SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MIBG (^{123}I) 74 MBq/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 74 MBq of iobenguane (^{123}I) at the date and time of calibration and iobenguane sulfate 0.5 mg. Iodine-123 (^{123}I) decays to stable Tellurium-123 with a half-life of 13.2 hours by emitting pure gamma radiations with predominant energies of 159 keV (83.6%) and X-rays of 27 keV.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless or slightly yellow solution.
The pH of the product is 4.0 - 5.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

- Detection of neuroendocrine tumours such as pheochromocytomas, paragangliomas, chemodectomas and ganglioneuromas.
- Detection, staging and follow-up on therapy of neuroblastomas.
- Evaluation of the uptake of iobenguane (^{123}I) for therapy planning.
- Functional studies of the adrenal medulla (hyperplasia) and the myocardium (sympathetic innervation).

4.2 Posology and method of administration

Posology

Adults
The recommended activity range is 110-400 MBq based on a patient of average weight (70 kg).

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

Renal impairment
Careful consideration of the activity to be administered is required since an

increased radiation exposure is possible in these patients.

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 EANM dosage card (2016) by using the following formula:

*A***[***MBq***]**Administered **=** Baseline activity x Multiple (with a baseline activity of 28.0)

Weight (kg)	Multiple	Weight (kg)	Multiple	Weight (kg)	Multiple
3	1	22	5.29	42	9.14
4	1.14	24	5.71	44	9.57
6	1.71	26	6.14	46	10.00
8	2.14	28	6.43	48	10.29
10	2.71	30	6.86	50	10.71
12	3.14	32	7.29	52 - 54	11.29
14	3.57	34	7.72	56 - 58	12.00
16	4.00	36	8.00	60 - 62	12.71
18	4.43	38	8.43	64 - 66	13.43
20	4.86	40	8.86	68	14.00

In very young children (up to 1 year), a minimum dose of 37 MBq is necessary in order to obtain images of sufficient quality.
The safety and efficacy of MIBG (^{123}I) in paediatric patients < 1 month have not been established. No data are available.

Method of administration

Multidose vial.

MIBG (^{123}I) is administered by slow (at least 5 minutes) intravenous injection or by infusion (see sections 4.4 and 4.8). If desired, the volume to be administered can be increased by dilution.
The low pH of the solution may cause injection site pain (see section 4.8). Saline flush is recommended following MIBG (^{123}I) administration.

For instructions on dilution of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.

Image acquisition

- *Neuroendocrine tumours imaging*: whole body anterior and posterior scintigraphy images and/or relevant spot images and/or SPECT images may be performed 24 hours after the MIBG (^{123}I) administration. These scans are eventually repeated after 48 hours.
- *Myocardial imaging*: anterior planar imaging of the chest at 15 min (early image) and 4 hours (late image) following administration of MIBG (^{123}I) eventually followed by a single photon emission computed tomography (SPECT).

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

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.

Patients with sympathetic nervous system impairment

In patients suffering from clinical conditions that influence the nervous or sympathetic system functioning, such as Parkinsonian syndromes, a decrease in MIBG (^{123}I) cardiac uptake can be observed regardless of cardiac pathology.

Renal impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.
Severe renal insufficiency may cause impaired imaging results since iobenguane (^{123}I) is excreted mainly via the kidneys.

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).

Patient preparation

- Drugs known or expected to reduce the MIBG (^{123}I) uptake should be stopped before treatment (usually four biological half-lives) (see section 4.5).
- To minimize radiation dose to the thyroid gland, thyroid uptake of free iodide should be prevented using stable iodine administered orally:
    - In adults, thyroid blockade should be performed approximatively 1 hour before MIBG (^{123}I) injection, by a single administration of potassium iodide (130 mg) or potassium iodate (170 mg) (see Table 1 below).
    - In adolescents, children and infants, thyroid blockade should be performed by administration of potassium iodide or potassium iodate, approximately 1 hour before MIBG (^{123}I) injection, in the evening of the day of injection and the following day (in total, 3 intakes in 2 days). Recommended doses for thyroid blockade should be based according to patient's age group (see Table 1 below).

Table 1: Recommended doses per administration, for thyroid blockade, in infants, children, adolescents and adults

Patient's age group	Potassium iodide (mg)	Potassium iodate (mg)
Infants (1 month-3 year old)*	32	42

Children (3 – 12 year old)*	65	85
Adolescents (> 12 year old)*	130	170
Adults **	130	170

** 3 administrations required in 2 days*

*** only a single administration required*

- Potassium perchlorate or sodium perchlorate may be used in patients with a previous history of incompatibility to iodine.
- In children and infants, sedation may be required to perform SPECT acquisitions.
- 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.

Specific warnings

The uptake of iobenguane (^{123}I) in the chromaffin granules might cause rapid noradrenalin secretion which can induce a hypertensive crisis. This necessitates constant monitoring of the patient during administration. MIBG (^{123}I) must be administered slowly (see sections 4.2 and 4.8).

Paravenous injection must be avoided due to the risk of local tissue necrosis (see section 4.8). Injection should be strictly intravenous to avoid MIBG (^{123}I) local deposit and irradiation. In the event of paravenous injection, the injection should be immediately stopped, and the site of injection should be warmed and rested in elevated position. When radiation necrosis occurs, surgical intervention may be necessary.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, 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 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

Woman of childbearing potential

When an administration of radiopharmaceuticals to 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

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

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the excretion of activity in breast milk.
Iobenguane (^{123}I) is partially excreted in human milk. If the administration is considered necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

MIBG (^{123}I) has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following table includes the adverse reactions sorted by system organ classes according to MedDRA.

The frequencies are defined as follows: very common ≥ 1/10; common from ≥ 1/100 to <1/10; uncommon from ≥ 1/1,000 to <1/100, rare from ≥ 1/10,000 to <1/1,000; very rare <1/10,000; frequency not known (cannot be estimated from the available data).

System Organ Class (SOCs)	***Adverse reactions****	***Frequency***
Immune system disorders	Hypersensitivity Anaphylactoid reactions	Not known
Nervous System disorders	Dizziness Headache Paraesthesia	Not known
Cardiac disorders	Tachycardia Palpitations	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea.	Not known
Vascular disorders	Transient hypertension. Flushing	Not known

Gastrointestinal disorders	Abdominal cramps, abdominal pain Nausea Vomiting	Not known
Skin and subcutaneous tissue disorders	Urticaria Rash Erythema	Not known
General disorders and administration site conditions	Injection site pain Localised oedema Injection site reaction Feeling hot Cold chills	Not known
Injury, poisoning and procedural complications	Radiation necrosis after paravenous drug administration.	Not known

** Adverse reactions derived from spontaneous reporting*

Description of selected adverse reactions

Catecholamine crisis
When the drug is administered too fast, palpitations, tachyardia, dyspnoea, feeling hot, transient hypertension, abdominal cramps and pain may occur already during or immediately after administration(see sections 4.2 and 4.4). Within one hour these symptoms disappear.

Hypersensitivity
Hypersensitivity has occurred e.g. flushing, rash, erythema, urticaria, nausea, cold chills and other symptoms of anaphylactic reactions (see section 4.4).

Injection site reactions due to paravenous administration
Local paravenous administrations have been reported and can cause local tissue reactions, such as injection site pain, localised oedema and radiation necrosis (see section 4.4).

General advice
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
As the effective dose is 5.2 mSv when the maximal recommended activity of 400 MBq is administered these adverse reactions 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 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

This product must be used by authorised personnel in a hospital setting. The risk of overdose is therefore theoretical.

In the event of administration of a radiation overdose with MIBG (^{123}I), the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding.

The effect of an overdose of MIBG (^{123}I) 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 (propranolol) is needed. Because of the renal elimination pathway, maintaining the highest possible urine flow is essential to reduce the influence of radiation.

MIBG (^{123}I) is not dialyzable. It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical, tumour detection.
ATC code: V09IX01.

Mechanism of action
Iobenguane (^{123}I) 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 gland, iobenguane (^{123}I) is able to localize preferentially in the medulla of the adrenal glands. In addition, localisation in the myocardium occurs.
Of the various aralkylguanidines, iobenguane (^{123}I) 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.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, iobenguane (^{123}I) does not appear to have any pharmacodynamic activity. However, iobenguane (^{123}I) may increase release of norepinephrine from chromaffin granules and produce a transient episode of hypertension (see also section 4.4).

5.2 Pharmacokinetic properties

Distribution and organ uptake
The distribution pattern of iobenguane (^{123}I) 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 adrenal glands (adrenal medulla) can lead to visualisation with iobenguane (^{123}I). Hyperplastic

adrenals show a high uptake.
Transport of iobenguane (^{123}I) 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 the administration of inhibitors such as cocaine or desmethylimipramine.
After uptake, an active mechanism transfers at least part of the intracellular iobenguane (^{123}I) into the storage granules within the cells.

Elimination
Iobenguane (^{123}I) is to a large extent excreted unaltered by the kidneys. 70-90% 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.

Half-life
The effective half-life is 11.4 hours.

Renal impairment
The pharmacokinetic in patients with renal impairment has not been characterised.

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 in rats 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 intravenous 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.
This medicinal product is not intended for regular or continuous administration.
In the test systems used, no mutagenic effect could be demonstrated.
Long-term carcinogenic studies have not been carried out.
Reproductive toxicity studies in animals have not been conducted so far.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid monohydrate, sodium citrate dihydrate and water for injections.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life
MIBG (^{123}I) solution for 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.
After first withdrawal from vial, store in a refrigerator (2°C – 8°C) in the original package and use within 8 hours without exceeding the expiry time.
Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C – 8°C. From a microbiological point of view, unless the method of opening and withdrawal precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after first withdrawal of the medicinal product from vial, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

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 crimp cap. The glass vial is supplied in a lead shielding.

MIBG (^{123}I) solution for injection is supplied in one vial containing either of the following activity amounts at activity reference date and 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 and other handling

General warnings
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 dilution of the medicinal product before administration, see sections 12.
If at any time in the preparation of the product the integrity of this vial is compromised, it should not be used.

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

The administration of radiopharmaceuticals creates risks to other persons, from external radiation or contamination from spills of urine, vomiting or any other

biological fluids. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7 MARKETING AUTHORISATION HOLDER

Curium Netherlands B.V.
Westerduinweg 3
1755 LE 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

May 2024

11 DOSIMETRY

The data listed below are from the ICRP publication 80 "Radiation dose to patients from radiopharmaceuticals" and are calculated according to the following assumptions:
Total body retention is described by half-times of 3 hr (0.36) and 1.4 d (0.63), with a small fraction (0.01) retained in the liver. Blocking of the thyroid is assumed.
Total body residence time is 9.97 hours.
The data listed below 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.

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year old**	**10 year old**	**5 year old**	**1 year old**
Adrenals	0.017	0.022	0.032	0.045	0.071
Bladder	0.048	0.061	0.078	0.084	0.15
Bone surfaces	0.011	0.014	0.022	0.034	0.068
Brain	0.0047	0.0060	0.0099	0.016	0.029
Breast	0.0053	0.0068	0.011	0.017	0.032
Gall bladder	0.021	0.025	0.036	0.054	0.10
Gastrointestinal tract:					
Stomach	0.0084	0.011	0.019	0.030	0.056
Small intestine	0.0084	0.011	0.018	0.028	0.051
Colon	0.0086	0.011	0.018	0.029	0.052
(Upper large	0.0091	0.012	0.020	0.033	0.058)

intestine					
(Lower large intestine	0.0079	0.010	0.016	0.023	0.043)
Heart	0.018	0.024	0.036	0.055	0.097
Kidneys	0.014	0.017	0.025	0.036	0.061
Liver	0.067	0.087	0.13	0.18	0.33
Lungs	0.016	0.023	0.033	0.049	0.092
Muscles	0.0066	0.0084	0.013	0.020	0.037
Oesophagus	0.0068	0.0088	0.013	0.021	0.037
Ovaries	0.0082	0.011	0.016	0.025	0.046
Pancreas	0.013	0.017	0.026	0.042	0.074
Red marrow	0.0064	0.0079	0.012	0.018	0.032
Skin	0.0042	0.0051	0.0082	0.013	0.025
Spleen	0.020	0.028	0.043	0.066	0.12
Testes	0.0057	0.0075	0.012	0.018	0.033
Thymus	0.0068	0.0088	0.013	0.021	0.037
Thyroid	0.0056	0.0073	0.012	0.019	0.036
Uterus	0.010	0.013	0.020	0.029	0.053
Remaining organs	0.0067	0.0085	0.013	0.020	0.037
Effective dose (mSv/MBq)	**0.013**	**0.017**	**0.026**	**0.037**	**0.068**

The effective dose resulting from the administration of a maximal recommended activity of 400 MBq for an adult weighing 70 kg is about 5.2 mSv.
For an administered activity of 400 MBq, the typical radiation dose to the target organ adrenals is 6.8 mGy and the typical radiation doses to the critical organs (liver and bladder) are 26.8 mGy and 19.2 mGy respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This is a ready-to-use medicinal product. However, 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.

Withdrawals should be performed under aseptic conditions. The vials must never be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposal sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

Detailed information on this medicinal product is available on the website of HPRA, www.hpra.ie.