SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Meta-Iodobenzylguanidine (\(^{131}\)I) for Diagnostic Use 9.25-18.5 MBq/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
\([^{131}\text{I}]\text{iobenguane: 9.25-18.5 GBq/ml (0.05-0.5 mg/ml)}\]

Summary of the physical characteristics of the radioactive isotope in the active substance: Iodine-131: physical half-life 8.08 days.

The most important radiation emissions are as below:

<table>
<thead>
<tr>
<th>Energy level</th>
<th>Abundance(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta)-247 keV</td>
<td>1.8</td>
</tr>
<tr>
<td>(\beta)-334 keV</td>
<td>7.2</td>
</tr>
<tr>
<td>(\beta)-606 keV</td>
<td>89.7</td>
</tr>
<tr>
<td>(\beta)-806 keV</td>
<td>0.7</td>
</tr>
<tr>
<td>(\gamma)-364 keV</td>
<td>82.0</td>
</tr>
</tbody>
</table>

This medicinal product contains:
- Benzyl alcohol: 10 mg/ml
- Sodium: 3.54 mg/ml.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
This medicinal is for diagnostic use only.
Calculation of a therapeutic \([^{131}\text{I}]\text{iobenguane dose from a prior tracer-dose. The sensitivity to diagnostic visualisation, and therefore also to therapeutic efficacy, is different for the listed pathologic entities. Pheochromocytomas and neuroblastomas are sensitive in approximately 90% of patients, carcinoids in 70% and medullary carcinomas of the thyroid gland (MCT) in only 35%.

4.2 Posology and method of administration
“Tracer”-dose to acquire dosimetric information (20-40 MBq). Distribution measurement prior to administration of a therapeutic dose is recommended in order to establish the retention time of the radiopharmaceutical in organs, tumour tissue and normal structures. These recommended dosages are identical for children (must not be given to premature babies or neonates) and adults. The dose is administered intravenously, the duration of the injection should be 30-300 seconds.

4.3 Contraindications
Pregnancy is an absolute contraindication. Hypersensitivity to the active substance or to any of the excipients. Must not be given to premature babies or neonates.

4.4 Special warnings and precautions for use
This medicinal 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 [131I]iobenguane should be stopped before treatment (see section 4.5).
Prior to administration, ensure emergency cardiac antihypertensive treatments are readily available.
The uptake of iobenguane in the chromaffin granules might, though rarely, cause rapid noradrenalin secretion which can induce a hypertensive crisis although the likelihood of such an occurrence is believed to be extremely low. Monitoring of both E.C.G. and blood pressure during administration could be indicated in some patients. This necessitates constant monitoring of the patient during administration. [131I]iobenguane must be administered slowly (take at least one minute for the administration of a patient dose).
When diagnostic administration for pheochromocytoma is planned attention is to be given to the interference with uptake of [131I]iobenguane 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.
As with all iodine-131 containing products, a substantial proportion of the absorbed radiation dose is to the thyroid gland as a consequence of concentration of iodine by thyroid tissue. Blocking of the uptake of iodine-131 by the thyroid is therefore recommended to reduce radiation dose.
Blockade may be undertaken using non-radioactive iodine. A daily dose of approximately 100 mg iodine should be administered. This should commence 24-48 hours before the [131I]iobenguane is administered and should be continued for at least 5 days after its administration, when the estimated activity of iodine-131 in the body will have fallen to an acceptably low level.
Iodine may be administered either as potassium iodide, potassium iodate or Aqueous Iodine Oral solution (Lugol’s iodine). If further information is required, refer to literature provided with the blocking agent.
In patients where the diagnostic evaluation shows diffuse bone marrow uptake of $[^{131}\text{I}]$iobenguane, bone marrow suppression may occur after administration of a therapeutic dose.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum recommended dose, i.e. essentially ‘sodium-free’.

### 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. 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 uptake of iobenguane 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).

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy:

The product 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.

#### Breastfeeding:


Before administering a radioactive medicinal product to a mother who is breastfeeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breastfeeding. Breastfeeding should be discontinued after administration of the product.

**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**
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.

When administering \(^{131}I\)iobenguane in diagnostic usage, no significant undesirable effects are anticipated.

**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 (phenotolamine) 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**

\(^{131}I\)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 localise preferentially in the medulla of the adrenal glands. In addition localisation in the myocardium occurs.

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: diagnostic radiopharmaceuticals, tumour detection, iobenguane (\(^{131}I\)), ATC code V09IX02.

Of the various aralklyguanidines iobenguane is the preferred substance 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 neutral 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 usages) passive diffusion processes also become 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 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: iodide-131, \([{^{131}\text{I}}\text{-metaiodohippuric~acid}]\), \([{^{131}\text{I}}\text{-hydroxy-iodobenzylguanidine}]\) and \([{^{131}\text{I}}\text{-metaiodobenzoic~acid}]\). 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 can not be visualised with \([{^{131}\text{I}}]\text{iobenguane}\).

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.

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
Sodium chloride
Water for injections
Benzyl alcohol

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

6.3 Shelf life
The shelf life is 3 days from the activity reference date stated on the label.
6.4 Special precautions for storage
Store below 25°C. Do not freeze.
Store in original lead container or in equivalent shielding.

6.5 Nature and contents of container
The product is supplied in a clear neutral glass vial sealed with a PTFE-faced butyl rubber closure.
Pack sizes: single vials containing 18.5 MBq to 185 MBq in 18.5 MBq steps
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

7 MARKETING AUTHORITYHOLDER
GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

8 MARKETING AUTHORIZATION NUMBER
UK: PL 00221/0124

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization: 14 February 1997
Date of last renewal: 10 October 2001

10 DATE OF REVISION OF THE TEXT
11/11/2010

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 *).

<table>
<thead>
<tr>
<th>Organ</th>
<th>Absorbed dose per unit activity administered (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>15 year</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>6.1E-02</td>
</tr>
<tr>
<td>Breast</td>
<td>6.9E-02</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1.2E-01</td>
</tr>
<tr>
<td>Lungs</td>
<td>1.9E-01</td>
</tr>
<tr>
<td>Gonads</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>6.6E-02</td>
</tr>
<tr>
<td>Testes</td>
<td>5.9E-02</td>
</tr>
<tr>
<td>Red marrow</td>
<td>6.7E-02</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5.0E-02</td>
</tr>
<tr>
<td>*Adrenals</td>
<td>1.7E-01</td>
</tr>
<tr>
<td>*Bladder wall</td>
<td>5.9E-01</td>
</tr>
<tr>
<td>*Liver</td>
<td>8.3E-01</td>
</tr>
<tr>
<td>*Salivary glands</td>
<td>2.3E-01</td>
</tr>
<tr>
<td>*Spleen</td>
<td>4.9E-01</td>
</tr>
<tr>
<td>Uterus</td>
<td>8.0E-01</td>
</tr>
<tr>
<td>Effective dose equivalent (mSv/MBq)</td>
<td>2.0E-01</td>
</tr>
</tbody>
</table>

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

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are
subject to the regulations and/or appropriate licences of the local competent official organisations (see section 6.6).

The administration of the radiopharmaceuticals creates 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. Normal safety precautions for the handling of radioactive materials should be observed in addition to the use of septic technique to maintain sterility of the vial contents.

**Radiochemical purity measurement**

The radiochemical purity of $[^{131}I]$iobenguane can be determined by high performance liquid chromatography on a silica gel (5 µm) column, 0.25 m x 4 mm, eluted isocratically with a mixture of ammonium nitrate solution (8%) : dilute ammonia : methanol (1:2:27). Peak detection is by the use of a suitable radioactivity detector and by ultraviolet spectrophotometry at 254 nm. Peaks are identified by reference to standard solutions of sodium iodide (1 mg/ml) and iobenguane sulphate (0.2 mg/ml).