GE Healthcare

TECHNICAL LEAFLET

[^{131}I] Meta-Iodobenzylguanidine for Therapeutic Use

IBS 6712

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Meta-Iodobenzylguanidine (^{131}I) for Therapeutic Use 185–740 MBq/ml solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

[^{131}I]iobenguane: 185–740 MBq/ml
(Not more than 0.67 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:

Energy level	*Abundance (%)*
ß-247 keV	1.8
ß-334 keV	7.2
ß-606 keV	89.7
ß-806 keV	0.7
ϒ 364 keV	82.0

Excipients with known effect:

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 infusion.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Radiation therapy of tumour-tissue that is capable of retaining iobenguane. These are tumours arising from cells originating embryologically from the neural crest;pheochromocytomas, neuro-blastomas, carcinoids and medullary carcinomas of the thyroid gland (MCT).

4.2 Posology and method of administration

Posology

Therapeutic dose with an amount of [^{131}I]iobenguane individually tailored on the basis of a dosimetric study. 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 rate of progression of the tumour, the shorter the interval. Repeat doses may be administered at 6-8 month intervals. The number of doses may vary between 1 and 5. The "fixed" therapeutic dose is (3.7-7.4 GBq).

Elderly population

No special dosage-scheme is required for the elderly patient.

Renal/Hepatic impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients (see section 5.2).

Paediatric population

The recommended dosages are identical for children and adults. Meta-iodobenzylguanidine (rnl) for Therapeutic Use is contraindicated in premature babies and neonates.

Method of administration

The therapeutic dose is administered intravenously, generally as an infusion over a period of 1- 4 hours. lt is recommended that the dose be diluted with 50 ml sterile physiological saline for infusion on thawing and immediately prior to administration by intravenous infusion.

Radioactivity

The volume of iobenguane [^{131}I] for therapeutic use to be injected is calculated by reference to the radioactive concentration at 1200 hours GMT on the day of administration. This is obtained by multiplying the radioactive concentration on the activity reference date by the decay factor given in the following table:

Day*	Factor	Day*	Factor
-6	1.677	1	0.917
-5	1.539	2	0.842
-4	1.412	3	0.772
-3	1.295	4	0.708
-2	1.188	5	0.650
-1	1.090	6	0.597
0	1.000	7	0.547

*Days before (-) or days after the reference date stated on the container label.

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

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.

Normal tissue adjacent to the radiated cancer tissue may become damaged (e.g. gonadal dysfunction in patients with pelvic metastases).

Additive toxicity may occur in patients on chemotherapy (e.g. lung fibrosis, hypergonadotropic hypogonadism).

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 therapeutic effect.

Paediatric population

Children treated with [^{131}I]iobenguane are at risk of developing irreversible thyroid function loss, growth retardation and hypergonadotropic hypogonadism. During follow up it is therefore recommended that special attention is paid to their endocrine status.

This medicinal product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Renal/Hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required, since an increased radiation exposure is possible (see section 5.2).

Patient Preparation

Drugs that may interfere with uptake and retention of [^{131}I]iobenguane should be stopped before treatment (see section 4.5).

Several drugs used in the treatment of high blood pressure and in psychiatry, interact with [^{131}I]iobenguane. Concomitant use therefore may interfere with the uptake and retention of [^{131}I]iobenguane and thus in-

fluence 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 blockade is started 24-48 hours before the [131I]iobenguane is administered and continued for at least 5 days. Blockade by potassium perchlorate is achieved by administration of approximately 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 patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the study in order to reduce radiation.

[131I]iobenguane 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 (thrombo-cytopenia) must be monitored carefully and frequently.

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 in 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 29.6 GBq have been reported; bone marrow toxicity is the limiting factor.

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. [131I]iobenguane must be administered slowly.

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

When the therapeutic administration for pheochromo-cytoma is planned attention is to be given to possible interference between the medication for control of hypertension and the uptake of [131I]iobenguane. Incompatible medication should be stopped at least 2 weeks prior to the planned therapeutic administration. If necessary propranolol can be used instead.

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

Women receiving [131I]iobenguane should be advised not to become pregnant within at least 6-12 months of administration.

Specific warnings

This medicinal product contains sodium: 3.54 mg/ml. This needs to be taken into consideration for patients on a controlled sodium diet.

Precautions with respect to environmental hazard see section 6.6.

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 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 amitriptyline 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).

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.

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.

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.

Breastfeeding:

Before administering a radiopharmaceutical to a mother who is breast feeding, consideration should be given as to the possibility of delaying the administration until the mother has ceased breast feeding.

Breast-feeding should be discontinued after administration of the product and the expressed feeds discarded.

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. The radiation dose resulting from therapeutic exposure may result in higher incidence 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.

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).

Infections and infestations

Not known: Infection susceptibility increased.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known: Leukaemias, malignant secondary cancers.

Blood and lymphatic system disorders

Not known: Bone marrow depression, anaemia, thrombocytopenia, neutropenia.

Vascular disorders

Common: Hypertension including acute episodes of hypertensive crisis (observed with the therapeutic use of [^{131}I] iobenguane).

Endocrine disorders

Not known: Hypothyroidism, possibly leading to growth retardation in children. Hyperthyroidism.

Gastrointestinal disorders

Very common: Nausea, vomiting.

Not known: Salivary gland conditions.

Injury, poisoning and procedural complications

Not known: Radiation injury (including radiation associated pain, interstitial lung disease, transient sialoadenitis, hypogonadism, ovarian failure).

Paediatric Population

The main adverse reactions in children are thrombocytopenia (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.

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:

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: therapeutic radiopharmaceuticals, other therapeutic radiopharmaceuticals, iobenguane (^{131}I), ATC code V10XA02.

Mechanism of action

[^{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.

Pharmacodynamic effects

Of the various aralkylguanidines 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 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

Distribution

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}I]iobenguane. Hyperplastic adrenals show a high uptake.

Elimination

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: iodide-131, [^{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.

Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

5.3 Preclinical safety data

In dogs 20 mg/kg is a lethal dose. Lower dose levels (14mg/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

Benzyl alcohol
Sodium chloride
Water for injections

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 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) until approximately one hour before use.

About 1 hour prior to administration the vial contained within its lead shield should be thawed by placing it in a water bath not exceeding 50°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

Store in original lead container or equivalent shielding.

6.5 Nature and contents of container

The product is supplied in a clear neutral 10 ml glass vial sealed with a PTFE-faced butyl rubber closure.

Pack sizes: single vials containing
0.37 to 3.7 GBq in 0.185 GBq steps

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning

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 licenses of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

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.

If at any time in the preparation of this product the integrity of the vial is compromised it should not be used.

This preparation is likely to result in relatively high radiation dose to most patients. The administration of Meta-Iodobenzylguanidine (^{131}I) for Therapeutic Use may result in significant environmental hazard. This may be of concern to the immediate family of patients or the general public. Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated from patients, in order to avoid any contamination.

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

7 PRODUCT OWNER

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8 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 *).

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Bone surfaces	6.1E-02	7.2E-02	1.1E-01	1.8E-01	3.6E-01
Breast	6.9E-02	6.9E-02	1.1E-01	1.8E-01	3.5E-01
Kidneys	1.2E-01	1.4E-01	2.1E-01	3.0E-01	5.1E-01
Lungs	1.9E-01	2.8E-01	3.9E-01	6.0E-01	1.2E+00
Gonads					
Ovaries	6.6E-02	8.8E-02	1.4E-01	2.3E-01	4.2E-01
Testes	5.9E-02	7.0E-02	1.1E-02	1.9E-01	3.6E-01
Red marrow	6.7E-02	8.3E-02	1.3E-01	1.9E-01	3.5E-01
Thyroid	5.0E-02	6.5E-02	1.1E-01	1.8E-01	3.5E-01
*Adrenals	1.7E-01	2.3E-01	3.3E-01	4.5E-01	6.9E-01
*Bladder wall	5.9E-01	7.3E-01	1.1E+00	1.7E+00	3.3E+00
*Liver	8.3E-01	1.1E+00	1.6E+00	2.4E+00	4.6E+00
*Salivary glands	2.3E-01	2.8E-01	3.8E-01	5.1E-01	7.5E-01
*Spleen	4.9E-01	6.9E-01	1.1E+00	1.7E+00	3.2E+00
Uterus	8.0E-02	1.0E-01	1.6E-01	2.6E-01	4.8E-01
Effective dose equivalent (mSv/MBq)	2.0E-01	2.6E-01	4.0E-01	6.1E-01	1.1E+00

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.

9 DATE OF REVISION OF THE TEXT

January 2020

[^{131}I] Meta-Iodobenzylguanidine for Therapeutic Use

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