SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
IOBENGUANE (\(^{131}\text{I}\)) PRETHERAPEUTIC CIS BIO INTERNATIONAL 9.25 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each mL contains 9.25 MBq of iobenguane (\(^{131}\text{I}\)) at calibration date, equivalent to 0.2 mg of iobenguane.

Iodine-131 is obtained by the fission of uranium-235 or by neutron bombardment of stable tellurium. The physical half-life of iodine-131 is 8.02 days. It decays to stable xenon-131, with the following as the principal emissions:

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean Energy (MeV)</th>
<th>Abundance (%)</th>
<th>Type</th>
<th>Energy (MeV)</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta^+)</td>
<td>0.069</td>
<td>2.1</td>
<td>(X)</td>
<td>0.029-0.030</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>0.097</td>
<td>7.3</td>
<td>(\gamma)</td>
<td>0.080</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>0.192</td>
<td>89.9</td>
<td></td>
<td>0.284</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.365</td>
<td>81.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.637</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.723</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Not more than 0.1% of the total radioactivity is due to other iodine isotopes (\(^{133}\text{I}, \(^{135}\text{I}\) and \(^{131}\text{I}\)).

Excipient with a known effect: sodium, 1.7 mg/mL.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear and colourless solution with a pH ranging from 4 to 6.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
This medicinal product is for diagnostic use only.
To calculate the therapeutic dose of iobenguane (\(^{131}\text{I}\)) by administering a previous tracer dose. Further treatment with iobenguane (\(^{131}\text{I}\)) should be indicated.
4.2. **Posology and method of administration**

**Posology**

**Adults and elderly population**
Administration of a tracer dose in order to obtain dosimetry data: 20-40 MBq for an adult weighing about 70 kg. Iobenguane (\(^{131}\)I) distribution measurement prior to administration of a therapeutic dose is recommended in order to establish the radiopharmaceutical retention time in organs and normal or tumour tissue structures.

**Paediatric population**
The recommended dosages are identical for children and adults.

**Method of administration**
The tracer dose should be administered by slow intravenous injection over a period of 30 to 300 seconds.

For patient preparation, see section 4.4.

4.3. **Contraindications**

- Pregnancy
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. **Special warnings and precautions for use**
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. \(^{131}\)Iiobenguane must be administered slowly.

**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.

**Paediatric population**
For information on the use of this product in children, see section 4.2. Carefully consideration of the indication is required the effective dose per MBq is higher than in adults (see section 11).

**Patient preparation**
Medicines that could interfere with the uptake and retention of \(^{131}\)I-labelled iobenguane should be stopped before treatment (see section 4.5).

During diagnostic administration to investigate phaeochromocytoma, the effect of antihypertensive agents on the uptake of \(^{131}\)I-labelled iobenguane should be taken into account. Medicines that interact with this product should be stopped prior to the planned diagnostic exploration (see section 4.5). If an interaction does occur, propranolol could be used instead.

Before administering \(^{131}\)I-labelled iobenguane, the patient’s thyroid gland should be blocked with non-radioactive iodine. Thyroid uptake of free radioactive iodine is prevented using orally-administered stable iodine.
In adults, thyroid blockade is started the day before iobenguane (\(^{131}\)I) administration and continued for 3 days.

Blockade by potassium iodide or Lugol’s solution must be performed with an equivalent of 100 mg of iodine/day.

For the paediatric population, thyroid blockade against circulating iodine is particularly important because the thyroid is more radiosensitive in children than in adults. Beginning on the day prior to and continuing until the day after the tracer injection, children weighing 5 to 15 kg should be given 32 mg potassium iodide daily, those from 15 to 50 kg should get a 65 mg dose, and those over this weight 130 mg daily. Neonates weighing less than 5 kg should only be given 16 mg of potassium iodide on the day before the tracer injection.

The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first few hours afterwards in order to reduce exposure to ionising radiations.

**Specific warnings**

In patients where the diagnostic evaluation shows diffuse bone marrow iobenguane (\(^{131}\)I) uptake, bone marrow suppression may occur after administration of the therapeutic dose.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

For precautions associated with environmental risks, see section 6.6.

**4.5. Interaction with other medicinal products and other forms of interaction**

The following medicines are known, or may be expected, to prolong or to reduce the uptake of iobenguane in neural crest tumours.

Nifedipine (calcium-channel blocker) is reported to prolong the retention time of iobenguane.

Decreased uptake was observed with therapeutic regimens involving the administration of:

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

Inhibition of iobenguane uptake is to be expected with the following medicines, though no evidence of this is yet available:

- Adrenergic neuron-blocking antihypertensive agents (bethanidine, debrisoquine, bretylium and guanethidine).
- Antidepressants such as maprotiline and trazodone.

These medicines should be stopped before iobenguane (\(^{131}\)I) administration. Five half-lives are necessary to eliminate a medicine from the organism.
4.6. Pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether she is pregnant or not. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about a possible pregnancy (amenorrhea, very irregular cycles, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

Use of (\(^{131}\text{I}\))-labelled iobenguane is contraindicated during pregnancy due to foetal radiation exposure (see section 4.3).

Breast-feeding

Before administering any radiopharmaceutical to a mother who is breast-feeding, the possibility of delaying administration until the mother has stopped breast-feeding should be considered, as well as the most appropriate choice of radiopharmaceutical considering the secretion of radioactivity in breast milk.

If administration of the medicine is deemed necessary, breast-feeding should be discontinued.

4.7. Effects on ability to drive and use machines

The effects on the ability to drive and use machines have not been studied.

4.8. Undesirable effects

The following table lists the types of reactions observed and the symptoms according to System Organ Class. The frequency listed below is defined using the following convention:

Very common (\(\geq 1/10\)); common (\(\geq 1/100 \text{ to } \geq 1/10\)); uncommon (\(\geq 1/1,000 \text{ to } <1/100\)); rare (\(\geq 1/10,000 \text{ to } <1/1,000\)); very rare (\(<1/10,000\)); not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System organ class, MedDRA</th>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Anaphylactoid reaction</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chills</td>
<td></td>
</tr>
</tbody>
</table>

In rare cases, severe anaphylactoid reaction with hypotension, facial flushing, urticaria, nausea and chills have been observed.

Exposure to ionising radiation is linked with cancer induction and a potential for developing hereditary defects. As the effective dose in adults is 6 mSv when the maximal recommended activity of 40 MBq is administered, the likelihood of these side effects is low.
Reporting of suspected adverse events

The reporting of suspected adverse events after the approval of the drug is important. This allows continuous monitoring of the drug’s risk/benefit ratio. Health professionals report any suspected adverse reactions via the national reporting system.

4.9. Overdose

The effects of an iobenguane overdose is due to the release of adrenaline. These effects are of short duration and require supportive measures aimed at lowering the blood pressure: an immediate injection of a fast-acting alpha-adrenergic blocking agent (phentolamine) followed by a beta-blocker (propranolol).
In the event of an accidental iobenguane ($^{131}$I) overdose, the amount absorbed by the patient should be reduced as much as possible by increasing the elimination of the radionuclide from the body with forced diuresis and frequent urination.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals
ATC code: V10XA02

Mechanism of action

Iobenguane ($^{131}$I) is a radioiodinated aralkylguanidine. It comprises a guanidine-group found in guanethidine linked to a benzyl-iodine ring. Like guanethidine, aralkylguanidines are adrenergic neuron-blocking agents. Due to the functional similarities between adrenergic neurons and chromaffin cells of the adrenal medulla, iobenguane has an affinity for the adrenal medulla. There is also some myocardial uptake.

Pharmacodynamic effects

Of the various aralkylguanidines, meta-iodobenzylguanidine was selected as it has the lowest liver uptake and best in vivo stability, which results in minimising the uptake of free iodine by the thyroid. With low concentrations (like those used for diagnostic purposes), iobenguane actively crosses the cell membranes of tissues derived from the neural crest. The uptake mechanism can be inhibited by other inhibitors such as cocaine or desmethyli mipramine. When higher concentrations (like those used for therapeutic purposes), passive diffusion also plays a major role in transmembrane transport. Any possible clinical implications as regards to dosimetry remain unclear.

Subsequently, an active mechanism transports at least part of the intracellular iobenguane into the storage granules within the cells.

5.2. Pharmacokinetic properties

Distribution/Organ uptake

The distribution pattern of iobenguane includes rapid initial uptake in the liver (33% of the administered dose) followed by much lower uptake in the lungs (3%), myocardium (0.8%), spleen (0.6%) and salivary glands (0.4%). Uptake in healthy adrenal (medulla) glands is so low that they cannot be visualised with iobenguane ($^{131}$I). Hyperplastic adrenals show a high uptake.

Elimination/Half-life

Iobenguane is largely excreted unaltered by the kidneys. After 4 days, 70 to 90% of administered doses is recovered in the urine. The following products of catabolism are recovered in the urine: radioactive iodine ($^{131}$I), radioactive meta-iodohippuric acid ($^{131}$I), radioactive hydroxy-iodobenzylguanidine ($^{131}$I) and radioactive meta-iodobenzoic acid ($^{131}$I). These substances account for approximately 5 to 15% of the administered dose.
5.3. Preclinical safety data

The lethal dose in dogs is 20 mg/kg. Lower doses (14 mg/kg) cause transient clinical signs of toxicity. Repeated intravenous administration of 20 to 40 mg/kg in rats induced signs of severe clinical toxicity. Repeated IV administration of 5 to 20 mg/kg induced toxic effects, including respiratory distress, but long-term effects included only a slight increase in the weight of the liver and heart. Repeated administration in dogs of 2.5 to 10 mg/kg induced clinical effects, including increased blood pressure and abnormalities in heart rate and cardiac pulse propagation, but all signs were transient.

The safety margin between the iobenguane dose administered and the concentration at which undesirable effects might occur is not very wide. Patients should therefore be kept under close surveillance during administration and for at least a few hours afterwards.

This medicine is not intended to be administrated regularly or continuously.

No mutagenic effect was observed in the experimental models used. Long-term studies of its carcinogenic potential have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate trihydrate
Acetic acid
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

From the date of manufacture, 19 days.
The expiry date is indicated on the label of each vial.

After thawing, use within 5 hours.

6.4. Special precautions for storage

The solution is delivered frozen in dry ice.

If the product is not injected on the day of reception, store the vial at -18°C in the original shielded protection (see section 6.6).

The product should not be frozen again once thawed.

Storage procedures should be in accordance with national regulations for radioactive materials.

6.5. Nature and contents of container

15 ml, colourless, European Pharmacopoeia type I, drawn glass vial, closed with Teflon-coated rubber stoppers and aluminium caps.

Pack size: Each single-dose vial contains 46.25 MBq at calibration date (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. The receipt, storage, use and disposable of radiopharmaceuticals are subject to regulations and/or appropriate licenses of the competent official organisation.
Radiopharmaceuticals should be prepared by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements. Usual precautions regarding aseptic techniques should be respected.

If the integrity of the vial is compromised during preparation of the product, it should not be used.

Administration procedures must be conducted to minimise the risk of product contamination or radiation exposure of operators. Adequate shielding is obligatory.

Before use, the product should be thawed to room temperature within its lead shield protection.

The product should be in liquid state before injection.

After thawing, this product should not be frozen again.

Before use, the packaging, pH, radioactivity and gamma spectrum should be checked.

The vial should be stored inside its lead shield and must never be opened. After disinfecting the stopper, the solution should be aseptically drawn-up through the stopper using a disposable syringe with an appropriate protective shield and a sterile disposable needle.

Administrating radiopharmaceuticals creates risks for other persons in the vicinity of the patient either from external radiation or contamination from urine, vomiting or expectoration. Radiation protection measures in accordance with national regulations must therefore be taken.

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

7. MARKETING AUTHORISATION HOLDER

Country specific

8. MARKETING AUTHORISATION NUMBER(S)

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

08/2016
11. DOSIMETRY

These data are obtained from ICRP publications 53 and 60 of the International Commission on Radiological Protection (ICRP):

Radiation doses to any given organ, which may not necessarily be the target organ of the treatment, can be greatly affected by pathophysiological changes caused by the underlying disease. This should be taken into consideration when using the following information.

Radiation doses delivered to standard organs, target organs (*) and the uterus are used to calculate the effective dose.

<table>
<thead>
<tr>
<th>Organ</th>
<th>DOSE ABSORBED PER UNIT OF ACTIVITY ADMINISTERED (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.061</td>
</tr>
<tr>
<td>Breast</td>
<td>0.069</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.12</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.19</td>
</tr>
<tr>
<td>Gonads</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.066</td>
</tr>
<tr>
<td>Testes</td>
<td>0.059</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>0.067</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.05</td>
</tr>
<tr>
<td>* Adrenals</td>
<td>0.17</td>
</tr>
<tr>
<td>* Bladder wall</td>
<td>0.59</td>
</tr>
<tr>
<td>* Liver</td>
<td>0.83</td>
</tr>
<tr>
<td>* Salivary glands</td>
<td>0.23</td>
</tr>
<tr>
<td>* Spleen</td>
<td>0.49</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.08</td>
</tr>
<tr>
<td>Effective dose</td>
<td>0.15</td>
</tr>
</tbody>
</table>

The effective dose resulting from the administration of the maximum recommended activity of 40 MBq for an adult weighing 70 kg is about 6 mSv.

To administer an activity of 40 MBq, the typical radiation dose delivered to target organs is: adrenal glands 6.8 mGy and thyroid 2 mGy; while the typical radiation dose delivered to critical organs is: bladder wall 23.6 mGy, liver 33.2 mGy, salivary glands 9.2 mGy and spleen 19.6 mGy.

The above data are valid in cases of normal pharmacokinetics. The effective dose and the radiation dose to organs (particularly to bone, red marrow and lungs) could be considerably higher, especially when renal function is impaired due to the disease or previous therapy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not relevant.