SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

^{131}I-MIBG 20 MBq/ml injection for diagnostic use

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of the components	***Quantity per volume unit***	***Function***
Active ingredient		
^{131}I-meta-iodobenzyl-guanidine sulphate	20 MBq/ml contains not more than 0.75 mg/ml of the labelled substance	Organ-specific labelled compound providing diagnostic information

List of excipients is given in point 6.1

3 PHARMACEUTICAL FORM

Radioactive sterile injection solution
The active ingredient of the radioactive solution for injection for intravenous use is ^{131}I radioisotope labelled meta-iodobenzylguanidine (MIBG).

4 CLINICAL PARTICULARS

4.1 Indications

This medicinal product is for diagnostic use only.
Indication field: radioisotope diagnostics:
Lesion specific localization of neuroendocrine tumours, especially phaeochromocytoma, neuroblastoma

4.2 Posology and method of administration

Use of ^{131}I-MIBG 20 MBq/ml injection for diagnostic use is contraindicated in case of children, with exception of the indication of neuroblastoma.

The recommended individual patient dose is 20 – 40 MBq ^{131}I-MIBG. To prevent the uptake of the free radioiodine evolving in vivo, thyroid blockade is recommended before the examination. The injection should be administered slowly; time of administration is 2 – 4 minutes. Rapid administration of MIBG can result in blood pressure increase, allergic symptoms, flush or asthmatic spasms.

To monitor MIBG-uptake, use gamma-camera imaging technique. Pictures should be taken 24, 48, 72 and 96 hours after administration.

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients.
-Under 18 years of age, except the indication of neuroblastoma
-Pregnancy or lactation
-If the patient does not provide an oral or written consent of being examined by using radionuclide

4.4 Special warnings and special precautions for use

This drug product contains radioactive isotope. For handling, shipping and storage of this product the rules and regulations referring to the radioactive materials should be observed. This drug product can only be applied by properly qualified and trained personnel within designated clinical settings, which possess the appropriate government authorisation for the use and manipulation of radioisotopes. Way of handling of radiopharmaceuticals should meet the criteria both of radiation safety and pharmaceutical quality requirements.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium channel blocking agents, labetalol, reserpine, tricyclic anti-depressants, phenylpropanolamine and cimetidine may inhibit the uptake of MIBG. These drugs should not be used concomitant and it is advised to stop their administration in the pre-treatment period. MIBG uptake can also be inhibited by cocain or desmethyl-imipramine.

4.6 Pregnancy, lactation and paediatrics

Pregnancy
Use of the product is contraindicated in case of pregnancy.
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 pregnant until proven otherwise.

Lactation
The product must not be used in case of lactation, because ^{131}I-MIBG is excreted in the breast milk, causing significant risk to the infants.

4.7 Effects on ability to drive and use machines

The product has no direct influence on ability of car driving or on the use of dangerous machines. In occurrence of unexpected adverse reactions, driving and/or working with machines should be reconsidered.

4.8 Undesirable effects, adverse reactions

Appearance of undesirable effects or symptoms is not expected insofar as ^{131}I-MIBG injection is administered slowly, according to point 4.2. Rapid administration can result in blood pressure increase, allergic symptoms, flush or asthmatic spasms.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However these effects are hardly expected regarding the applied low amount of activity.

4.9 Overdose

No case of overdose has been reported.
In the unlikely event of overdose, the vital functions of the patient should be supported.

Administration of higher activities than prescribed is unnecessary and must be avoided in order not to cause excess of absorbed radiation dose to the patient and his/her environment.

In case of incidental overdose, the absorbed radiation dose must be calculated by using the data of the dosimetric table of point 11. On the strength of the results, the necessity and method of further treatment should be concluded. If the whole content of the vial containing the labelled substance is administered to one patient by mistake, 0.0214 mg/kg of bodyweight of ^{131}I-MIBG (= 1.5 mg ^{131}I-MIBG/ 70 kg of bodyweight) is introduced in the body which represents 1.2% of the no observed effect level (1.8 mg/kg bodyweight). In case of accidental administration of the content of a second vial of ^{131}I-MIBG the patient receives only 2.4 % of the no observed effect level. Due to these facts overdose of MIBG can not come about, only overdose of radioactivity represents the risk.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Group: Diagnostic radiopharmaceutical, ATC code V091X02

Hormones produced by the adrenal medulla take part in the synthesis and storage of catecholamine. Neuroendocrine tumours (phaeochromocytoma, neuroblastoma, paraganglioma, medullar thyroid carcinoma, and carcinoid) consist of cells of analogous nature with those of the adrenal medulla tissue. They excrete hormones specific to the adrenal medulla. Due to the functional similarity of the adrenergic neurones and the chromaffin cells of the adrenal medulla the molecules that are able to bind to the receptors of the adrenergic terminal filaments have anti-adrenergic effect and they tend to be accumulated in the cells of the adrenal medulla or other cells of similar type. Therefore, bretylium, guanethidine and MIBG, which bears functional groups analogous to them, are expected to bind to neuroendocrine receptors.

^{131}I-MIBG strongly binds to the chromaffin cells of the adrenal medulla and the uptake is proportional to the density of the neuroendocrine receptors present. The MIBG uptake may be hindered by cocaine and desmethyl-imipramine.

Due to the low amount of cold MIBG and activity administered, the diagnostic effect is not a consequence of the pharmacodynamic action of concentration of MIBG, but it is the result of the gamma particle emission of ^{131}I nuclide, which can be detected by using gamma camera imaging.

^{131}I-MIBG leaves the via the urine: 82% as unchanged ^{131}I-MIBG, 16% as metabolised to meta-iodine hippuric acid and 2% as free radioiodine.

5.2 Pharmacokinetic properties

10-15% of ^{131}I-MIBG introduced into the body appears in the cells, which are in functional relationship with the adrenal medulla tissues. 1 hour after administration ^{131}I-MIBG appears in the lungs, from where it leaves in 1-2 hours and binds to the neuroendocrine receptors of the myocardium. The highest radioactivity in the heart-muscle can be observed 2-3 hours after administration. After 24 hours the maximal activity can be found in the adrenal glands. ^{131}I-MIBG accumulates in the neuroendocrine tumours and metastases after 24-96 hours.

The not receptor-bounded proportion of ^{131}I-MIBG leaves the body via the kidneys and the urinary bladder (55% within 24 hours and 90% within 4 days).

5.3 Preclinical safety data

According to acute toxicity studies*) on mice there are no clinical symptom if less than 1.8 mg/kg of bodyweight is administered. The highest dose of ^{131}I-MIBG is equivalent to 0.0214 mg/kg bodyweight (= 1.5 mg ^{131}I-MIBG / 70 kg of bodyweight), which represents 1.2% of the no observed effect level. Therefore, it is obvious that the use of the product is safe in regard of MIBG intake.
*)*Radiopharmaceuticals product specification, Isopharma AS, Institutetveien 18, N2007 Kjeller, Norway, 1996., p74.*

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of the components	***Quantity per volume unit***	***Function***
Ammonium sulphate	0.7 mg/ml	Catalyst of labelling with radioiodine
Copper sulphate	0.025 mg/ml	Catalyst of labelling with radioiodine
Sodium acetate	19.1 mg/ml	Component of Walpole's buffer
Acetic acid	3.3 mg/ml	Component of Walpole's buffer
Water for injection	1.0 g/ml	Solvent

6.2 Incompatibilities

Above all, the product is incompatible with oxidising agents and chloride ions because these agents facilitate the elimination of radioiodine from ^{131}I-MIBG molecule. For the same reason the product is to be protected from light and radiating heat.
Strong acidic medium can release radioiodine which becomes volatile radical or elementary iodine. These substances may cause radioactive contamination of the environment when the vial of the product is being opened.

6.3 Shelf life

5 days from manufacture.

6.4 Special precautions for storage

Store in refrigerator at 2–8 ºC. Comply with the regulations for radiation safety.

6.5 Nature and contents of container

^{131}I-MIBG solution is supplied in glass injection vial of 6 ml, closed with rubber stopper and aluminium cap. The labelled vial is placed in a lead container, which contains a paper insert and has a wall thickness of a 15-30 mm (KT 1-6). The lead container is packed in a labelled tear-off metal can containing plastic insert (Type A packaging).

Pack size: 20 MBq, 40 MBq or 80 MBq (at the indicated calibration date)

6.6 Special precautions for disposal and handling

Any unused product or waste material should be disposed of in accordance with local requirements.
Way of handling of radiopharmaceuticals should meet the criteria both of radiation safety and pharmaceutical quality requirements.

7 MARKETING AUTHORIZATION HOLDER

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8 MARKETING AUTHORISATION NUMBERS

OGYI-T-09205/01 20 MBq
OGYI-T-09205/02 40 MBq
OGYI-T-09205/03 80 MBq

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

25.04.1989. / 17.12.2009.

10 DATE OF REVISION OF THE TEXT

17.12.2009.

This SPC was translated by the manufacturer based on the original Hungarian document, authorized by the Hungarian National Institute of Pharmacy on 17.12.2009.

11 DOSIMETRY

Estimated absorbed dose values of the administered ^{131}I-MIBG for an average body weight of 70 kg are given in the table below:

Organ	***Absorbed dose [mGy / MBq]***
Adrenal gland	9.5
Liver	0.1
Urinary bladder	2.1
Spleen	0.4
Ovaries	0.3
Thyroid	0.3

Radiation properties:

Physical half-life:	8.04 days	
	Energy	Intensity
Photons emitted:	80 keV	2.6 %
	164 keV	0.6 %
	177 keV	0.26 %
	284 keV	6.14 %
	325 keV	0.274 %
	364 keV	**81.7 %**
	503 keV	0.36 %
	636 keV	7.2 %
	722 keV	1.8 %
Beta particles emitted	250 keV	2.1 %
	304 keV	0.6 %
	330 keV	7.27 %
	608 keV	**89.9 %**
	810 keV	0.48 %

During the beta decay ^{131}Xe is produced (stable isotope)

Radioactive specifications:
Specific activity: > 26.7 GBq/g
Activity concentration: 20 MBq/ml
Radionuclidic purity at the time of application: impurities < 0.1 %
Radiochemical purity: > 90 %

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

^{131}I-MIBG is a radioactive product supplied in Type A packaging. To open the packaging, follow the instruction given below:
Tear off cover of the metal can. Remove the upper part of the foam insert. Lift the lead container containing the glass vial out from the metal can. Remove the upper part of the lead container to open it. Now the glass vial containing the radioactive material can be easily taken out from the lead container. Comply with the regulations referring to radiation safety.

To prevent the uptake of the free radioiodine evolving in vivo, thyroid blockade is recommended before radioiodine therapy.
Administer the injection slowly; time of administration should be in the range of 2 –4 minutes.

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

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PACKAGE LEAFLET: INFORMATION FOR THE USER

^{131}I-MIBG 20 MBq/ml injection for diagnostic use
^{131}I-meta-iodobenzyl-guanidine sulphate

Read all of this leaflet carefully before this medicine is used for your examination.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1 WHAT ^{131}I-MIBG 20 MBq/ml INJECTION FOR DIAGNOSTIC USE IS AND WHAT IT IS USED FOR

This medicinal product is for diagnostic use only.

^{131}I-MIBG 20 MBq/ml injection for diagnostic use is a radiopharmaceutical preparation which is used for the local lesion-specific treatment of neuroendocrine tumours.
After intravenous administration the active ingredient of the injection accumulates in cells, which are in functional relationship with the adrenal medulla, and binds to the neuroendocrine receptors of the myocardium. It appears in the adrenal gland 24 hour after administration afterwards in the neuroendocrine tumours and metastasis. As the injection contains radioactive isotope, it can be detected from outside the body using special cameras. The pictures taken by this camera show the distribution of the radioactive isotope in your body and organs. The pictures can give your doctor valuable information about the structure and working of the organ helping this way to choose the best treatment.

2. BEFORE YOU USE ^{131}I-MIBG 20 MBq/ml INJECTION FOR DIAGNOSTIC USE

^{131}I-MIBG 20 MBq/ml injection for diagnostic use cannot be used

- if you are allergic (hypersensitive) to ^{131}I-MIBG or to any ingredients of ^{131}I-MIBG 20 MBq/ml injection for diagnostic use
- If you are pregnant or breast feeding
- If you are under 18 years of age, with exception of indication of neuroblastoma
- if you do not provide an oral or written consent of being examined by using radionuclide

Make sure you carry out the doctor's instructions both before and after the examination in order to avoid radioactive exposure of other people and the radioactive contamination of the environment.. The non-bounded proportion of the radioactive isotope is excreted in the urine.
Flush your urine with abundant quantity of water two or three times and wash your hands thoroughly for several hours after administration of the injection. Be careful not to drop urine drips to other places than the WC. Change your underwear if it becomes contaminated and wash it separately by using abundant quantities of water.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
You should not take in the following medicines before the examination: calcium channel blocking agents, labetalol, reserpine, tricyclic anti-depressants, phenylpropanolamine and cimetidine. These drugs should not be used concomitant and it is advised to stop their administration in the pre-treatment period. MIBG uptake can also be inhibited by cocain or desmethyl-imipramine.

Using ^{131}I-MIBG 20 MBq/ml injection for diagnostic use with foods and drinks
You can have ^{131}I-MIBG 20 MBq/ml injection for diagnostic use with any food or drink.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.
It is important to tell your doctor if there is any possibility that you are pregnant or if you breast-feeding.
^{131}I-MIBG 20 MBq/ml injection for diagnostic use must not be used if you are pregnant or breast-feeding.

Driving and using machines
You can drive and use machines. In occurrence of unexpected adverse reactions driving and/or working with machines should be reconsidered.

Important information about ^{131}I-MIBG 20 MBq/ml injection for diagnostic use
^{131}I-MIBG 20 MBq/ml injection for diagnostic use contains ^{131}I radioactive isotope; after its administration you are exposed to radiation.
Receipt, storage, use, transfer and disposal of the radioactive medicinal products are subject to the regulations and appropriate licences of the competent authorities. Radioactive medicinal products should be received, used and administered only by authorised person in designated clinical settings.
These people give you instructions about the precautions and warnings. Comply with their instructions.

3. HOW TO USE ^{131}I-MIBG 20 MBq/ml INJECTION FOR DIAGNOSTIC USE

^{131}I-MIBG 20 MBq/ml injection for diagnostic use is administered intravenously. The dose is a function of the severity of your disease and is determined by your physician.

What to do in case of overdose?
Since the use of ^{131}I-MIBG 20 MBq/ml injection for diagnostic use is strictly controlled thus the probability of overdose is low. However, it has been clearly proven by experiments that administration of excess injection does not bring about damaging effects.
If you have any further questions on the use of this medicine, ask your doctor.

4 POSSIBLE SIDE EFFECTS OF ^{131}I-MIBG 20 MBq/ml INJECTION FOR DIAGNOSTIC USE

Like every medicinal product, ^{131}I-MIBG 20 MBq/ml injection for diagnostic use might cause adverse reactions, but such effects do not appear in every case.

If the product is injected according to the prescriptions, adverse reactions are not expected. On the other hand, rapid administration can result in blood pressure increase, allergic symptoms, flush or asthmatic spasms.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However these effects are hardly expected regarding the applied low amount of activity.

If any adverse reaction becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5 HOW TO STORE ^{131}I-MIBG 20 MBq/ml INJECTION FOR DIAGNOSTIC USE?

Keep the product out of the reach and sight of children and people who are not authorized to handle, use or transport this product!
Store at 2 – 8 °C, in its own container, in refrigerator.

Hospital staff will ensure that the product is stored correctly and not used after expiry date stated on the label.

Expiry: 5 days from the manufacturing

The rules and regulations referring to the radioactive materials should be observed. The rest of radioactive solution and the stripes used chromatography must be handled as radioactive waste, in accordance with the regulations on radiation. Any unused product or waste material should be disposed of in accordance with local requirements.

6. FURTHER INFORMATION

What ^{131}I-MIBG 20 MBq/ml injection for diagnostic use contains

- Active substance of this drug product is ^{131}I-meta-iodobenzyl-guanidine sulphate
- Excipients are: ammonium sulphate, copper sulphate, sodium acetate, acetic acid cc, water for injection.

How ^{131}I-MIBG 20 MBq/ml injection for diagnostic use looks like and what the packaging contains

The ^{131}I-MIBG 20 MBq/ml injection for diagnostic use is clear, colourless solution.
Packaging:
^{131}I-MIBG 20 MBq/ml injection for diagnostic use injection is supplied in a labelled glass vial, closed with rubber stopper and aluminium cap. The labelled vial is placed in a lead container, which contains a paper insert. The lead container is packed in a metal can, which contains plastic insert.
The packaging contains 1 piece of SPC and Patient Information Leaflet.

The Marketing authorization holder and manufacturer is

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