SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

(131I) 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 6-(131I) iodomethyl norcholesterol 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

This product is indicated in adults for:
1. Diagnostic evaluation of the functional state of adrenal cortical tissue

In general prior to scintigraphy, the morphological aspects of the adrenal glands (location, size) are evaluated by computer tomography supported by echography. The diagnosis of adrenal dysfunction (hypercortisonism, hyperaldosteronism or hyperandrogenism) is established on the basis of endocrine biochemistry. Scintigraphy is used as the follow-up procedure in which the location of hyperfunctioning tissue (diffuse hyperplasia or local adenoma) may be established.
2. Differentiation between metastatic disease to the adrenals ("cold" area) and non-malignant adrenal enlargement in cancer patients.

3. Detection of remnants of functioning tissue in hypercortisonism after adrenalectomy or of ectopic endocrine tissue.

4. Detection and follow-up of euadrenal tumours.

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 is 20 MBq for a 50 to 60 kg patient and should not exceed 40 MBq.

*Paediatric population*
In general, administration to children is not indicated. However if diagnostic administration to persons under 18 years is necessary, The use has to be considered carefully based upon clinical needs and assessing the risk/benefit ratio in this patient group.

**Method of administration**
This product may only be administered by intravenous injection.

For patient preparation, see section 4.4.
The injection should be done slowly over a time period of at least 30 seconds so as to minimise the possibility of inducing undesirable effects. Great care should be taken that no extravasal deposition occurs.

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.
- Breastfeeding
- Premature babies or neonates.

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. Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
In hyperaldosteronism or hyperandrogenism, it may be necessary to suppress the uptake of the radiopharmaceutical in normal functioning tissue by the administration of dexamethasone (1 mg 4 times/day, starting 7 days before the administration of the radiopharmaceutical and continuing throughout the duration of the imaging period).

The thyroid gland must be protected against uptake of iodide released from the radioiodinated compound. This blockade must be started a few hours before the radiopharmaceutical is administered and should be continued for at least 7 days. Blockade by potassium perchlorate is achieved by the administration of approx. 400 mg/day. Blockade by potassium-iodate or Lugol solution must be performed with an equivalent of 100 mg of iodine/day.

Appearance of conjugates of the original radiopharmaceutical or of its metabolites in the intestines (following accumulation in the liver and subsequent excretion via the bile) can adversely affect the diagnostic accuracy because of bowel background activity. Administration of a laxative is therefore desirable. Bisacodyl, administered daily through the whole imaging period, is preferred because this drug only influences colonic motility and does not interfere with the enterohepatic re-utilisation of the radiopharmaceutical.

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

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

Specific warnings
The presence of ethanol (80 mg/mL) in the product may be dangerous for alcoholic patients, and should be taken into account nursing women, children and high risk groups such as patients with hepatic impairment or epilepsy. The presence of ethanol can modify or increase the effect of other drugs.

The presence of benzyl alcohol (9,4 mg/mL) in the product may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

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 which exert pharmacological influence at the level of the adrenal cortex. It is therefore necessary to withdraw the administration of the following drugs for a minimum of 48 hours prior to administration of the radiopharmaceutical:

- oral contraceptives,
- inhibitors of the biosynthesis of adrenocortical steroids: mitotane, ketoconazole, metyrapone, aminogluthethimide,
- adrenocortical steroids, including their synthetic analogues, e.g. dexamethasone,
- diuretic active at the adrenal cortex, e.g. spironolactone.

When the indication for the study is a possible aldosterone producing adenoma, eventual spironolactone medication must be withdrawn for at least 6 weeks before the start of the study. Drugs aimed at inducing hypocholesterolaemia can cause increased uptake which can interfere with diagnostic interpretation. Ideally, cholesterol lowering drugs should be excluded but if this is not possible, their effect on imaging must be taken into account. Drug-induced suppression of uptake in normal tissue can be used to enhance the diagnostic accuracy of the scintigraphic method.

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
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be terminated.

Close contact with infants should be restricted during 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 subsumes the observed reaction types and symptoms sorted by System Organ Class. The frequency listed below is defined using the following convention:

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).

<table>
<thead>
<tr>
<th>MedDRA Body system SOCs</th>
<th>Preferred term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactoid reaction</td>
<td>Frequency not known</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Circulatory collapse Hypotension Hypertension Hot flush</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria Skin disorder</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chest discomfort</td>
<td></td>
</tr>
</tbody>
</table>

Intravenous administration of $^{131}$I iodomethyl norcholesterol can provoke an adverse reaction of an anaphylactoid nature [Anaphylactoid reaction]. The symptoms are identical to the symptoms of a hypersensitivity reaction without any proof that sensitisation has occurred at an earlier time. The symptoms of an anaphylactoid reaction [Anaphylactoid reaction] are generally mild (a warm flush [Hot flush], urticaria [Urticaria], nausea [Nausea], hypotension[Hypotension]) but serious symptoms like bronchostriction [Bronchospasm] and circulatory collapse[Circulatory collapse] can occur. Generally, anaphylactoid reactions [Anaphylactoid reaction] occur immediately after administration but the possibility of a delayed onset (15 minutes after intravenous injection) must be kept in mind. Facilities for the administration of antihistamines, corticosteroids and, if necessary, adrenaline should be present.

It has been reported that intravenous administration of $^{131}$I iodomethyl norcholesterol can provoke hypertension [Hypertension], back pain [Back pain] and chest discomfort [Chest discomfort].
Extravasal deposition of the radiopharmaceutical can cause local tissue reactions [Skin disorder] and must therefore be avoided.

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.

4.9 Overdose

In the event of administration of a radiation dose with (¹³¹I) 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 (¹³¹I) compounds.
ATC code: V09XA01

Mechanism of action
(¹³¹I) iodomethyl norcholesterol is an analogue of cholesterol which follows the pathway of cholesterol up to active accumulation in the adrenal gland but does not take part in hormone synthesis.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, 6-(¹³¹I) iodomethyl norcholesterol does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Distribution / Organ uptake
Less than 1 % of a dose of (¹³¹I) iodomethyl norcholesterol accumulates in the adrenals. The majority of this uptake takes place within the first 48 hours following administration. Part of the fraction that accumulates in the adrenals does so after one or more entero-hepatic circulation 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). At that time 1/3 is still retained in the body, mainly diffusely distributed but with approx. 2 % 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 \((131\text{I})\) 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.

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 \((2^\circ\text{C} – 8^\circ\text{C})\) and use within 8 hours.

6.4 Special precautions for storage

Store in a freezer at \(\leq -18^\circ\text{C}\).

The product is delivered frozen in a refrigerated packaging containing dry ice. Upon reception it should be stored frozen at \(\leq -18^\circ\text{C}\). If the product at reception is thawed, do not freeze again and do not use.

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.

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

CIS BIO INTERNATIONAL
RN 306- SACLAY
BP 32
91192 Gif-sur-Yvette Cedex
France

8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

04/2012
11 DOSIMETRY

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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Absorbed dose per unit activity administered (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>Adrenals</td>
<td>3.5</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.38</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.40</td>
</tr>
<tr>
<td>Brain</td>
<td>0.32</td>
</tr>
<tr>
<td>Breast</td>
<td>0.31</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>0.47</td>
</tr>
<tr>
<td>GI-tract</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.39</td>
</tr>
<tr>
<td>SI</td>
<td>0.40</td>
</tr>
<tr>
<td>Colon</td>
<td>0.40</td>
</tr>
<tr>
<td>(ULI)</td>
<td>0.40</td>
</tr>
<tr>
<td>(LLI)</td>
<td>0.39</td>
</tr>
<tr>
<td>Heart</td>
<td>0.39</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.39</td>
</tr>
<tr>
<td>Liver</td>
<td>1.1</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.36</td>
</tr>
<tr>
<td>Muscles</td>
<td>0.35</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>0.36</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.40</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.43</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.37</td>
</tr>
<tr>
<td>Skin</td>
<td>0.29</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.37</td>
</tr>
<tr>
<td>Testes</td>
<td>0.33</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.36</td>
</tr>
<tr>
<td>Thyroid</td>
<td>29</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.40</td>
</tr>
<tr>
<td>Remaining organs</td>
<td>0.35</td>
</tr>
<tr>
<td>Effective dose (mSv/MBq)</td>
<td><strong>1.8</strong></td>
</tr>
</tbody>
</table>

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 20 MBq the typical radiation dose to the target organ (adrenal glands) is 70 mGy, and the typical radiation dose in the critical organs are: liver 22 mGy and thyroid 580 mGy.