ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS,

LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dopacis 90 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 90 MBq of fluorodopa (^{18}F) at calibration time.

The total activity per vial ranges from 90 MBq to 900 MBq at the date and time of calibration.

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Excipient with known effect:

One mL of Dopacis contains 2.6 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution, with a pH between 4.0 and 5.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Fluorodopa (^{18}F) is indicated for use with positron emission tomography (PET).

Neurology

PET with fluorodopa (^{18}F) is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain parkinsonian syndromes. It can be used to differentiate essential tremor from parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system (Parkinson disease (PD), multisystem atrophy and progressive supranuclear palsy).

PET with fluorodopa (^{18}F), on its own, is unable to discriminate between different parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system. It is also unable to discriminate between PD with and without tremor.

Oncology

From imaging studies, PET with fluorodopa (^{18}F) allows a functional approach to pathologies, organs or tissues in which an increase of intracellular transport and of decarboxylation of the amino acid dihydroxyphenylalanine is sought. The following indications were particularly documented:

<u>Diagnosis.</u>

- Diagnosis and localisation of an insulinoma in case of hyperinsulinism in infants and children

- Diagnosis and localisation of glomus tumors in patients with a mutation of the succinate dehydrogenase sub-unit D gene

- Localisation of pheochromocytomas and paragangliomas.

<u>Staging</u>

- Pheochromocytomas and paragangliomas

- Well-differentiated carcinoid tumors of the intestinal tract

<u>Detection in case of reasonable suspicion of recurrent or residual disease</u>

- Primary brain tumors restricted to high grade gliomas (grade III and IV)

- Pheochromocytomas and paragangliomes

- Medullary thyroid carcinoma with elevated serum calcitonin level

- Well-differentiated carcinoid tumors of the intestinal tract

- Other endocrine digestive tumors when somatostatin receptors scintigraphy is negative

Dopacis is indicated:

- in adults for neurology and oncology,
- in newborn infants to adolescents in oncology.

4.2 Posology and method of administration

Posology

In oncology, the activity usually recommended for an adult can vary from 2 to 4 MBq/kg of body weight, depending on the PET equipment and acquisition mode used.

In neurological indications, the activity usually recommended for an adult can vary from 1 to 2 MBq/kg of body weight, depending on the PET equipment and acquisition mode used.

For repeated use, see section 4.4.

Paediatric population

There is very limited clinical data on safety and efficacy of this product in patients under 18, except in the search of insulinoma in infants or in very young children. The use in paediatric children and adolescents in the oncological indications has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activity to be administered to children and adolescents can vary from 2 to 4 MBq/kg of body weight, depending on the PET equipment and acquisition mode used.

Patients with renal impairment

Extensive dose-range and adjustment studies with this product in normal and special populations have not been performed. The pharmacokinetics of fluorodopa (^{18}F) in patients with renal impairment has not been characterised.

Method of administration

For patient preparation, see section 4.4.

Precautions to be taken before handling or administering the medicinal product

The activity of fluorodopa (18F) should be measured with an activimeter just before injection.

The injection of fluorodopa (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

The product should be administered **slowly** by direct intravenous injection **over a period of about one minute.**

Image acquisition

Neurology

- Acquisition of “dynamic” PET brain images from the injection during 90 to 120 min, or
- Single “static “PET acquisition starting 90 min after injection.

Oncology

- Foci in the hepatic, pancreatic and cervical area: early “static “ images from 5 min after injection, or “dynamic” acquisition starting immediately after injection for about ten minutes.
- Brain tumors: “static” acquisition between 10 and 30 min after injection.
- Whole body: images generally acquired 60 min after injection.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy.

4.4 Special warnings and precautions for use

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.

In patients with reduced kidney function, careful consideration of the indication is required since an increased radiation exposure is possible in these patients.

In patients with a mutation of the succinate dehydrogenase sub-unit B gene, Dopacis is not indicated in diagnosis and localisation of glomus tumors.

Paediatric population

Paediatric population, see section 4.2. or 5.1., as appropriate.

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

Repeated use

Data on repeated use of fluorodopa (^{18}F) are limited. It is recommended to not inject Dopacis before 5 days after the first administration.

Patient Preparation

Patients should be fasting for at least 4 hours, with unlimited amounts of water, before administering Dopacis.

In order to obtain images of best quality and to reduce the radiation exposure of the bladder, patients should be encouraged to drink sufficient amounts and to empty their bladder prior to, and after the PET examination.

In the neurological indications, it is recommended to stop any antiParkinsonian treatment at least 12 hours before the test.

In the oncological indications, it is recommended to stop any treatment with glucagon at least 12 hours before the test.

In neurological indications, the administration of 200 mg of entacapone one hour prior to the injection of fluorodopa (^{18}F) is common practice.

General warnings

It is recommended to avoid close physical contact between the patient and young children during the first 12 hours following the injection.

Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Specific warnings

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.

Warnings related to excipients:

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium- free'.

Precautions with respect to environmental hazard are in Section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Carbidopa, inhibitors of the enzyme catechol-O-methyl transferase (COMT) such as entacapone or nitecapone): administration before fluorodopa (^{18}F) injection can increase the bioavailability of fluorodopa (^{18}F) in the brain by inhibiting the peripheral decarboxylase and reducing the peripheral metabolism of fluorodopa (^{18}F) with a formation of 3-O-methyl-6-fluoro (^{18}F)-L-DOPA. The bioavailability of fluorodopa in the brain can be increased by pre-treatment with either inhibitors of the enzyme aromatic amino acid decarboxylase (AAAD) such as carbidopa which block peripheral conversion of fluorodopa to fluorodopamine, or inhibitors of the enzyme catechol-O-methyl transferase (COMT) such as entacapone and nitecapone which decrease peripheral degradation of fluorodopa to 3-O-methyl-6-fluorodopa.

Carbidopa: a case of congenital hyperinsulinism has been reported where fluorodopa uptake in the pancreas was no longer detectable after carbidopa administration.

Glucagon: Glucagon affects fluorodopa (^{18}F) uptake in pancreas by interacting with pancreatic beta-cell function.

Haloperidol: an increase in intracerebral dopamine caused by haloperidol may increase the accumulation of fluorodopa (^{18}F) in the brain.

Reserpine: Reserpine can empty the contents of intraneuronal vesicles and thus prevent the retention of fluorodopa (^{18}F) in the brain.

MAO inhibitors (Monoamine Oxidase): concomitant use of MAO inhibitors may increase the accumulation of fluorodopa (^{18}F) in the brain.

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

Dopacis is contraindicated in pregnancy (see section 4.3).

Available data is insufficient to address the effects of the product during pregnancy. No reproductive studies have been carried out in animals.

Breastfeeding

Fluorodopa (^{18}F) will be excreted into breast milk.

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 interrupted for 12 hours and the expressed feeds discarded.

Close contact with infants should be restricted during the first 12 hours following injection.

4.7 Effects on ability to drive and use machines

Dopacis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The reported adverse events are presented below by System Organ Class and with a not known frequency (cannot be estimated from the available data):

MedDRA System Organ Classes	**Adverse reactions (Preferred Term)**	**Frequency**
Nervous system disorders	Burning sensation	Not known
General disorders and administration site conditions	Application site pain, pain, application site warmth	Not known

Pain on injection site was reported to have disappeared in a few minutes, without treatment.

A case of carcinoid crisis related to an injection administrated too fast has been reported in the literature.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 7 mSv when the maximal recommended activity of 280 MBq (for an individual of 70 kg) 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 listed in Appendix V

4.9 Overdose

In the event of administration of a radiation overdose with fluorodopa (^{18}F) 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: Other radiopharmaceutical products for diagnostic use,

ATC code: V09IX05

At the chemical concentrations and activities recommended for diagnostic examinations, fluorodopa (^{18}F) does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Distribution

Studies in healthy subjects after administration of fluorodopa (^{18}F) showed an ubiquitous distribution of activity in all body tissues.

Organ uptake

Fluorodopa (^{18}F) is an analogue of an aromatic amino acid rapidly accumulated by target tissues, especially in the striatum of the human brain, and converted into dopamine, neurotransmitter of the catecholamines family.

Elimination

Fluorodopa (^{18}F) is eliminated by the kidney, 50% is removed after 0.7 hours, and 50% after 12 hours.

Half-Life

Fluorodopa (^{18}F) is eliminated by a bi-exponential kinetics with a biological half-life of 12 hours (67-94%) and a physical half-life of 1.7 to 3.9 hours (6-33%). These two half-lives seem to depend on age.

5.3 Preclinical safety data

Toxicological studies with rats have demonstrated that with a single IV injection at 5 mL/kg of a preparation of inactive fluorodopa containing more than 100 times the amount of active substance and impurities contained in Dopacis, no deaths were observed. The same preparation did not present any mutagenic activity in the Ames test.

Repeated toxicity studies, long-term carcinogenicity studies and reproductive function studies have not been carried out.

This agent is not intended for regular or continuous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid

Sodium acetate

Ascorbic acid

Disodium edetate

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

12 hours from manufacturing time.

After the first withdrawal, store in a refrigerator (2-8°C).

The expiry date and time are mentioned on the original packaging and on the vial label.

6.4 Special precautions for storage

Store in the original lead shielding.

For storage conditions after first opening of the medicinal product, see section 6.3.

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

6.5 Nature and contents of container

15 mL colorless type I multidose glass vial, closed with a teflon-coated rubber stopper and sealed with an aluminium cap.

Packaging : One multidose vial containing 1 to 10 mL of solution, corresponding to 90 to 900 MBq at calibration time.

6.6 Special precautions for disposal

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.

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

7. MARKETING AUTHORISATION HOLDER

In Belgium, France, Luxembourg, Malta ,The Netherlands, Portugal, Slovenia, Spain

CIS bio international

RN 306-Saclay

B.P. 32

F-91192 Gif-sur-Yvette Cedex

In Italy :

Curium Italy S.r.l.

Via Enrico Tazzoli, 6

I-20154 Milano

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/03/2010

Date of last renewal: 11/03/2015

10. DATE OF REVISION OF THE TEXT

10/2021

11. DOSIMETRY

The data listed below are from ICRP No 106 and are calculated according to the following assumptions:

100% of the activity of fluorine-18 is distributed homogeneously in the body and eliminated through the kidneys with biological half-times of 1 hour (50%) and 12 hours (50%), independently of age.

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.0099	0.0130	0.0190	0.0310	0.0550
Bladder	0.3000	0.3800	0.5700	0.7800	1.0000
Bone surfaces	0.0096	0.0120	0.0180	0.0280	0.0510
Brain	0.0071	0.0088	0.0150	0.0240	0.0440
Breasts	0.0067	0.0085	0.0130	0.0210	0.0390
Gallbladder	0.0100	0.0130	0.0200	0.0290	0.0500
Gastrointestinal tract					
Stomach	0.0095	0.0120	0.0180	0.0280	0.0500
Small intestine	0.0130	0.0170	0.0260	0.0390	0.0650
Colon	0.0150	0.0180	0.0270	0.0410	0.0630
(Upper large intestine)	0.0120	0.0150	0.0230	0.0360	0.0590)
(Lower large intestine)	0.0180	0.0220	0.0330	0.0470	0.0690)
Heart	0.0089	0.0110	0.0180	0.0280	0.0500
Kidneys	0.0310	0.0370	0.0520	0.0780	0.1400
Liver	0.0091	0.0120	0.0180	0.0290	0.0520
Lungs	0.0079	0.0100	0.0160	0.0250	0.0460
Muscles	0.0099	0.0120	0.0190	0.0300	0.0510
Oesophagus	0.0082	0.0100	0.0160	0.0250	0.0470
Ovaries	0.0170	0.0220	0.0330	0.0470	0.0740
Pancreas	0.0100	0.0130	0.0200	0.0310	0.0560
Red marrow	0.0098	0.0120	0.0190	0.0270	0.0470
Skin	0.0070	0.0085	0.0140	0.0220	0.0400
Spleen	0.0095	0.0120	0.0180	0.0290	0.0530
Testes	0.0130	0.0180	0.0300	0.0450	0.0700
Thymus	0.0082	0.0100	0.0160	0.0250	0.0470
Thyroid	0.0081	0.0100	0.0170	0.0270	0.0500
Uterus	0.0280	0.0330	0.0530	0.0750	0.1100
Remaining organs	0.0100	0.0130	0.0190	0.0300	0.0520
Effective+ dose (mSv/MBq)	**0.0250**	**0.0320**	**0.0490**	**0.0700**	**0.1000**

The effective dose resulting from the administration of an activity of 280 MBq for an adult weighing of 70 kg is about 7 mSv. For an administered activity of 280 MBq the typical radiation dose to the target organs are: adrenals 2.8 mGy, brain 2.0 mGy, pancreas 2.8 mGy and thyroid 2.3 mGy and the typical radiation doses to the critical organs are: bladder 84 mGy, uterus 7.8 mGy, kidneys 8.7 mGy.

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.

The packaging must be checked before use and the activity measured with an activity meter. The solution should be visually inspected before use and only a clear solution without any visible particles should be used.

The vial must be kept inside its lead shielding and should not be opened. After disinfecting the stopper, draw the solution through the stopper using a sterile disposable syringe fitted with appropriate protection and a disposable sterile needle.

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

Detailed information on this medicinal product is available on the website of {name of MS/Agency}