



SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

¹³¹I-MIBG 370 MBq/ml injection for therapy

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of the components	Quantity per volume unit	Function
<i>Active ingredient</i>		
¹³¹ I-meta-iodobenzylguanidine 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

List of excipients is given in point 6.1

3 PHARMACEUTICAL FORM

Radioactive, sterile solution for injection.

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

4 CLINICAL PARTICULARS

4.1 Indications

Indication field: radionuclide therapy.

Local, lesion-specific treatment of neuroendocrine tumours, especially, phaeochromocytoma, neuroblastoma, paraganglioma, medullar thyroid carcinoma, carcinoma.

4.2 Posology and method of administration

Posology

The recommended individual dose is 3.3 – 4.1 GBq. To prevent the uptake of the free radioiodine evolving *in vivo*, blockade of thyroid is recommended before radioiodine therapy.

Paediatric population

Use of ¹³¹I-MIBG 370 MBq/ml injection for therapy, is contraindicated in case of children, with exception of the indication of neuroblastoma.

Method of administration

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.

Image acquisition

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.

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

Pregnancy, see section 4.6.

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.

General warning

This drug product contains radioactive isotope. 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 licences of the competent official organisation. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Aseptic precautions should be taken.

To protect patients and hospital staff suitable lead shielding should be applied when ¹³¹I-MIBG 370 MBq/ml injection for therapy is handled.

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

Women of childbearing potential

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. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.) alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

Use of the product is contraindicated in case of pregnancy.

Lactation

The product must not be used in case of lactation, because ¹³¹I-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 ¹³¹I-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 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

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 carcinoma) 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. ¹³¹I-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 ¹³¹I-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 ¹³¹I nuclide. Energy of the beta particles is transmitted to the cell which brings about cell death.

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

5.2 Pharmacokinetic properties

Distribution, organ uptake

10-15% of ¹³¹I-MIBG introduced into the body appears in the cells, which are in functional relationship with the adrenal medulla tissues. 1 hour after administration ¹³¹I-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. ¹³¹I-MIBG accumulates in the neuroendocrine tumours and metastases after 24-96 hours.

Elimination

The not receptor-bounded proportion of ¹³¹I-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 ¹³¹I-MIBG is equivalent to 0.0857 mg/kg bodyweight (= 6 mg ¹³¹I-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, Instituttveien 18, N2007 Kjeller, Norway, 1996., p/4.}

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 ¹³¹I-MIBG molecule. For the same reason the product is to be stored at -18°C in frozen 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

¹³¹I-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 paper insert and has a wall thickness of a 1.5-30 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 handling

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

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must be therefore be taken.

Way of handling of radiopharmaceuticals should meet the criteria both of 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.

7 MARKETING AUTHORIZATION HOLDER



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8 MARKETING AUTHORISATION NUMBERS

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9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

28.06.1993/17.12.2009.

10 DATE OF REVISION OF THE TEXT

17.12.2009.



PACKAGE LEAFLET: INFORMATION FOR THE USER

¹³¹I-MIBIG 370 MBq/ml injection for therapy ¹³¹I-meta-iodobenzyl-guanidine sulphate

Estimated absorbed dose values of the administered ¹³¹I-MIBIG 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
Photons emitted:	Intensity 80 keV 2.6 % 164 keV 0.6 % 177 keV 0.26 % 284 keV 6.14 % 325 keV 0.274 %
Beta particles emitted	81.7 % 0.36 % 503 keV 7.2 % 636 keV 1.8 % 722 keV
	2.1 % 304 keV 0.6 % 330 keV 7.27 %
	89.9 % 0.48 %

During the beta decay ¹³¹Xe is produced (stable isotope).

Radioactive specifications:

Specific activity: > 555 GBq/g
Activity concentration: 333 – 410 MBq/ml
Radiochemical 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.

¹³¹I-MIBIG 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 MIBIG 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 product or waste material should be disposed of in accordance with local requirements.

treatment period. MIBIG 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.

Using ¹³¹I-MIBIG 370 MBq/ml injection for therapy with foods and drinks

You can have ¹³¹I-MIBIG 370 MBq/ml injection for therapy 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-feed.

¹³¹I-MIBIG 370 MBq/ml injection for therapy 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 ¹³¹I-MIBIG 370 MBq/ml injection for therapy

¹³¹I-MIBIG 370 MBq/ml injection for therapy contains ¹³¹I 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. ¹³¹I-MIBIG 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.

3. HOW TO USE ¹³¹I-MIBIG 370 MBq/ml INJECTION FOR THERAPY

¹³¹I-MIBIG 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 ¹³¹I-MIBIG 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 OF ¹³¹I-MIBIG 370 MBq/ml INJECTION FOR THERAPY

Like every medicinal product, ¹³¹I-MIBIG 370 MBq/ml injection for therapy 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 ¹³¹I-MIBIG 370 MBq/ml INJECTION FOR THERAPY

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 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.

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 strips 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 ¹³¹I-MIBIG 370 MBq/ml injection for therapy contains

- Active substance is ¹³¹I-meta-iodobenzyl-guanidine sulphate.
- Excipients are: ammonium sulphate, copper sulphate, sodium acetate, acetic acid cc, water for injection.

How ¹³¹I-MIBIG 370 MBq/ml injection for therapy looks like and what the packaging contains

The ¹³¹I-MIBIG 370 MBq/ml injection for therapy is a colourless solution.

Packaging:

¹³¹I-MIBIG 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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