

SUMMARY OF PRODUCT CHARACTERISTICS

for

MIBG (I-123), solution for injection

1. NAME OF THE MEDICINAL PRODUCT

MIBG (I-123)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per ml, at activity reference date and time

^{123}I as Iobenguane	74 MBq
3-iodobenzylguanidine sulphate	0.5 mg

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

^{123}I -Iobenguane:	$\geq 95 \%$
Meta-iodo (^{123}I) benzylamine:	$\leq 0.5 \%$
Free iodide (^{123}I):	$\leq 5 \%$

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

^{123}I	: > 99.9 %
^{121}Te	: $\leq 500 \text{ Bq/MBq}$

^{123}I is obtained by proton irradiation of enriched Xenon.

Summary of the physical characteristics of the radioactive isotope in the active substance:

^{123}I .

Physical half-life 13.2 hours

Most important radiation emitted

Energy level	Abundance
γ - rays 159 keV	83.6 %

Excipient:

Sodium citrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

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
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		

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

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and special precautions for use

Drugs known or expected to reduce the ¹²³I-Iobenguane uptake should be stopped before treatment (usually four biological half-lives).

Thyroid blockade is started 24-48 hours before the ¹²³I-Iobenguane and continued for at least 3 days. 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.

The dose is slowly administered intravenously over several minutes.

Whole body anterior and posterior scintigraphic images and/or relevant spot images and/or SPECT images are obtained 24 hours after the ¹²³I-Iobenguane administration. These views are eventually repeated after 48 hour.

The uptake of meta-iodobenzylguanidine in the chromaffin granules might, in theory, cause rapid noradrenaline 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).

This medicinal product contains 0.18 mmol (4.23 mg) sodium per ml. This needs to be taken into consideration for patients on a controlled sodium diet.

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:

- Nifedepine (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, nifedepine, 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 ¹²³I-Iobenguane (usually for four biological half-lives to allow complete wash out).

4.6 Pregnancy and lactation

Pregnancy

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.

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.

Lactation

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.

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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.

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

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 already during or immediately after administration. Within one hour these symptoms disappear.

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.

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 (propranolol) is needed. 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 makes overdosing improbable.

5. PHARMACOLOGICAL PROPERTIES

ATC: V09IX01 - Diagnostic radiopharmaceutical, tumour detection.

¹²³I-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.

5.1 Pharmacodynamic properties

Of the various aralkylguanidines meta-iodobenzylguanidine 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 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

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 ¹²³I-Iobenguane. Hyperplastic adrenals show a high uptake.

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**

MIBG (I-123) is an aqueous solution containing:

Water for injections, citric acid, sodium citrate, gentisic acid, copper sulphate and stannous (II) sulphate.

The pH of the product is 3.5-4.5.

6.2 **Incompatibilities**

MIBG (I-123) is not compatible with sodium chloride solutions. In vitro the presence of chloride-ion may cause the release of radioiodide. Dilution of MIBG (I-123) is preferably done with water for injection.

6.3 **Shelf life**

MIBG (I-123) 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.

6.4 **Special precautions for storage**

When the product is not used immediately upon arrival it may be stored for later use in the intact packaging.

Do not store above 25°C.

However, if multi-dose use is intended, each aliquot should be removed under aseptic conditions and then the vial should be stored in a refrigerator (2°C-8°C) after removal of the first aliquot and for no longer than 24 hours or up to end of shelf life, whichever comes first.

Storage should take place in accordance with national regulations for 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.

MIBG (I-123) is supplied in 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 and other handling

This radiopharmaceutical may be used and administered only by authorised persons. Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.

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.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

DK R 1115

9. DATE OF FIRST AUTHORISATION

31 January 1995

10. DATE OF REVISION OF THE TEXT

17. December 2008

11. DOSIMETRY

Data are cited from the ICRP publication 53 (Vol.18-No 1-4, 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	5 year	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 resulting from 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

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. Dilution must not be done with sodium chloride solutions. *In-vitro*, the presence of chloride-ion may cause the release of radioiodide.

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.

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