

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Ioflupane (123I) Rotop 74 MBq/ml Solution for injection

### 2. Qualitative and Quantitative composition

Each ml of solution contains ioflupane (<sup>123</sup>I) 74 MBq at reference time (0.07 to 0.13 µg/ml of ioflupane).

Each 2.5 ml single dose vial contains 185 MBq ioflupane (<sup>123</sup>I) (specific activity range 2.5 to 4.5 x 10<sup>14</sup> Bq/mmol) at reference time.

Each 5 ml single dose vial contains 370 MBq ioflupane (<sup>123</sup>I) (specific activity range 2.5 to 4.5 x 10<sup>14</sup> Bq/mmol) at reference time.

Excipient(s) with known effect:

This medicinal product contains 31.6 g/l ethanol. For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Ioflupane (123I) Rotop is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. Ioflupane (123I) Rotop is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease.

Ioflupane ( $^{123}\text{I}$ ) Rotop is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

## 4.2 Posology and method of administration

Prior to administration appropriate resuscitation equipment should be available.

Ioflupane ( $^{123}\text{I}$ ) Rotop should only be used in adult patients referred by physicians experienced in the management of movement disorders and/or dementia. Ioflupane ( $^{123}\text{I}$ ) Rotop should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides within a designated clinical setting.

### Posology

Clinical efficacy has been demonstrated across the range 111 to 185 MBq. Do not exceed 185 MBq and do not use when the activity is below 110 MBq.

Patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1 to 4 hours prior to injection of Ioflupane ( $^{123}\text{I}$ ) Rotop.

### Special populations

#### *Renal and hepatic impairment*

Formal studies have not been carried out in patients with significant renal or hepatic impairment. No data are available (see section 4.4).

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

#### *Paediatric population*

The safety and efficacy of Ioflupane ( $^{123}\text{I}$ ) Rotop in children aged 0 to 18 years has not been established. No data are available.

### Method of administration

For intravenous use.

For patient preparation, see section 4.4.

Ioflupane ( $^{123}\text{I}$ ) Rotop should be used without dilution. To minimise the potential for pain at the injection site during administration, a slow intravenous injection (not less than 15 to 20 seconds) via an arm vein is recommended.

### Image acquisition

SPECT imaging should take place between three and six hours post-injection. Images should be acquired using a gamma camera fitted with a high-resolution collimator and calibrated using the 159 keV photopeak and a  $\pm 10\%$  energy window. Angular sampling should preferably be not less than 120 views over 360 degrees. For high resolution collimators the radius of rotation should be consistent and set as small as possible (typically 11 - 15 cm). Experimental studies with a striatal phantom, suggest that optimal images are obtained with matrix size and zoom factors selected to give a pixel size of 3.5 - 4.5 mm for those systems currently in use. A minimum of 500 k counts should be collected for optimal images.

## **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pregnancy (see section 4.6)

## **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 in every case be as low as reasonably achievable to obtain the required diagnostic information.

### Renal impairment / Hepatic impairment

Formal studies have not been carried out in patients with significant renal or hepatic impairment. In the absence of data, Ioflupane ( $^{123}\text{I}$ ) Rotop is not recommended in cases of moderate to severe renal or hepatic impairment. Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

### Patient preparation

The patient should be well hydrated before and after the examination and urged to void as often as possible during the first 48 hours after the procedure in order to minimise radiation exposure.

### Interpretation of Ioflupane ( $^{123}\text{I}$ ) Rotop Images

Ioflupane ( $^{123}\text{I}$ ) Rotop images are interpreted visually, based upon the appearance of the striata.

Optimum presentation of the reconstructed images for visual interpretation is transaxial slices parallel to the anterior commissure-posterior commissure (AC-PC) line. Determination of whether an image is normal or abnormal is made by assessing the extent (as indicated by shape) and intensity (in relation to the background) of the striatal signal.

Normal images are characterised by two symmetrical crescent-shaped areas of equal intensity. Abnormal images are either asymmetric or symmetric with unequal or reduced intensity and/or loss of crescent.

As an adjunct, visual interpretation may be assisted by semi-quantitative assessment using CE-marked software, where Ioflupane ( $^{123}\text{I}$ ) Rotop uptake in the striatum is compared with uptake in a reference region and ratios are compared against an age adjusted healthy subjects' database. The evaluation of ratios, such as the left/right striatum Ioflupane ( $^{123}\text{I}$ ) Rotop uptake (symmetry) or caudate/putamen uptake, may further help with the image assessment.

The following precautions should be taken when using semi-quantitative methods:

- Semi-quantification should only be used as an adjunct to visual assessment
- Only CE marked software should be used
- Users should be trained in the use of CE marked software by the manufacturer and follow EANM practice guidelines for image acquisition, reconstruction and assessment
- Readers should interpret the scan visually and then perform the semi-quantitative analysis according to manufacturer's instructions including quality checks for the quantitation process
  - ROI /VOI techniques should be used to compare uptake in the striatum with uptake in a reference region
  - Comparison against an age adjusted healthy subjects database is recommended to account for age-expected decrease in striatal binding
  - The reconstruction and filter settings (including attenuation correction) used can affect the semi-quantitative values. The reconstruction and filter settings recommended by the manufacturer of the CE marked software should be followed and should match those used for semi-quantification of the healthy subjects database.
  - The intensity of the striatal signal as measured by SBR (striatal binding ratio) and asymmetry and caudate to putamen ratio provide objective numerical values corresponding to the visual assessment parameters and can be helpful in difficult to read cases
  - If the semi-quantitative values are inconsistent with the visual interpretation, the scan should be evaluated for appropriate placement of the ROIs /VOIs, correct image orientation and appropriate parameters for image acquisition and attenuation correction should be verified. Some software packages can support these processes to reduce operator-dependent variability
  - Final assessment should always consider both visual appearance and semi-quantitative results

#### Specific warnings

This medicinal product contains 31.6 g/l (4 % volume) ethanol (alcohol), up to 158 mg per dose, equivalent to 4 ml beer or 1.6 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Precautions with respect to environmental hazard see section 6.6.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed in humans.

Ioflupane binds to the dopamine transporter. Medicines that bind to the dopamine transporter with high affinity may therefore interfere with ioflupane ( $^{123}\text{I}$ ) diagnosis. These include amphetamine, bupropion, cocaine, codeine, dexamphetamine, methylphenidate, modafinil, and phentermine. Selective serotonin reuptake inhibitors, such as sertraline, may increase or decrease ioflupane binding to the dopamine transporter.

Medicines shown during clinical trials not to interfere with ioflupane ( $^{123}\text{I}$ ) imaging include amantadine, trihexyphenidyl, budipine, levodopa, metoprolol, primidone, propranolol and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with ioflupane ( $^{123}\text{I}$ ) imaging and can therefore be continued if desired. Medicinal products shown in animal studies not to interfere with ioflupane ( $^{123}\text{I}$ ) imaging include pergolide.

#### **4.6 Fertility, pregnancy and lactation**

##### Women of childbearing potential

Where 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. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving satisfactory imaging. Alternative techniques which do not involve ionising radiation should be considered.

##### Pregnancy

Animal reproductive toxicity studies have not been performed with this product. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of 185 MBq of ioflupane ( $^{123}\text{I}$ ) results in an absorbed dose to the uterus of 2.6 mGy. The use of Ioflupane ( $^{123}\text{I}$ ) Rotop is contraindicated in pregnancy (see section 4.3).

##### Breast-feeding

It is not known whether ioflupane ( $^{123}\text{I}$ ) is excreted in human milk. Before administering a radioactive medicinal product to a breast-feeding mother, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of radioactivity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 3 days and substituted by formula feeding.

During this time, breast milk should be expressed at regular intervals and the expressed feeds should be discarded.

#### Fertility

No fertility studies have been performed. No data are available.

#### **4.7 Effects on ability to drive and use machines**

Ioflupane (123I) Rotop has no known influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

The following undesirable effects are recognised for ioflupane (<sup>123</sup>I).

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)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<b>MedDRA Body system SOCs</b>	<b>Adverse reaction Preferred term</b>	<b>Frequency</b>
<b>Immune system disorders</b>	Hypersensitivity	Not known
<b>Metabolism and nutrition disorders</b>	Appetite increased	Uncommon
<b>Nervous system disorders</b>	Headache	Common
	Dizziness, formication (paraesthesia), dysgeusia	Uncommon
<b>Ear and labyrinth disorders</b>	Vertigo	Uncommon
<b>Vascular disorders</b>	Blood pressure decreased	Not known
<b>Respiratory, thoracic and mediastinal disorders</b>	Dyspnea	Not known
<b>Gastrointestinal disorders</b>	Nausea, dry mouth	Uncommon
	Vomiting	Not known

<b>Skin and subcutaneous tissue disorders</b>	Erythema, pruritus, rash, urticaria, hyperhidrosis	Not known
<b>General disorders and administration site conditions</b>	Injection site pain (intense pain or burning sensation following administration into small veins)	Uncommon
	Feeling hot	Not known

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 4.63 mSv when the maximal recommended activity of 185 MBq is administered these adverse reactions 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 Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

In the event of administration of a radiation overdose, frequent micturition and defecation should be encouraged in order to minimise radiation dose to the patient.. Care should be taken to avoid contamination from the radioactivity eliminated by the patient using such methods.

## 5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Diagnostic radiopharmaceutical central nervous system, ATC code: V09AB03.

Due to the low quantities of ioflupane injected, pharmacological effects are not expected following intravenous administration of Ioflupane (<sup>123</sup>I) Rotop at the recommended dosage.

#### Mechanism of action

Ioflupane is a cocaine analogue. Studies in animals have shown that ioflupane binds with high affinity to the presynaptic dopamine transporter and so radiolabelled ioflupane (<sup>123</sup>I) can be used as a surrogate marker to examine the integrity of the dopaminergic nigrostriatal neurons. Ioflupane also binds to the serotonin transporter on 5-HT neurons but with lower (approximately 10-fold) binding affinity.

There is no experience in types of tremor other than essential tremor.

### Clinical efficacy

#### *Clinical studies in patients with dementia with Lewy bodies*

In a pivotal clinical trial including evaluation of 288 subjects with dementia with Lewy bodies (DLB) (144 subjects), Alzheimer's disease (124 subjects), vascular dementia (9 subjects) or other (11 subjects), the results of an independent, blinded visual assessment of the ioflupane ( $^{123}\text{I}$ ) images were compared to the clinical diagnosis as determined by physicians experienced in the management and diagnosis of dementias. Clinical categorisation into the respective dementia group was based on a standardised and comprehensive clinical and neuropsychiatric evaluation. The values for the sensitivity of ioflupane ( $^{123}\text{I}$ ) in determining probable DLB from non-DLB ranged from 75.0 % to 80.2 % and specificity from 88.6 % to 91.4 %. The positive predictive value ranged from 78.9 % to 84.4 % and the negative predictive value from 86.1 % to 88.7 %. Analyses in which both possible and probable DLB patients were compared with non-DLB dementia patients demonstrated values for the sensitivity of ioflupane ( $^{123}\text{I}$ ) ranging from 75.0 % to 80.2 % and specificity from 81.3 % to 83.9 % when the possible DLB patients were included as non-DLB patients. The sensitivity ranged from 60.6 % to 63.4 % and specificity from 88.6 % to 91.4 % when the possible DLB patients were included as DLB patients.

#### *Clinical studies demonstrating adjunctive use of semi-quantitative information for image interpretation*

The reliability of using semi-quantitative information as an adjunct to visual inspection was analysed in four clinical studies where sensitivity, specificity or overall accuracy between the two methods of image interpretation were compared. In the four studies (total n=578), CE-marked DaTSCAN semi-quantitation software was used. The differences (i.e., improvements when adding semi-quantitative information to visual inspection) in sensitivity ranged between 0.1 % and 5.5 %, in specificity between 0.0 % and 2.0 %, and in overall accuracy between 0.0 % and 12.0 %.

The biggest of these four studies retrospectively assessed a total of 304 DaTSCAN exams from previously conducted Phase 3 or 4 studies, which included subjects with a clinical diagnosis of PS, non-PS (mainly ET), probable DLB, and non-DLB (mainly AD). Five nuclear medicine physicians who had limited prior experience with DaTSCAN interpretation assessed the images in 2 readings (alone and combined with semi-quantitative data provided by DaTQUANT 4.0 software) at least 1 month apart. These results were compared with the subject's 1-to 3-year follow-up diagnosis to determine diagnostic accuracy. The improvements in sensitivity and specificity [with 95 % confidence intervals] were 0.1 % [-6.2 %, 6.4 %] and 2.0 % [-3.0 %, 7.0 %]. Also, the results of the combined reading were associated with an increase in reader confidence.

## **5.2 Pharmacokinetic properties**

### Distribution

Ioflupane ( $^{123}\text{I}$ ) is cleared rapidly from the blood after intravenous injection; only 5% of the administered activity remains in whole blood at 5 minutes post-injection.

### Organ uptake

Uptake in the brain is rapid, reaching about 7% of injected activity at 10 minutes post-injection and decreasing to 3% after 5 hours. About 30% of the whole brain activity is attributed to striatal uptake.

### Elimination

At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine, with faecal excretion calculated at approximately 14%.

### Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

## **5.3 Preclinical safety data**

Non-clinical data for ioflupane reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

Studies on reproductive toxicity and to assess the carcinogenic potential of ioflupane have not been performed.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Acetic acid (for pH adjustment)

Sodium acetate (for pH adjustment)

Ethanol, anhydrous

Water for injections

### **6.2 Incompatibilities**

Studies have shown that the product is compatible with water for injection and saline.

### **6.3 Shelf life**

*2.5 ml vial:* 7 hours from the activity reference time stated on the label.

*5 ml vial:* 20 hours from the activity reference time stated on the label.

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

#### **6.5 Nature and contents of container**

2.5 ml or 5 ml solution in a colourless glass vial (Type I, Ph. Eur.) of 10 mL nominal capacity, closed with a butyl rubber stopper and metal overseal. Pack size of 1 vial.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

##### 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 this product 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.

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 therefore be taken.

### Disposal

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

## **7      MARKETING AUTHORISATION HOLDER**

ROTOP Radiopharmacy GmbH  
Bautzner Landstrasse 400  
01328 Dresden  
Germany

## **8      MARKETING AUTHORISATION NUMBER(S)**

PL 53373/0001

## **9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/02/2025

## **10     DATE OF REVISION OF THE TEXT**

17/10/2025

## **11     DOSIMETRY**

Iodine-123 has a physical half-life of 13.2 hours. It decays emitting gamma radiation with a predominant energy of 159 keV and X-rays of 27 keV.

The biokinetic model for ioflupane (<sup>123</sup>I) adopted by ICRP 128 (International Commission on Radiological Protection, 2015) assumes initial uptake of 31 % of the administered activity in the liver, 11 % in the lungs, and 4 % in the brain. The rest is assumed to be distributed uniformly in the remaining organs and tissues. For all organs and tissues, 80 % is assumed to be excreted with a biological half-time of 58 h, and 20 % with a half-time of 1.6 h. It is further assumed that 60 % of the injected activity is excreted to the urine, and 40 % is excreted to the gastrointestinal tract for all organs and tissues. Activity in the liver is excreted according to the Publication 53 gallbladder model (ICRP, 1987), where 30 % is eliminated via the gallbladder and the remainder passes directly into the small intestine.

The estimated absorbed radiation doses to an average adult patient (70 kg) from intravenous injection of ioflupane ( $^{123}\text{I}$ ) are listed below. The values are calculated assuming urinary bladder emptying at 4.8-hour intervals and appropriate thyroid blocking (Iodine-123 is a known Auger electron emitter). Frequent bladder emptying should be encouraged after dosing to minimise radiation exposure.

<b>Organ</b>	<b>Absorbed radiation dose <math>\mu\text{Gy}/\text{MBq}</math></b>
Adrenals	17.0
Bone surfaces	15.0
Brain	16.0
Breasts	7.3
Gallbladder wall	44.0
Gastrointestinal tract	
Stomach wall	12.0
Small intestine wall	26.0
Colon wall	59.0
(Upper large intestine wall)	57.0
(Lower large intestine wall)	62.0
Heart wall	32.0
Kidneys	13.0
Liver	85.0
Lungs	42.0
Muscle	8.9
Oesophagus	9.4
Ovaries	18.0
Pancreas	17.0
Red marrow	9.3
Salivary glands	41.0
Skin	5.2
Spleen	26.0
Testes	6.3
Thymus	9.4
Thyroid	6.7
Urinary bladder wall	35.0
Uterus	14.0
Remaining organs	10.0
<b>Effective Dose (<math>\mu\text{Sv}/\text{MBq}</math>)</b>	<b>25.0</b>

Ref.: Publication 128 of the Annals of ICRP (Radiation dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances, 2015)

The effective dose (E) resulting from administration of 185 MBq of Ioflupane ( $^{123}\text{I}$ ) ROTOP injection is 4.63 mSv (per 70 kg individual). The above data are valid in normal pharmacokinetic behaviour. When renal or hepatic function is impaired, the effective dose and the radiation dose delivered to organs might be increased.

For an administered activity of 185 MBq the typical radiation dose to the target organ (brain) is 3 mGy and the typical radiation doses to the critical organs: liver and colon wall are 16 mGy and 11 mGy, respectively.

## **12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. See also section 6.6.