8. MARKETING AUTHORISATION NUMBER(S)
19000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 30.03.2001

Date of latest renewal: 31.07.2013

10. DATE OF APPROVAL / PARTIAL REVISION OF THE TEXT
September 2016

11. DOSIMETRY
The table below shows the dosimetry as calculated according to the publication 53 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1987).

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

With the exception of "uterus" the list includes only those organs which are used in the calculation for the effective (whole body) dose equivalent. These are the seven standard organs and the additional five organs with the highest absorbed dose (marked with *).

Absorbed dose per unit activity administered (mGy/MBq)					
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Bone surfaces	0.061	0.072	0.11	0.18	0.36
Breast	0.069	0.069	0.11	0.18	0.35
Gastrointestinal tract					
Stomach wall	0.077	0.093	0.15	0.25	0.47
Small intestine	0.074	0.091	0.15	0.24	0.45
ULI wall	0.080	0.096	0.16	0.26	0.48
LLI wall	0.068	0.081	0.13	0.21	0.39
Heart	0.072	0.091	0.14	0.20	0.35
Kidneys	0.12	0.14	0.21	0.3	0.51
Lungs	0.19	0.28	0.39	0.6	1.2
Ovaries	0.066	0.088	0.14	0.23	0.42
Testes	0.059	0.07	0.11	0.19	0.36
Red marrow	0.067	0.083	0.13	0.19	0.35
Thyroid	0.05	0.065	0.11	0.18	0.35
*Adrenals	0.17	0.23	0.33	0.45	0.69
*Bladder wall	0.59	0.73	1.1	1.7	3.3
*Liver	0.83	1.1	1.6	2.4	4.6
*Salivary glands	0.23	0.28	0.38	0.51	0.75
*Spleen	0.49	0.69	1.1	1.7	3.2
Pancreas	0.10	0.13	0.20	0.32	0.57
Uterus	0.08	0.1	0.16	0.26	0.48
Other tissues	0.062	0.075	0.12	0.19	0.37
Effective dose equivalent (mSv/MBq)	**0.2**	**0.26**	**0.4**	**0.61**	**1.1**

The above data are valid in normal pharmacokinetic behaviour. Especially when renal function is impaired, due to disease or due to previous therapy, the effective dose equivalent and the radiation dose delivered to organs (notably to bone, red marrow and lungs) might be increased considerably.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
The radiopharmaceutical is delivered in portions containing required activity (certified on 12.00 CET of the reference day) and volume according to the placed order.

During the preparation and administration of the radiopharmaceutical, regulations for work under exposure to ionising radiation should be observed.

Handling procedure
1. Tear off the seal of the metal tin.
2. Remove the upper part of the styrofoam insert.
3. Take the lead container with vial out of the box.
4. Remove the upper part of the lead container.
5. Without removing the vial from the container, remove or tear off the central part of the aluminum cap.
6. Pierce the rubber septum with a needle and draw the solution to the syringe.
7. Any materials contaminated with the radioactive product: liquid leftovers of the radiopharmaceutical and solids (vials, stoppers, needles, syringes, paper, cotton wool, etc.) should be stored in separate, securely sealed containers and should be disposed of in accordance to local regulations.
8. The shielding container should be returned to the manufacturer.

During the preparation and administration of the radiopharmaceutical, regulations for work under exposure to ionising radiation should be observed.

When drawing the radiopharmaceutical and administering it to the patient, work safety regulations for working under exposure to ionising radiation should be observed.

Any unused products and material waste: liquid (radiopharmaceutical solution residuals), solid (vials, stoppers, needles, syringes, lignin, cotton, etc.) should be disposed of accordance with regulations for radioactive materials.

Quality Control MIBG-^{131}I
Determination of the radiochemical purity using thin-layer chromatography in the following system:
Plate: silica gel (Kieselgel 60, Merck 5748)
Developing solution: 13.6% sodium acetate.

R_f coefficients:
- iobenguane (^{131}I) R_f = 0.15
- unbound ^{131}I R_f = 0.90

Any unused products and material waste should be disposed of accordance with regulations for radioactive materials.

Detailed information on this medicinal product is available on the website of Office for Registration of Medicinal Products, Medical Devices and Biocidal Products http://www.urpl.gov.pl/.

POLATOM

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metaiodobenzylguanidine-^{131}I (MIBG-^{131}I) for diagnostic use, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Iobenguane (^{131}I): 10 – 37 MBq/ml

Excipients with known effect:
Benzyl alcohol - 10 mg/ml
Sodium chloride - 0.45 – 9 mg/ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless or light yellow solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.
Indications include:
- Isotope diagnostics (detection, localization, staging, treatment monitoring) of neuroendocrine tumors. These are in particular: pheochromocytoma, neuroblastoma, carcinoid tumors, medullary thyroid carcinoma.
- Evaluation of iobenguane (^{131}I) uptake and retention to determine a diagnostic dose of iobenguane (^{131}I).
- Treatment monitorig by assessing the uptake and spread of pathological foci taking up iobenguane (^{131}I).
- Confirmation of neuroendocrine character of tumors with unknown origin.

4.2 Posology and method of administration
The dose administered to adults is: 40-80 MBq (1.2 – 2.2 mCi).
The dose administered to children can be calculated by modifying adults dose considering the weight or body surface of child.

According to the European Association of Nuclear Medicine (EANM) paediatric dosage card the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent correction factor given in the table below:

Child weight	Dose (part of adult's dose)	Child weight	Dose (part of adult's dose)
3 kg	0.1	32 kg	0.65
4 kg	0.14	34 kg	0.68
6 kg	0.19	36 kg	0.71
8 kg	0.23	38 kg	0.73
10 kg	0.27	40 kg	0.76
12 kg	0.32	42 kg	0.78
14 kg	0.36	44 kg	0.80
16 kg	0.40	46 kg	0.82
18 kg	0.44	48 kg	0.85
20 kg	0.46	50 kg	0.88
22 kg	0.50	52 – 54 kg	0.90
24 kg	0.53	56 – 58 kg	0.92
26 kg	0.56	60 – 62 kg	0.96
28 kg	0.58	64 – 66 kg	0.98
30 kg	0.62	68 kg	0.99

In order to obtain images of sufficient quality the recommended minimum dose for children is 35 MBq.

No special dosage-scheme is required for the elderly patient.
The dose is administered intravenously; the duration of the injection should be 30-300 seconds.

According to European Directive 97/43/Euratom and medical practice, the above given recommended activities should be treated only as a general guide. It should be noted that in each country the nuclear medicine specialist should consider diagnostic reference levels (DRL) and the principles set out by local regulations. The administration of higher activities than local DRL should be justified.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).
- The product should not be administered to premature babies or new-born infants because it contains benzyl alcohol 10 mg/ml.

4.4 Special warnings and precautions for use
This product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.
Drugs that may interfere with uptake and retention of iobenguane (^{131}I) should be stopped before treatment (see section 4.5).

The uptake of iobenguane in the chromaffin granules might, though rarely, cause rapid noradrenalin secretion which can induce a transient hypertensive crisis. This necessitates constant monitoring of the patient during administration. Monitoring of both ECG and blood pressure during administration could be indicated in some patients.

Prior to administration, ensure emergency cardiac antihypertensive treatments are readily available. Iobenguane (^{131}I) must be administered slowly.
When diagnostic administration for pheochromocytoma is planned attention is to be given to the interference with uptake of iobenguane (^{131}I) by medication for control of hypertension (see section 4.5). Incompatible medication should be stopped at least 2 weeks prior to the planned diagnostic administration. If necessary propranolol can be used instead. Patients are to be well hydrated.

Thyroid blockade using stable iodine should be started 1 day before the iobenguane (^{131}I) is administered and continued for at least 2-3 days (according to EANM 2008).
Blockade by potassium iodide, potassium-iodate or Lugol's solution must be performed with an equivalent of 100 mg of iodine/day. Blockade by potassium perchlorate is achieved by administration of approximately 400 mg/day.

It is recommended for children to administered potassium iodide (started 1 day before examination and finishing 1 day after) in the following dosese:
- children from 1 month up to 3 years - 32 mg potassium iodide per day,
- children from 3 years up to 13 years - 65 mg per day,
- children over 13 years - 130 mg per day.

Newborn children can be given 16 mg of potassium iodide in a single dose only on the day before examination.

For each patient, exposure to ionising 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 reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Excipients: This medicinal product contains
- Benzyl alcohol: 10 mg/ml. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.
- Sodium: 3.54 mg/ml. This medicinal product is essentially sodium free.

4.5 Interactions with other medicinal product 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.

There are additional drugs that may interfere, but no formal proof exists:
- Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane.

Decreased uptake was observed under therapeutic regimens involving the administration of:
- Antihypertensive drugs such as reserpine, labetalol, calcium-channel blockers (diltiazem, nifedipine, verapamil).
- Sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine).
- Cocaine.
- Tricyclic antidepressants such as amitryptiline and derivatives, imipramine and derivatives, doxepin, amoxepine and loxapine.

For the following drugs inhibition of the iobenguane uptake is expected to occur, but no proof is yet available:
- Antihypertensives acting through adrenergic neuron blockade (betanidine, debrisoquine, bretylium and guanethidine).
- Antidepressants such as maprotiline and trazolone.

These drugs should be stopped before treatment (usually for four biological half-lives).

Anti-emetics
Special care must be given to the selection of anti-emetics that are often given to suppress the nausea that generally accompanies the administration of iobenguane in therapeutic quantities. Anti-emetics that are dopamine/serotonin receptor antagonists do not interfere with iobenguane uptake at concentrations as are used in clinical practice.
The wide list of medicines that may cause interactions with iobenguane is listed below:

Table. Iobenguane (^{131}I) interactions and recommended drugs withdrawal time before administration iobenguane (^{131}I) (based on EANM procedure guidelines for ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) therapy)

CARDIOVASCULAR AND SYMPATHOMIMETIC DRUGS	
Anti-arrhythmics for ventricular arrhythmias	
Amiodarone	Not practical to withdraw
Combined alpha and beta blocker	
Labetalol	72 h
Adrenergic neurone blockers	
Brethylium Guanethidine Reserpine	48 h 48 h 48 h
Alfa blockers	
Phenoxybenzamine (IV doses only)	15 days
Calcium channel blockers	
Amlodipine Diltiazem Felodipine Isradipine Lacidipine Lerkanidipine Nikardipine Nifedipine Nimodipine Nisoldipine Verapamil	48 h 24 h 48 h 48 h 48 h 48 h 48 h 24 h 24 h 48 h 48 h
Inotropic sympathomimetics	
Dobutamine Dopamine Dopexamine	24 h 24 h 24 h
Vasoconstrictor sympathomimetics	
Ephedrine Metaraminol Norepinephrine Phenylephrine	24 h 24 h 24 h 24 h
Beta$_2$ stimulants (sympathomimetics)	
Salbutamol Terbutaline Eformoterol Bambuterol Fenoterol Salmeterol	24 h 24 h 24 h 24 h 24 h 24 h
Other adrenoreceptor stimulants	
Orciprenaline	24 h
Systemic and local nasal decongestants, compound cough and cold preparations	
Pseudoephedrine Phenylephrine Ephedrine Xylometazoline Oxymetazoline	48 h 48 h 24 h 24 h 24 h
Sympathomimetics for glaucoma	
Brimonidine Dipivefryne	48 h 48 h

NEUROLOGICAL DRUGS	
Antipsychotics (neuroleptics)	
Chlorpromazine Benperidol Flupentixol Fluphenazine Haloperidol Levomepromazine Pericyazine Perphenazine Pimozide Pipotiazine Prochlorperazine Promazine Sulpiride Thioridazine Trifluoperazine Zuclopenthixol Amisulpride Clozapine Olanzapine Quetiapine Risperidone Sertindole Zotepine	24 h 48 h 48 h or 1 month for depot 24 h or 1 month for depot 48 h or 1 month for depot 72 h 48 h 24 h 72 h 1 month for depot 24 h 24 h 48 h 24 h 48 h 48 h, or 1 month for depot 72 h 7 days 7 – 10 days 48 h 5 days or 1 month for depot 15 days 5 days
Sedating antihistamines	
Promethazine	24 h
Opioid analgesics	
Tramadol	24 h
Tricyclic anti-depressants	
Amitriptyline Amoxapine Clomipramine Dosulepin (Dothiepin) Doxepin Imipramine Lofepramine Nortriptyline Trimipramine	48 h 48 h 24 h 24 h 24 h 24 h 48 h 24 h 48 h
Tricyclic-related anti-depressants	
Maprotiline Mianserin Trazolone Venlaflaxine Mirtazepine Reboxetine	48 h 48 h 48 h 48 h 8 days 3 days
CNS Stimulants	
Amphetamines, e.g. Dexamfetamine Atomoxetine Methylphenidate Modafinil Cocaine Caffeine	48 h 5 days 48 h 72 h 24 h 24 h

4.6 Pregnancy and lactation
Pregnancy
Iobenguane (^{131}I) is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).
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.

Alternative techniques which do not involve ionising radiation should be considered. Women receiving diagnostic iobenguane (^{131}I) should be advised NOT to become pregnant within at least 2 months of administration.

Breast-feeding
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 breastfeeding. Breastfeeding should be discontinued before administering iobenguane (^{131}I).

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
The frequencies of 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 estimated from the available data).

The frequency of undesirable effects after administration of iobenguane (^{131}I) is given in the table below:

Cardiac disorders: Tachycardia	Not known (cannot be estimated from the available data)
Gastrointestinal disorders: vomiting, stomach ache	Not known (cannot be estimated from the available data)
Vascular disorder: Hypertension including acute episodes of hypertensive crisis (observed with the therapeutic use of iobenguane (^{131}I)).	Common

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.

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 national reporting system.

Adverse reactions may be reported to Marketing Authorisation Holder.

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). Because of the renal elimination pathway maintaining the highest possible urine flow is essential to reduce the influence of radiation.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmaceutical group: Other diagnostic radiopharmaceuticals for tumor detection

ATC code: V10X A02

Of the various aralkylguanidines the iobenguane (^{131}I), is the preferred substance because of its lowest liver uptake and its best *in vivo* stability, resulting in the lowest achievable uptake of liberated iodide by the thyroid. 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 of inhibitors such as cocaine or desmethylimipramine. When the drug is administered in higher concentrations as in therapeutic dosages passive diffusion processes become also important. The clinical implications towards dosimetry, if any, are unclear.

Subsequently 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: ^{131}I-iodide, ^{131}I-meta iodohippuric acid, ^{131}I-hydroxy-iodobenzylguanidine and ^{131}I-metaiodobenzoic 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) is so low that these cannot be visualised with iobenguane (^{131}I). Hyperplastic adrenals show a high uptake.

5.3 Preclinical safety data
The LD_{50} value of inactive iobenguane in intravenous administration is equal 30 mg/kg of mice body mass, and LD_{50} value of rats is equal 47.7 mg/kg body mass.
Repeated intravenous administrations can cause clinical effects such as: flushing, vomiting, hives, cold chills. When to fast administration, the product can cause: cardiac pulse propagation, dyspnoea, hypertension and stomach cramps.
The margin of safety between administered amounts of iobenguane (notably in therapeutic doses) and the level at which unwanted secondary effects might occur is not very wide, therefore patients should be kept under close surveillance during and for at least some hours after the infusion or injection of the drug.
In the test systems used no mutagenic effect could be demonstrated. Studies of carcinogenic potential of iobenguane have not been published.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- bis[(3-iodobenzyl)guanidine]sulphate
- sodium metabisulphite
- copper(II) sulphate pentahydrate
- sodium acetate trihydrate
- acetic acid
- benzyl alcohol
- sodium chloride
- water for injection

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

6.3 Shelf-life
9 days from the manufacturing date (expiry date is stated on the label).

6.4 Special precautions for storage
Store in original in temperature below [–15°C] in accordance with regulations for radiation safety (Atomic Low).
Protect from light.
After defrosting store below 25°C for up to 4 hours. Transport in dry ice.

6.5 Nature and contents of container
The product is supplied in 10 ml glass vials, with a possibility of drawing multidoses in an aseptic way. The vials are capped with rubber stoppers and aluminium caps and placed inside a shielded lead container. The outer transport packaging is a metal tin with styrofoam insert.
Every source is accompanied with a certificate of radioactivity.

6.6 Special precautions for disposal
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.
The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.
The residual activity of the generator must be estimated before disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Narodowe Centrum Badań Jądrowych
ul. Andrzeja Sołtana 7
05-400 Otwock, Poland
Tel.: +48 22 7180700
Fax: +48 22 7180350
e-mail: polatom@polatom.pl