IZOTOP

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

^{131}I-MIBG 370 MBq/ml injection for therapy

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of the components	*Quantity per volume unit*	*Function*
Active ingredient		
^{131}I-meta-iodobenzyl-guanidine sulphate	333-410MBq/ml contains not more than 0.6 mg/ml of the labelled substance in 10 ml solution	Local, lesion-specific radiation therapeutic effect

Excipients with known effect: Ammonium sulphate, Copper sulphate, Sodium acetate, Acetic acid cc.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radioactive, sterile solution for injection.
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 Therapeutic indications

Indication field: radionuclide therapy.
Local, lesion-specific treatment of neuroendocrine tumours, especially, phaeochromocytoma, neuroblastoma, paraganglioma, medullar thyroid carcinoma, carcinoid.

4.2 Posology and method of administration

Posology

Paediatric population

^{131}I-MIBG solution for injection is contraindicated for paediatric population except in case indication of neuroblastoma.
The recommended individual dose is 3.3 – 4.1 GBq.

Method of administration
To prevent the uptake of the free radioiodine evolving in vivo, blockade of thyroid is recommended before radioiodine therapy.
The injection vial containing 3.3 – 4.1 GBq of radioactivity represents the dose to be administered for one patient. Do not administer the solution directly. 10 ml of the MIBG solution for injection must be mixed with 90 ml of 5% glucose injection. The obtained solution which has a total volume of 100 ml should be administered to the patient slowly. Time of administration is 2 – 4 hours. Rapid administration of MIBG can result in blood pressure increase, allergic symptoms, flush or asthmatic spasms.
To monitor MIBG therapy imaging technique (nuclear scan test) can be used. Gamma scanning should be performed 24, 48, 72 and 96 hours after administration.
For instructions on dilution of the medicinal product before administration, see section 12.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 precautions for use

This drug product contains radioactive isotope. Receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation. Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Way of handling of radiopharmaceuticals should meet the criteria both o f radiation safety and pharmaceutical quality requirements. To protect patients and hospital staff suitable lead shielding should be applied when 131I-MIBG 370 MBq/ml injection for therapy is handled.
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}I]iobenguane must be administered slowly. 10 ml of the MIBG solution for injection must be mixed with 90 ml of 5% glucose injection. The obtained solution which has a total volume of 100 ml should be administered to the patient slowly. Time of administration is 2 – 4 hours.

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 cocaine or desmethyl-imipramine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use of the product is contraindicated in case of pregnancy.
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who missed a period should be assumed to be pregnant until proven otherwise.

Breast-feeding
The product must not be used in case of breast-feeding, 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

^{131}I-MIBG 370 MBq/ml solution for injection has no or negligible influence on the ability to drive and use machines. In occurrence of unexpected adverse reactions driving and/or working w ith machines should be reconsidered.

4.8 Undesirable effects

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:
Vascular disorders: Common (≥1/100 to <1/10): Hypertension including acute episodes of hypertensive crisis
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 amount of activity.

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 via the national reporting system (In Hungary: www.ogyei.gov.hu)

4.9 Overdose

No case of overdose has been reported.
In the unlikely event of administration of radiation overdose the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, ATC code: V10XA02
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.
Since radioiodine labelled bretylium is unstable and guanethidine can only be labelled with carbon, nitrogen or hydrogen isotopes while MIBG can be labelled with radioiodine easily the latter has been introduced to the clinical practice. ^{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 inhibited by cocaine and desmethyl-imipramine.
The highest administered quantity of MIBG is 6 mg and the administered ^{131}I-activity is 3.3 – 4.1 GBq. Therefore, the therapeutic effect is not a consequence of the pharmacodynamic action of concentration of MIBG, but it is the result of the beta particle emission of ^{131}I nuclide. Energy of the beta particles is transmitted to the cell which brings about cell death.
^{131}I-MIBG leaves the body in 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

Distribution, organ uptake
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.
Elimination
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 0.0857 mg/kg bodyweight (= 6 mg ^{131}I-MIBG / 70 kg of bodyweight), which represents 4.8% 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	1.4 mg/ml	Catalyst of labelling with radioiodine
Copper sulphate	0.040 mg/ml	Catalyst of labelling with radioiodine
Sodium acetate	19.1 mg/ml	Component of Walpole's buffer
Acetic acid, cc.	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 stored at -18°C in freezed state. Furthermore, another hazard of strong acidic medium is that it can release radioiodine which becomes to volatile radical or elementary iodine. These substances may bring about the radioactive contamination of the environment upon the vial of the product is being opened.

6.3 Shelf life

5 days from manufacture.

6.4 Special precautions for storage

Store in a freezer, below -18°C. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

^{131}I-MIBG solution is supplied in glass injection vial of 12 ml, closed with rubber stopper and aluminium cap. The labelled vial is placed in a lead container, which contains a plastic 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). To ensure the low temperature during shipping dry-ice is used to cool the container.

Pack size: 3300–4100 MBq (at indicated calibration date)
Content of the packaging: 1 piece of vial, 1 Summary of Product Characteristics and Package Information Leaflet

6.6 Special precautions for disposal and other handling

Way of handling of radiopharmaceuticals should meet the criteria both of radiation safety and pharmaceutical requirements.
To protect patients and hospital staff suitable lead shielding should be applied when ^{131}I-MIBG 370 MBq/ml injection for therapy is handled.

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

Medicine subject to prescripition.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-9197/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28.06.1993
Date of latest renewal: 17.12.2009

10. DATE OF REVISION OF THE TEXT

8 April 2016

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: > 555 GBq/g
Activity concentration: 333 – 410 MBq/ml
Radionuclidic purity at the time of application: impurities < 0.1 %
Radiochemical purity: > 90 %

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised it should not be used.
^{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.

Method of preparation
The injection vial containing 3.3 – 4.1 GBq of radioactivity represents the dose for one patient. Do not administer the solution directly. 10 ml of the MIBG solution for injection must be mixed with 90 ml of 5% glucose injection. The obtained solution which has a total volume of 100 ml should be administered to the patient slowly. Time of administration is 2 – 4 hours.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

^{131}I-MIBG 370 MBq/ml injection for therapy
^{131}I-meta-iodobenzyl-guanidine sulphate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ^{131}I-MIBG 370 MBq/ml injection for therapy is and what it is used for

^{131}I-MIBG 370 MBq/ml injection for therapy is a radiopharmaceutical preparation for the local lesion-specific treatment of neuroendocrine tumours.

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 metastases. The radiation emitted by the radioactive isotope can directly destroy cancer cells.

2. What you need to know before you take ^{131}I-MIBG 370 MBq/ml injection for therapy

Do not take ^{131}I-MIBG 370 MBq/ml injection for therapy:
- if you are allergic to ^{131}I-MIBG or any of the other ingredients of this medicine (listed in section 6).
- 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

Warnings and precautions
^{131}I-MIBG 370 MBq/ml injection for therapy 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. ^{131}I-MIBG 370 MBq/ml injection for therapy 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.
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.

Children and adolescents
^{131}I-MIBG solution for injection is contraindicated for paediatric population (under 18 years) except in case indication of neuroblastoma.

Other medicines and ^{131}I-MIBG 370 MBq/ml injection for therapy
Tell your doctor if you are taking, have recently taken or might take any other medicines.
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 cocaine or desmethyl-imipramine.

You should check with your doctor before the administration of this product if you are unsure.

^{131}I-MIBG 370 MBq/ml injection for therapy with food and drink
You can have ^{131}I-MIBG 370 MBq/ml injection for therapy with any food or drink.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

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.

^{131}I-MIBG 370 MBq/ml injection for therapy contains ammonium sulphate, copper sulphate, sodium acetate, concentrated acetic acid

3. How to use ^{131}I-MIBG 370 MBq/ml injection for therapy

^{131}I-MIBG 370 MBq/ml injection for therapy is administered intravenously. The radioactivity to be administered 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 370 MBq/ml injection for therapy 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

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If the product is injected according to the prescriptions, adverse reactions are not expected. Rapid administration of MIBG can result in blood pressure increase, allergic symptoms, flush or asthmatic spasms: Common (may affect up to 1 in 10 people): High blood pressure including acute episodes of high blood pressure which might be severe.
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 amount of activity.
Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system (In Hungary: www.ogyei.gov.hu). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ^{131}I-MIBG 370 MBq/ml injection for therapy

Keep this medicine out of the sight and reach of children.

Store in a freezer, below -18°C. Observe the regulations referring to radiation protection.

Hospital staff will ensure that the product is stored correctly and not used after expiry date stated on the label.
The medicine should be kept out of the reach of people not authorised for handling, use and transportation.

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 containers 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. Contents of the pack and other information

What ^{131}I-MIBG 370 MBq/ml injection for therapy contains
- The active substance is: 131I-meta-iodobenzyl-guanidine sulphate
- The other excipients are: ammonium sulphate, copper sulphate, sodium acetate, acetic acid cc, water for injection

What ^{131}I-MIBG 370 MBq/ml injection for therapy looks like and contents of the pack
The ^{131}I-MIBG 370 MBq/ml injection for therapy is a colourless solution.
Packaging:
^{131}I-MIBG injection is supplied in a labelled glass vial, closed with rubber stopper and aluminium cap. The labelled vial is placed in a lead container, with plastic insert. The lead container is packed in a metal can, which contains polystyrene foam insert.
The packaging contains 1 piece of SPC and Patient Information Leaflet.

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