdreView administration. If a sudden rise in blood pressure is observed, appropriate antihypertensive treatment should be initiated.

Drugs known or expected to reduce the iobenguane (^{123}I) uptake should be stopped before administration of AdreView (usually 4 biological half-lives). Whether a particular medication is to be stopped may depend on which type of investigation with iobenguane (^{123}I) is intended. Consultation with the responsible physician for treatment of the patient will be useful. For details, please refer to section 4.5.

Specific warnings

This medicine contains 10.4 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or who are pregnant or breastfeeding because of the risk of accumulation and toxicity (metabolic acidosis).

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. There is also an increased risk due to accumulation in young children (less than 3 years old).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

Precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs are known or may be expected to prolong or to reduce the uptake of iobenguane in neural crest tumours:

- Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane.
- Decreased uptake was observed under therapeutic regimens involving the administration of antihypertensives that deplete norepinephrine stores or reuptake (reserpine, labetalol), calcium-channel blockers (diltiazem, nifedipine, verapamil), tricyclic antidepressives that inhibit norepinephrine transporter function (amitryptiline and derivates, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine, pseudoephedrine or phenylpropanolamine), cocaine, and phenothiazine. These drugs should be stopped before administration of iobenguane (^{123}I) (usually for four biological half-lives to allow complete wash out).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

No data are available on the use of this product in human pregnancy.

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and the foetus.

Benzyl alcohol can cross the placenta (see section 4.4).

Breastfeeding

Before administering radiopharmaceuticals to a mother who is breastfeeding

consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for three days and the expressed feeds discarded. Breastfeeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv.

4.7 Effects on the ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

In rare cases the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions. When the drug is administered too fast palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. Within one hour these symptoms disappear.

Tabulated summary of adverse reactions

The frequencies of the undesirable effects are defined as follows:
Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000) and not known (cannot be determined with the data available).

System organ class	**Frequency not known (cannot be estimated from the available data)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Cancer induction.
Immune system disorders	Blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions, hypersensitivity.
Cardiac disorders	Palpitations.
Vascular disorders	Transient hypertension.
Respiratory, thoracic and mediastinal disorders	Dyspnoea.
Gastrointestinal disorders	Abdominal cramps.
Congenital, familial and genetic disorders	Hereditary defects.
General disorders and administration site conditions	Heat sensations.

Description of selected adverse reactions
For each patient, exposure to ionizing radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonable achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 5 mSv when the maximal recommended activity of 370 MBq is administered these adverse events are expected to occur with a low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the reporting card found of the website of the Norwegian Medicines Agency: www.legemiddelverket.no/meldeskjema

4.9 Overdose
The effect of an overdose of iobenguane is due to the release of adrenaline. This effect is of short duration and requires supportive measures aimed at lowering the blood pressure: Prompt injection of a rapidly acting alpha-adrenergic blocking agent (phentolamine) followed by a beta-blocker (propanolol) is needed. In the event of administration of a radiation overdose with iobenguane the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition by forced diuresis and frequent bladder voiding. The nature of the radioisotope and the amount of iobenguane present makes overdosing improbable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals for tumour detection.
ATC-code: V09IX01

Mechanism of action
Iobenguane is a radioiodinated aralkylguanidine. Its structure contains the guanidine-group from guanethidine linked to a benzyl-group into which iodine is introduced. Like guanethidine the aralkylguanidines are adrenergic neuron blocking agents. As a consequence of a functional similarity between adrenergic neurons and the chromaffin cells of the adrenal medulla, iobenguane is able to localize preferentially in the medulla of the adrenal glands. In addition localisation in the myocardium occurs.

Of the various aralkylguanidines, iobenguane is the preferred substance because of its lowest liver uptake and its best *in vivo* stability, resulting in the lowest achievable thyroid uptake of liberated iodide.

Transport of iobenguane across the cell membranes of cells originating from the neural crest is an active process when the concentration of the drug is low (as in diagnostic dosages). The uptake mechanism can be inhibited by uptake inhibitors such as cocaine or desmethylimipramine. After

uptake an active mechanism transfers at least part of the intracellular iobenguane into the storage granules within the cells.

5.2 Pharmacokinetic properties

Distribution/Organ uptake
The distribution pattern of iobenguane includes rapid initial uptake in liver (33 % of the administered dose) and much less in lungs (3 %), myocardium (0.8 %), spleen (0.6 %), and salivary glands (0.4 %). Uptake in normal adrenals (adrenal medulla) can lead to visualisation with iobenguane (^{123}I). Hyperplastic adrenals show a high uptake.

Elimination
Iobenguane is to a large extent excreted unaltered by the kidneys. Of the administered doses, 70 to 90% are recovered in urine within 4 days. The following metabolic breakdown products were recovered in urine: radioiodide, radioiodinated meta-iodohippuric acid, radioiodinated hydroxy-iodobenzylguanidine and radioiodinated meta-iodobenzoic acid. These substances account for approximately 5 to 15 % of the administered dose.

5.3 Preclinical safety data

In dogs 20 mg/kg is a lethal dose. Lower dose levels (14 mg/kg) cause transient clinical signs of toxic effect. Repeated intravenous administrations in rats of 20 to 40 mg/kg induce signs of serious clinical toxicity.

Repeated intravenous administrations of 5 to 20 mg/kg do induce effects, including respiratory distress, but long-term effects are only a slight increase in weight of liver and heart. Repeated administration in dogs of 2.5 to 10 mg/kg do induce clinical effects, including increased blood pressure and abnormalities in heart rate and in cardiac pulse propagation, but all signs were of a transient nature.

In the test systems used, no mutagenic effect could be demonstrated.
Studies of carcinogenic effects of iobenguane have not been published.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
3-iodobenzylguanidine
Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Can be used up to 36 hours post calibration time indicated on the label.
Once opened, store in a refrigerator (2°C – 8°C) and use within one working day.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Store either in original lead container or in equivalent shielding.

Storage should take place in accordance with national regulations for radioactive materials.

For storage conditions of the opened product, see section 6.3.

6.5 Nature and contents of container

10 ml medicinal glass vial, closed with a teflon coated rubber stopper and sealed with an aluminium cap. Each vial is enclosed in a lead container of appropriate thickness.

Pack size: 37 to 740 MBq.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instructions on preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Disposal

After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare B.V.
De Rondom 8
5612 AP Eindhoven
The Netherlands

8. MARKETING AUTHORISATION NUMBER

MTnr. 94-00191

9. DATE OF FIRST AUTHORISATION

1997-06-24/2005-01-31

10. DATE OF REVISION OF THE TEXT

24.04.2020

11. DOSIMETRY

The table below shows the dosimetry as calculated according to the publication 80 of the ICRP (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1998.)

Organ	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
Gall bladder	2.1E-02	2.5E-02	3.6E-02	5.4E-02	1.0E-01
GI-tract					
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

Effective dose (mSv/MBq)	1.3E-02	1.7E-02	2.6E-02	3.7E-02	6.8E-02

The effective dose resulting from an administered activity amount of 200 MBq for an adult weighing 70 kg is about 2.6 mSv.

The effective dose resulting from an administered activity amount of 370 MBq for an adult weighing 70 kg is about 4.8 mSv.

The above data are valid in normal pharmacokinetic behaviour. When renal function is impaired due to disease or due to previous therapy, the effective dose equivalent and the radiation dose delivered to organs might be increased.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Solution for intravenous injection, ready to use. A clear, colourless aqueous solution.

See special handling precautions in section 6.6.

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. After removal of a dose from the vial, store at 2°C - 8°C and use within one working day.