

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MIBG (I123) 74 MBq/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per ml, at activity reference date and time.

¹²³ I as Iobenguane	74 MBq
iobenguane sulphate	0.5 mg

The radiochemical purity of the product at expiry date and time:

¹²³ I-Iobenguane	: ≥ 95 %
Meta-iodo(¹²³ I)benzylamine	: ≤ 0.5 %
Free iodide(¹²³ I)	: ≤ 5 %

The radionuclidic purity of the product at expiry date and time:

¹²³ I	: ≥ 99.7%
¹²¹ Te	: ≤ 0.9 kBq/MBq
¹²⁵ I	: ≤ 1.5 kBq/MBq

¹²³I is obtained by proton irradiation of enriched Xenon.

Summary of the physical characteristics of the radioactive isotope in the active substance: ¹²³I.

Physical half-life 13.2 hours.

Most important radiation emitted

Energy level	Abundance (%)
159 keV-γ-rays	83.6

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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 pathologic entities. Pheochromocytomas and neuroblastomas are sensitive in approx. 90% of patients, carcinoids in 70% and MCT in only 35%.

Functional studies of the adrenal medulla (hyperplasia) and the myocardium (sympathetic innervation).

4.2 Posology and method of administration

¹²³I-Iobenguane is administered according to the following dosage scheme:
Children under 6 months: 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:
3kg	20 MBq	15kg	76 MBq	35kg	140 MBq
4kg	28 MBq	20kg	92 MBq	40kg	152 MBq
6kg	38 MBq	25kg	110 MBq	45kg	162 MBq
8kg	46 MBq	30kg	124 MBq	50kg	176 MBq
10kg	54 MBq				

Adults: The recommended dosage is 80-200 MBq.
No special dosage-scheme is required for the elderly patient.

¹²³I-Iobenguane is administered by slow i.v. injection or infusion. If desired the administration volume can be increased by dilution (*see 6.1*).

4.3 Contraindications

No absolute contraindications are known.

4.4 Special warnings and precautions for use

- o Drugs known or expected to reduce the ¹²³I-Iobenguane uptake should be stopped before treatment (usually four biological half-lives).
- o Thyroid blockade is started 24-48 hours before the ¹²³I-Iobenguane and continued for at least 3 days afterwards. Blockade by potassium perchlorate is achieved by administration of approx. 400 mg/day. Blockade by potassium iodide, potassium-iodate or Lugol solution must be performed with an equivalent of 100 mg of iodine/day.
- o The dose is slowly administered intravenously over several minutes.
- o Whole body anterior and posterior scintigraphic images and/or relevant spot images and/or SPECT images are obtained 24 h after the ¹²³I-Iobenguane administration. These views are eventually repeated after 48h.
- o The uptake of iobenguane in the chromaffin granules might, in theory, cause rapid noradrenalin secretion which can induce a hypertensive crisis. This necessitates constant monitoring of the patient during administration. ¹²³I-Iobenguane must be administered slowly (take at least one minute for the administration of a patient dose).
- o This radiopharmaceutical may be used and administered only by authorised persons.
- o Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.

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.
- o Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane.
 - o Decreased uptake was observed under therapeutic regimens involving the administration of reserpine, labetalol, calcium-channel blockers (diltiazem, nifedipine, verapamil), tricyclic antidepressives

(amitryptiline, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine), cocaine, phenothiazine. These drugs should be stopped before administration of ^{123}I -iobenguane (usually for four biological half-lives to allow complete wash out.)

4.6 Fertility, pregnancy and lactation

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when likely benefit exceeds the risks incurred by mother and foetus.

Before administering a radioactive medicinal product to a mother who is breast-feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded. Breast-feeding 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 ability to drive and use machines

Administration of diagnostic doses has no effect on the ability to drive.

4.8 Undesirable effects

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

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. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred.

For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (Effective Dose Equivalent) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

This product contains no excipients that have a recognised action or effect, or knowledge of which is important for safe use of the product.

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 HPRA Pharmacovigilance; Earlsfort Terrace; IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The effect of an overdose of iobenguane is due to the release of adrenaline. The 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 (propranolol). Because of the renal elimination pathway, maintaining the highest possible urine flow is essential to reduce the influence of radiation.

The nature of the radioisotope and the amount of meta-iodobenzylguanidine present make overdosing improbable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: V09I X01

^{123}I -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 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 cellmembranes 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 of inhibitors such as cocaine or desmethyylimipramine.

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

5.2 Pharmacokinetic properties

Iobenguane is to a large extent excreted unaltered by the kidneys. 70 to 90% of administered doses 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.

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 ^{123}I -Iobenguane. Hyperplastic adrenals show a high uptake.

5.3 Preclinical safety data

In dogs 20 mg/kg is a lethal dose. Lower dose levels (14mg/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 administrations 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 (^{123}I) have not been published.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Citric acid monohydrate
Sodium citrate dihydrate

6.2 Incompatibilities

MIBG (I123) Injection is not compatible with sodium chloride solutions. *In vitro* the presence of chloride-ion may cause release of radioiodide. Dilution of MIBG (I123) Injection is preferably done with water for injection.

6.3 Shelf life

MIBG (I123) Injection expires 20 hours after the activity reference date and time. Activity reference date and time and expiry date and time are stated on the label of the shielding and in the shipping papers accompanying each shipment. Shelf-life after removal of the first aliquot: 8 hours

6.4 Special precautions for storage

Store below 25°C.

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

The vial should be stored between 2-8° C after removal of the first aliquot.

6.5 Nature and contents of container

10 ml glass vial (Type 1 Ph. Eur.) closed with a bromobutyl rubber stopper, sealed with an aluminium crimpcap.

MIBG (I123) Injection is supplied in one vial containing one of the following activity amounts at activity reference time:

74 MBq in 1 ml
148 MBq in 2 ml
222 MBq in 3 ml
296 MBq in 4 ml
370 MBq in 5 ml

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The product may be diluted with water for injection or with a solution of 5% glucose in water if increasing the volume to ease the administration is desirable.

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

Waste must be disposed of according to national regulations radioactive material.

7 MARKETING AUTHORISATION HOLDER

Mallinckrodt Medical B.V.
Westerduinweg 3
P.O. Box 3
1755 ZG Petten
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0690/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 2000

Date of last renewal: 18 February 2010

10 DATE OF REVISION OF THE TEXT

December 2015

11 DOSIMETRY

Data from ICRP publication 53 (VoI.18-No1-4, 1987) “Radiation dose to patients from radiopharmaceuticals”.

The list includes only the organs which are used in the calculation for the effective (whole body) dose equivalent,the seven standard organs and the additional five with the highest absorbed dose (marked with *).

Absorbed dose per unit activity administered (mGy/MBq).					
Organ	Adult	15 year	10 year	5year	1 year
Bone surfaces	0.0076	0.0093	0.015	0.023	0.045
Breast	0.0062	0.0062	0.0098	0.016	0.03
Lungs	0.016	0.023	0.032	0.048	0.091
Gonads					
Ovaries	0.008	0.01	0.016	0.026	0.047
Testes	0.0054	0.0073	0.012	0.02	0.038
Red marrow	0.0092	0.012	0.017	0.025	0.045
Thyroid	0.0042	0.0062	0.01	0.017	0.031
Adrenals	0.011	0.015	0.022	0.031	0.051
*Kidneys	0.014	0.017	0.025	0.036	0.06
*Bladder wall	0.07	0.087	0.13	0.19	0.35
*Liver	0.071	0.089	0.13	0.19	0.34
*Salivary glands	0.017	0.022	0.031	0.045	0.072
*Spleen	0.02	0.028	0.043	0.066	0.12
Effective dose equivalent (mSv/MBq)	0.018	0.023	0.034	0.05	0.09

The effective dose equivalent resultingfrom an administered activity amount of 200 MBq is 3.6 mSv in the adult.

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

Any unused product or waste materials should be disposed of in accordance with local requirements.