SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

(^{131}I) IODOMETHYL NORCHOLESTEROL CIS bio international 7.5 to 15 MBq/mL solution for injection
Reference : NORCHOL-131

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1mL of solution contains 7.5 to 15 MBq of iodinated norcholesterol (^{131}I) at calibration date corresponding to 0.9 to 1.2 mg/mL.

The activity per vial varies from 37 MBq to 74 MBq at calibration date.

Iodine-131 is produced by fission of uranium-235 or neutron bombardment of stable tellurium in a nuclear reactor. Iodine-131 has a half life of 8.02 days. It decays by emission of gamma radiations of 365 keV (81.7%), 637 keV (7.2%) and 284 keV (6.1%) and beta radiations of maximal energy of 606 keV to stable Xenon-131.

Excipients with known effect: ethanol (80 mg/mL), benzyl alcohol (9.4 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, or slightly turbid, colourless or pale yellow solution, with a pH ranging between 3.5 and 8.5.

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S0700nL – 01/2024

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

This product is indicated in adults and children over one month of age for:

1. Localization of hyperfunctional adrenal tissue

   In general prior to scintigraphy, the morphological aspects of the adrenal glands (location, size) are evaluated by computer tomography supported by echography. Adrenal dysfunction (hypercortisonism, hyperaldosteronism or hyperandrogenism) diagnosis is based on the hormone tests results.
   Scintigraphy enables to specify the location of the hyperfunctional tissue (diffuse hyperplasia or adenoma).

2. Characterization of bilateral adrenocortical lesions in patients with cancer of other origin, when fludeoxyglucose (^{18}F) positron emission tomography (PET FDG) is inconclusive or unavailable.

3. Localization of residual functional tissue in the context of hypercorticism after adrenalectomy or detection of ectopic endocrine tissue.

4. Exploration and follow-up of adrenal incidentalomas, when FDG PET is inconclusive or unavailable.

4.2 Posology and method of administration

This medicinal product is intended for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel.

Posology

Adults and elderly population

The recommended activity of iodinated norcholesterol (^{131}I) is 20-40 MBq depending on the patient's weight and on the camera used. No specific dosage adjustment is necessary in elderly.

Paediatric population

In general, administration to children is not recommended. Nevertheless if deemed necessary, the use has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group.

11 DOSIMETRY

According to Publication 80 of the ICRP (International Commission on Radiological Protection), doses of radiation absorbed by patients are as follows:

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	3.5	5.3	7.7	11	16
Bladder	0.38	0.47	0.74	1.2	2.2
Bone surfaces	0.40	0.50	0.78	1.2	2.4
Brain	0.32	0.41	0.68	1.1	2.1
Breast	0.31	0.39	0.63	1.0	2.0
Gall bladder	0.47	0.58	0.91	1.4	2.5
GI-tract					
Stomach	0.39	0.48	0.77	1.2	2.3
SI	0.40	0.51	0.81	1.3	2.5
Colon	0.40	0.49	0.79	1.3	2.4
(ULI	0.40	0.50	0.80	1.3	2.4)
(LLI	0.39	0.47	0.77	1.2	2.3)
Heart	0.39	0.50	0.81	1.3	2.4
Kidneys	0.39	0.50	0.78	1.3	2.4
Liver	1.1	1.5	2.3	3.4	6.5
Lungs	0.36	0.47	0.74	1.2	2.3
Muscles	0.35	0.44	0.71	1.1	2.2
Oesophagus	0.36	0.47	0.75	1.2	2.4
Ovaries	0.40	0.50	0.80	1.3	2.4
Pancreas	0.43	0.55	0.87	1.4	2.6
Red marrow	0.37	0.46	0.72	1.1	2.2
Skin	0.29	0.37	0.60	0.99	1.9
Spleen	0.37	0.48	0.76	1.2	2.3
Testes	0.33	0.42	0.67	1.1	2.1
Thymus	0.36	0.47	0.75	1.2	2.4
Thyroid	29	47	73	170	320
Uterus	0.40	0.50	0.81	1.3	2.4
Remaining organs	0.35	0.44	0.72	1.2	2.2
Effective dose (mSv/MBq)	**1.8**	**2.9**	**4.4**	**9.6**	**18**

The effective dose resulting from administration of the maximum recommended dose of 40 MBq for an adult weighing 60 kg is about 72 mSv.
For an administered activity of 40 MBq the typical radiation dose to the target organ (adrenal glands) is 140 mGy, and the typical radiation dose in the critical organs (liver and thyroid) are: 44 mGy and 1160 mGy respectively.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

Before use, packaging, pH, radioactivity and gamma spectrum should be checked.

The radiochemical purity is at least equal to 85 %. Not more that 5 % of the radioactivity corresponds to iodine-131 in the form of iodide.

The vial must be kept inside its lead shielding.

The vial must not be opened. After disinfection of the stopper, the solution should be withdrawn through the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

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.

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

7. MARKETING AUTHORISATION HOLDER

Country specific

8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

01/2024

Given the effective doses in adults and children (see section 11), the need to remain in the low dose range (<100 mSv) while maintaining a sufficient activity to carry ourt an informative examination, the possible improvement of the detection sensitivity by the lengthening acquisition time and the tomographic mode, the following iodinated norcholesterol (^{131}I) injection activities are proposed, depending on the age.

	Adult	10 – 15 years-old	5 – 10 years-old	1 – 5 years-old	1 month – 1 years -old
Administered Activity (MBq)	**40**	**30**	**20**	**10**	**5**
Effective Dose (mSv/MBq)	1.8	2.9	4.4	9.6	18
Effective Dose (mSv)	72	87	88	96	90

Method of administration
Iodinated norcholesterol (^{131}I) is administered by intravenous injection only.

For patient preparation, see section 4.4.

The injection has to be done slowly over a time period of at least 30 seconds so as to minimise the risk of inducing undesirable side effects. Particular care should be taken to avoid extravasation of the product.

Image acquisition:
Acquisition of static images centered on the adrenal areas.

1- Scintigraphy under basal conditions:

One or two planar acquisitions are obtained between D +4 and D +7 following the injection (D0). Late acquisitions can be obtained between D +10 and D +15 in order to increase the contrast. These planar acquisitions can be followed by an acquisition in tomographic mode centered on the adrenal glands.

2- Scintigraphy with dexamethasone suppression test:
Images are obtained early: between D +2 and D +4. After D +4, even if dexamethasone suppression test remains effective on cortisol secretion, normal adrenal fixation may occur.
Image acquisition can be renewed between D +5 and D +7, to improve location of the adrenal areas by the reduction of the hepatic and intestinal background noise.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy, see section 4.6.
- Breastfeeding, see section 4.6
- Premature babies or neonates (see section 4.4 Specific wamings).

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.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should be in every case as low as reasonably achievable to obtain the required diagnostic information.

Paediatric population
For information on the use in paediatric population, see section 4.2.
*C*areful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
Scintigraphy may be indicated either in basal conditions (without dexamethasone suppression test) or with suppressibility of cortisol with dexamethasone.
Suppression of cortisol is ensured by the oral administration of 2 mg dexamethasone per day (four oral doses of 0.5 mg, including one at bedtime) to begin two days prior the injection of norcholesterol iodine (^{131}I) and continue until the image acquisition (at least D +4).

Thyroid fixation of iodine released from the radioiodinated molecule should be prevented. Inhibition of thyroid fixation by potassium iodide or Lugol solution will be performed at dosages equivalent to 100 mg iodine / day. It must be started the day before the administration of the radiopharmaceutical and will be continued for at least 7 days.

The presence of conjugates of the radiopharmaceutical or its metabolites in the intestine (following a stage of hepatic accumulation followed by bile duct excretion) may compromise the quality of the results of the diagnostic test due to parasitic intestinal activity. It is therefore recommended to administer a laxative: bisacodyl is the laxative of choice because it induces a change in colic motor function without affecting the enterohepatic cycle of the radiopharmaceutical. Bisacodyl is administered at a dose of 5 to 10 mg / day. It is started 2 days prior the first image acquisition and continued during the entire image recording period.

The patient should be well-hydrated before the start of the examination and urged to void as often as possible during the frist hours after the examination in order to reduce radiation.

After the procedure
Close contact with infants and pregnant women should be restricted for 24 h following the procedure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, polysorbate 80, benzyl alcohol, 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

14 days from the date of its manufacture.
After the first withdrawal, store in a refrigerator (2°C – 8°C) and use within 8 hours.

6.4 Special precautions for storage

Store in a freezer at ≤ -18°C.

The product is delivered frozen in a refrigerated packaging containing dry ice. Upon reception it should be stored frozen at ≤ -18°C. If the product at reception is thawed, do not freeze again and do not use.
For storage conditions of the medicinal product after the first withdrawal, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of container

15 mL, colourless, European Pharmacopoeia type I, drawn glass vial, closed with chlorobutyl rubber stopper and aluminium capsule.

Pack-size : 1 multidose vial containing from 37 to 74 MBq at calibration date.

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 licences 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.

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

4.9 Overdose

In the event of administration of a radiation dose with (^{131}I) iodomethyl norcholesterol the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defecation

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Other Diagnostic Radiopharmaceuticals, Iodine (^{131}I) compounds.**
ATC code: **V09XA01**

Mechanism of action
(^{131}I) iodomethyl norcholesterol is an analogue of cholesterol which follows the pathway of cholesterol up to active accumulation in the adrenal gland but without taking part in the hormonal biosynthesis.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, (^{131}I) iodomethyl norcholesterol does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Distribution / Organ uptake
Less than 1 % of the administered dose of (^{131}I) iodomethyl norcholesterol accumulates in the adrenals. Most of this uptake occurs within the first 48 hours following administration. Part of the fraction that accumulates in the adrenals is subject to one or more enterohepatic cycles.

Elimination / half-life
The routes of elimination from the body are via urine and via the faeces (approx. 1/3 of the administered dose in 9 days for both routes).
After 9 days, 1/3 of the dose is still retained in the body, mainly diffusely distributed but approx. 2 % are found in the liver. Invariably some thyroid uptake will occur notwithstanding adequate blockade.

5.3 Preclinical safety data

Toxicological studies with mice have demonstrated that with a single intraperitoneal injection of (^{131}I) iodomethyl norcholesterol at 1000 mg/kg, no deaths were observed.

Subacute toxicity studies, mutagenicity studies and long-term carcinogenicity studies have not been carried out.
This medicinal product is not intended for regular or continuous administration.

Specific warnings

This medicine contains 80 mg of alcohol (ethanol) per mL of solution. The amount in 1 mL of this medicine is equivalent to less than 2 mL beer or 1 mL wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 9.4 mg benzyl alcohol per mL of solution. Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known (see section 4.3).

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

The uptake of (^{131}I) iodomethyl norcholesterol is generally strongly influenced by concomitant medications having a pharmacological effect on the adrenal cortex. It is therefore necessary to discontinue medications which may interfere with the hypothalamic-pituitary-adrenal function (eg glucocorticoids, corticosteroid biosynthesis inhibitors such as mitotane, metyrapone, aminoglutethimide) or with the renin-angiotensin-aldosterone system (eg spironolactone, most diuretics whose mechanism of action involves the adrenal cortex, calcium channel blockers, ACE inhibitors, and oral contraceptives containing estrogen) for at least 48 hours prior to administration of the radiopharmaceutical.

ACTH suppressibility by dexamethasone may however be necessary in some clinical settings.

Cholesterol lowering agents may induced increased uptake and should be considered when interpreting the results of the examination.

When the indication for the investigation is a possible aldosterone producing adenoma, spironolactone medication should be withdrawn for at least 6 weeks before the start of the study.

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 has 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
Diagnostic doses of (^{131}I) iodomethyl norcholesterol is contraindicated in pregnant women due to the radiation exposure of the foetus (see section 4.3).

Breastfeeding

The use of (^{131}I) iodomethyl norcholesterol is contraindicated in brestfeeding women due to the secretion of ativity in the breast milk (see section 4.3). If the administration is considered necessary, breastfeeding should be terminated.

Close contact with infants should be restricted for 24 h.

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

The following table presents how the frequencies are reflected in this section:

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)
Not known (cannot be estimated from the available data)

The following table subsumes the observed reaction types and symptoms sorted by System Organ Class.

MedDRA Body system SOCs	Preferred term	Frequency
Immune system disorders	Anaphylactic reaction	Frequency not known
Vascular disorders	Circulatory collapse Hypotension Hypertension Hot flush	
Respiratory, thoracic and mediastinal disorders	Bronchospasm	
Gastrointestinal disorders	Nausea	
Skin and subcutaneous tissue disorders	Urticaria Skin disorder	
Musculoskeletal and connective tissue disorders	Back pain	
General disorders and administration site conditions	Chest discomfort	

Intravenous administration of iodinated norcholesterol (^{131}I) may cause anaphylactic-type adverse reactions. The symptomatology is the same as that observed during a hypersensitivity reaction in the absence of evidence of previous sensitization. The symptoms of the anaphylactic reaction are generally of low intensity (erythema and heat sensation, urticaria, nausea, hypotension) but more severe signs such as bronchoconstriction or collapse can be observed. The anaphylactic reaction usually occurs immediately after the administration but the possibility of a later onset (15 minutes after intravenous injection) can not be ruled out. The equipment needed to administer antihistamines, corticosteroids and, possibly, adrenaline must be within reach.

It has been reported that intravenous administration of iodinated norcholesterol (^{131}I) can cause arterial hypertension, back pain and chest discomfort.

Extravasation of the radiopharmaceutical product should be avoided as it may result in local tissue reactions.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 72 mSv when the maximal recommended activity of 40 MBq is administered, these adverse events are expected to occur with a low probability.

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.