MIBG-131-D
IOBENGUANE [^{131}I] INJECTION FOR DIAGNOSIS
CIS bio international

USER PACKAGE LEAFLET

CIS bio international

MIBG-131-D
Iobenguane [^{131}I] Injection for Diagnosis，CIS bio international

IDENTIFICATION OF THE MEDICINAL PRODUCT

Trade name of the medicinal product

Iobenguane [^{131}I] Injection for Diagnosis，CIS bio international
Reference:： MIBG-131-D

Qualitative and quantitative composition

Iobenguane [^{131}I] Injection for Diagnosis ([^{131}I] meta-iodobenzylguanidine) is a sterile solution with a pH ranging between 4 and 6，a radiochemical purity at least equal to 94 % and a total radioactivity of 46.25 MBq (1.25 mCi) per vial at the reference date on the label (calibration date)。

Iobenguane [^{131}I] injection for diagnosis contains no antimicrobial preservative。

Composition of the medicinal product per vial：

Iobenguane [^{131}I]	： 46.25 MBq (1.25 mCi)
Iobenguane (INN)	： 1 mg
Saline acetate buffer	： 4.6 ml
Water for injections	： 0.4 ml

Composition of the saline acetate buffer：

Sodium acetate trihydrate	： 0.51 mg / ml
Acetic acid	： 0.072 mg / ml
Sodium chloride	： 4.50 mg / ml
Water for injections	： up to 1 ml

Iodine [^{131}I] (atomic number 53；atomic weight 131) has a physical half-life of 8.02 days。It decays to stable xenon [^{131}Xe] by emission of the most important following radiations ：

Mean energy level	Abundance (%)
ß$^-$ 247 keV	1.8
ß$^-$ 334 keV	7.2
ß$^-$ 606 keV	89.7
ß$^-$ 806 keV	0.7
γ 364 keV	82.0

Not more than 0.1 % of the total radioactivity is due to other isotopes of iodine (^{133}I，^{135}I and ^{130}I)。

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Decay of iodine [^{131}I]：

D	%	D	%
-2	118.9	7	54.6
-1	109.0	8	50.1
0	100.0	10	42.1
1	91.7	12	35.5
2	84.1	14	29.8
3	77.2	16	25.1
4	70.8	18	21.1
5	64.9	20	17.8
6	59.5		

Nature and contents of the container

15 ml，colourless，European Pharmacopoeia type I ，drawn glass vials，closed with chlorobutyl rubber stoppers coated with teflon and aluminum capsules。

Pharmaceutical form

Solution for injection。

Pharmaco-therapeutic group

Radiopharmaceutical preparation for diagnostic use。

Name and address of marketing authorization holder

Country specific。

Name and address of the manufacturer

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B.P.32-91192 Gif-sur-Yvette cedex
France
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PHARMACODYNAMIC PROPERTIES

Iobenguane [^{131}I] 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 localize preferentially in the medulla of the adrenal glands。In addition，localisation in the myocardium occurs。

Of the various aralkylguanidines meta-iodobenzylguanidine 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。

PHARMACOKINETIC PROPERTIES

Iobenguane is to a large extend 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] hydroxyl-iodobenzylguanidine and [^{131}I] meta-iodobenzoic acid。These substances account for approximatively 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 visualized with Iobenguane [^{131}I] 。Hyperplastic adrenals show a high uptake。

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 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 of the drug。

In the test systems used no mutagenic effect could be demonstrated。Studies of carcinogenic Potential of iobenguane have not been published。

RADIATION 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 or 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 OF ADMINISTERED RADIOACTIVITY (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
Kidneys	0.12	0.14	0.21	0.3	0.51
Lungs	0.19	0.28	0.39	0.6	1.2
Gonads					
Ovarise	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 increased considerably。

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DIAGNOSTIC INDICATIONS

Calculation of a therapeutic Iobenguane [^{131}I] 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 neuro-blastomas are sensitive in approximatively 90 % of patients，carcinoids in 70 % and Medullary Carcinomas of the Thyroid gland (MCT) in only 35 %。

NECESSARY INFORMATION BEFORE TAKING THE MEDICINAL PRODUCT

Contra-indications

Pregnancy is an absolute contraindication。

Special warnings and special precautions for use

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。Incompatible medication should be stopped at least 2 weeks prior to the planned diagnostic administration。If necessary propranolol can be used instead。

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 authorized 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。

Interaction with other medicaments 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 ：

— 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 as amitryptiline and derivatives，imipramine and derivatives，doxepin，amoxepine and loxapine。

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Of the following drugs ibhibition 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)。
— Antidepressants as maprotiline and trazolone。

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

Pregnancy and lactation

Women of childbearing potential ： 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 ioinising radiation should be considered 。

Lactation ： 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 breast-feeding，because of the long effective half-life。

Effects on ability to drive and use machines

Effects on the ability to drive or use machines have not been described。

List of excipients

Saline acetate buffer
Water for injections

Incompatibilities

None known。

NECESSARY AND USUAL INSTRUCTIONS FOR PROPER USE

Posology and method of administration

“ Tracer “ dose to acquire dosimetric information (20 – 40 MBq) (0.5 to 1.1 mCi)。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。

The tracer dose is administered intravenously；the duration of the injection should be 30 – 300 seconds。

The recommended dosages are identical for children and adults。
No special dosage-scheme is required for the elderly patient。

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Instructions for use / handing

Usual precautions regarding sterility and radioprotection should be respected。

Before use，the product must be allowed to thaw at room temperature in its protective lead

container and before injecting it must be checked that the product is liquid。
After thawing this product should not be frozen again。

Before use，packaging，pH，radioactivity and gamma spectrum will be checked。

The vial should never be opened and must be kept inside its lead shielding。

The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper。

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。

Radioactive waste must be disposed of in conformity with the relevant national and international regulations。

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。

UNDESIRABLE EFFECTS

In rare cases，the following undesirable effects ，attributable to an hypersensitivity towards iodine ，have occured ： severe anaphylactoid reaction accompanied with hypotension ，blush of the face ，urticaria ，nausea and cols chills 。

For each patient，exposure to ionizing radiation must be justifiable on the basis of likely benefit。
The radioactivity administered must be such that the resulting radiation dose is as low as reasonable achievable bearing in mind the need to obtain the intended diagnostic result 。
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。

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SHELF-LIFE

The expiry date for this product is 19 days from the date of manufacture。The expiry date is indicated on the outer packaging and on each vial。

The expiry date for this product after thawing is 5 hours。

Special precautions for storage

This product must be stored at -18℃。
The solution is delivered frozen in dry ice 。
If the product is not injected on the day of reception，store the vial frozen at -18℃。
The product should not be frozen and thawed more than once。
Storage procedures should be in accordance with national regulations for radioactive materials。

DATE OF REVISION OF THE TXET

09/1999

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