Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Meta-Iodobenzylguanidine [^{131}I] Solution for Therapeutic Use.
Meta-Iodobenzylguanidine [^{131}I] 185 – 740 MBq/ml Solution for Infusion or Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meta-Iodobenzlyguanidine [^{131}I] present as Iobenguane [^{131}I] chloride, providing 185-740 MBq/ml at the activity reference date. (Not more than 0.67mg/ml)

Summary of the physical characteristics of the radioactive isotope in the active substance: ^{131}I

Physical half-life 8.02 days.
Most important radiation emitted

Energy level	**Abundance%**
β-247keV	1.8
β-334 keV	7.2
β-606 keV	89.7
β-806 keV	0.7
γ 364 keV	82.0

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion or injection.
Clear, colourless, sterile solution for infusion or intravenous injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Radiation therapy of tumour-tissue that is capable of retaining meta-iodobenzyguanidine.

These are tumours arising from cells originating embryologically from the neural creat; pheochromocytomas, neuro-blastomas, carcinoids and medullary carcinomas of the thyroid gland (MCT).

4.2 Posology and method of administration

Therapeutic dose with an amount of Iobenguane [^{131}I] individually tailored on the basis of a dosimetric study mentioned above. The size of the dose as well as the interval(s) between possible multiple administrations are mainly determined by haematological radio-toxicity and the kind of tumour. The more rapid the rte of progression of the tumour, the shorter the interval.

“Fixed” therapeteutic dose (3.7-7.4 GBq).

These recommended dosages are identical for children and adults. No special dosage-scheme is required for the elderly patient.
The therapeutic dose is administered intravenously, generally as an infusion over a period of 1- 4 hours.

4.3 Contraindications

Pregnancy is an absolute contraindication.

4.4 Special warnings and precautions for use

Several drugs used in the treatment of high blood pressure and in psychiatry, interact with Iobenguane [^{131}I]. Concomitant use therefore may interfere with the uptake and retention of Iobenguane [^{131}I] and thus influence the radiation dose delivered both to normal – and to tumour-tissue, these drugs should be stopped before treatment (usually for four biological half-lives).

Thyroid blockage is started 24 – 48 hours before the Iobenguane [^{131}I]. Is administered and continued for at least 5 days. Blockage by potassium perchloarrte is achieved by administration of approx.400mg/day. Blockade by potassium iodide, potassium-iodate or Lugol solution must be performed with an equivalent of 100mg of iodine/day.

Patients are to be well hydrated for at least the first 24 hours.

Blood counts are to be controlled every 2 days during the first week and later once a week for the month following the last administration.

It is advisable but not mandatory to perform whole body scintigram for about 1 week on order to study the biodistribution of the agent and quantitate the uptake in tumour foci.

Repeated treatments can be considered at 6-8 months intervals. Cumulative doses up to 29.6GBq have been reported: bone marrow toxicity is the limiting factor. When the therapeutic administration for pheochromocytoma is planned attention is to be given to possible interference between the medication for control of hypertension and the uptake of Iobenguane [^{131}I]. Incompatible medication should be stopped at least 2 weeks prior to the planned therapeutic administration, if necessary propranolol can be used instead.

Iobenguane [^{131}I] therapy should be considered only in those patients where transplantation of autologous bone marrow (containing little or no tumour cells) is possible. The toxic effects on bone marrow (thrombocytopenia) must be monitored carefully and frequently.

Doses for patients, who have undergone prior to treatment with cytostatic drugs (e.g. cosplatinum compounds) resulting in reduced renal function, any have to be adjusted accordingly.

The main adverse reactions in children are threombocytopenia (isolated) or bone marrow suppression, the more so if there is tumour infiltration in bone marrow.adverse reactions related to the function of the salivary glands or of the myocardium, or toxic effects on the liver have not been described.

The uptake of meta-iodobenzylguanidine in the chromaffin granules might, though rarely, cause rapid noradrenalin secretion which can induce a hypertensive crisis. Monitoring of both ECG and blood pressure during administration of a therapeutic dose.

In patients where the diagnostic evaluation shows diffuse bone marrow uptake of Iobenguane [^{131}I], bone marrow suppression may occur after administration of a therapeutic dose.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs are known or may be expected to prolong or 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:

- Antihpertensive drugs as reserpine, labetalol, calcium-channel blockers (diltiazem, nifedipine, verapamil)
- Sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine).
- Cocaine
- Tricyclic antidepressants as amitryptiline and derivatives, imipramine and derivatives, doxepin, amoxepine and loxapine.

Of the following drugs inhibition of the uptake of Iobenguane is expected to occur, but no proof is yet available.

Antihypertensives acting through adrenergic neuron blockade (bethanidine, debrisoquine, bretylium and guanethidine).

Anridepressants as maprotiline and trazolone.

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

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.

4.6 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.

Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given as to whether the investigation could be reasonable delayed until the mother has ceased breast-feeding.

Especially in the case of a therapeutic administration of Iobenguane [^{131}I] a lactating mother would be advised to stop breast-feeding because of the long effective half-life.

4.7 Effects on ability to drive and use machines

Therapeutic doses are to be administered during hospitalisation only**.**

4.8 Undesirable effects

For each patient, exposure to ionising radiation must be justifiable on th ebasis 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.

Exposure to ionising radiation is linked with cancer induction and a potential for development or 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

The radiation dose resulting from therapeutic exposure may result in higher incidences of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself.

Effects expected to occur on administration of Iobenguane [^{131}I] in therapeutic usage:

In general, nausea or vomiting will occur within the first 24 hours after administration. Concerning anti-emetic medication consult chapter 4.5. In general, it is not possible to differentiate between adverse reactions as a result of early onset radiotoxic effects, reactions due to the administration of meta-iodobenzylguanidine or reactions resulting from infusing a large volume of fluid in patients who already have been infused extensively with cytostatics causing similar adverse reactions.

Myelosuppression and subsequently thrombocytopenia.

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 rapid 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

Iobenguane [^{131}I] is a radioiodinated aralkyguanidine. Its structure contains the guandine-group fromguanethidine linked to a benzy-group 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 localization in the myocardium occurs.

5.1 Pharmacodynamic properties

ATC code V10XA A02

Of the various aralkylguanidines meta-iodobenzylguanidine is the preferred substances because of its low 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 iodohippuricacid, ^{131}I hydroxyl-iodobenzyylguanidine and ^{131}I- metaiodobenzioc-acid. These substance 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 visualized with Iobenguane [^{131}I]. Hyperplastic adrenals show a high uptake.

5.3 Preclinical safety data

In dogs 20mg/kg is a lethal dose. Lower dose levels (14mg/kg) cause transient clinical signs of toxic effect. Repeated intravenous administrations in rates of 20 to 40mg/kg induce signs of serious clinical toxicity. Repeated intravenous administrations of 5 to 20mg/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 10mg/kg do induct clinical effects, including increased blood pressure and abnormalities in heart rate and in cardiac pulse propagation, but all signs were of a transient nature.

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 a 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

Sodium Chloride

Water for Injections

Benzyl alcohol

6.2 Incompatibilities

None known.

6.3 Shelf Life

Frozen: The shelf-life is 2 days from the activity reference date stated on the label.
Diluted: Use within 2 hours of dilution

6.4 Special precautions for storage

The product should be stored in dry ice (solid carbon dioxide) at –70^{o}C until approximately one hour before use. Storage should take place in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

10ml type I Ph. Eur., clear colourless, borosilicate glass vial sealed with a PTFE-faced butyl rubber closure and oversealed within aluminium overseal with central aperture. Each vial is packed within a radiation shielding container of lead metal and placed within a sealed metal tin.

Pack sizes: single vials contain 0.37-3.70Gbq in 0.175Gbq steps

6.6 Special precautions for disposal and other handling

Therapeutic doses of m-iodobenzylguanidine [^{131}I] should be stored in dry ice (solid carbon dioxide) prior to use.

About 1 hour prior to administration the vial m-iodobenzylguanidine [^{131}I] contained within its lead shield should be thawed by placing it in a water bath not exceeding 50^{o}C. The product is diluted with 50ml of sterile isotonic saline prior to intravenous infusion. The solution must be infused within two hours.

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

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

6.6.1 Instructions for quality control

The level of unbound iodide should be measured as specified in the Ph. Eur. or as appropriate.

7 MARKETING AUTHORISATION HOLDER

GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire
HP7 9NA
England

8 MARKETING AUTHORISATION NUMBER

PA 240/8/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 October 1999

Date of last renewal: 29 October 2009

10 DATE OF REVISION OF THE TEXT

October 2010

11 DOSIMETRY

Data from ICRP publication 53 (vol.18 – No 1-4, 1987): “Radiation dose to patients from radiopharmaceuticals”.

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 *).

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**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
Kidneys	0.12	0.14	0.21	0.3	0.51
Lungs	0.19	0.28	0.39	0.6	1.2
Gonads					
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
Uterus	0.08	0.1	0.16	0.26	0.48
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 increase considerably.