IASOdopa® 0.3 GBq/mL,
concentrate for solution for injection

SPC
Summary of Product Characteristics

English

MARKETING AUTHORISATION NUMBER(S)

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IASOdopa 0.3 GBq/mL, concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL contains 0.3 GBq of 6-fluoro-(^{18}F)-L-dihydroxyphenylalanine (or 6-fluoro-(^{18}F)-L-dopa) at date and time of calibration.
The activity per vial ranges from 0.15 GBq to 6.0 GBq 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 with a maximum energy of 634 keV followed by photonic annihilation radiations of 511 keV.

Excipient(s) with known effect: Acetic acid
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection.
Clear and colourless or slightly yellow solution.
The pH of this concentrate is between 2.3 and 3.0 and has to be adjusted prior to injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
6-fluoro-(^{18}F)-L-dopa is indicated for use with positron emission tomography (PET) in adults and paediatric population.

Neurology
PET with 6-fluoro-(^{18}F)-L-dopa is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum. It can be used for diagnosis of Parkinson's disease and differentiation between essential tremor and parkinsonian syndromes.

Oncology
Among medical imaging modalities, PET with 6-fluoro-(^{18}F)-L-dopa provides a functional approach of pathologies, organs or tissues where enhanced intracellular transport and decarboxylation of the amino acid dihydroxyphenylalanine is the diagnostic target. The following indications have been particularly documented:

Diagnosis
- Diagnosis and localisation of focal hyperplasia of beta islet cells in the case of hyperinsulinism in infants and children
- Diagnosis and localisation of paragangliomas in patients with a gene mutation of the succinate dehydrogenase D variant
- Localisation of pheochromocytoma

Staging

- Phaeochromocytoma and paraganglioma
- Well differentiated neuroendocrine tumours of midgut.

Detection in case of reasonable suspicion of recurrences or residual disease

- Primary brain tumours of all grades of differentiation.
- Phaeochromocytoma and paraganglioma
- Medullary thyroid cancer with elevated serum levels of calcitonin
- Well differentiated neuroendocrine tumours of midgut
- Other endocrine digestive tumours when somatostatin receptor scintigraphy is negative

4.2 Posology and method of administration

Posology

Adults and elderly population
In oncology, the recommended activity for an adult weighting 70 kg is 2 to 4 MBq/kg (this activity has to be adapted according to the body weight of the patient, the type of camera used PET(/CT), and acquisition mode), administered by direct slow intravenous injection over approximately one minute.
One half of this activity may be administered for neurological indications not requiring whole body images.

Renal / Hepatic impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the body-mass-dependent coefficients given in the table below.

$$\mathbf{A[MBq]_{Administered} = Baseline\ Activity \times Coefficient}$$

The Baseline Activity for 2D imaging is 25.9 MBq and for 3D imaging 14.0 MBq (recommended in children).

Weight [kg]	Multiple	Weight [kg]	Multiple	Weight [kg]	Multiple
3	1	**22**	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57
6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

Method of administration
For intravenous use : the fluoro-(^{18}F)-L-dopa must be administered by slow intravenous injection, over approximately one minute.
For multidose use.

The activity of 6-fluoro-(^{18}F)-L-dopa has to be measured with activimeter immediately prior to injection.
The injection of 6-fluoro-(^{18}F)-L-dopa must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

For instructions on extemporaneous preparation of the medicinal product before administration, see sections 6.6 and 12.

For patient preparation, see section 4.4.

Image acquisition

Neurology
- "dynamic" acquisition of PET images of the brain during 90 to 120 minutes right after injection,
- or one "static" PET acquisition starting 90 minutes after the injection.

Oncology
To detect foci in the liver, pancreas or brain area, early "static" images can be acquired starting 5 minutes after injection, or a "dynamic" acquisition starting right after the injection during 10 minutes.
- Brain tumours: "static" acquisition 10 to 30 minutes after injection.
- Whole-body: images are usually acquired 60 minutes after injection

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the pH-adjusted radiopharmaceutical.
- 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 / hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

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
IASOdopa should be given to patients fasting for a minimum of 4 hours without limiting water intake.
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 neurological indications, it is recommended to suspend any antiparkinsonian treatment at least 12 hours before the PET examination.
The administration of 100 to 200 mg of carbidopa one to one and a half hours before the injection of 6-fluoro-(^{18}F)-L-dopa is recognized for neurological indications but less frequent for oncological indications.

Interpretation of 6-fluoro-(^{18}F)-L-dopa PET images

Neurology
The interpretation of 6-fluoro-(^{18}F)-L-dopa uptake values in the different parts of the brain requires the comparison to age and sex matched controls. Recent publications refer to data base of normal cases and voxel-based Statistical Parametric Mapping (SPM) and automated region of interest (ROI) analysis.

Oncology
False positive results in inflammatory lesions seem to be very rare with 6-fluoro-(^{18}F)-L-dopa PET. Nevertheless, the possibility of an inflammatory lesion should be kept in mind when an unexpected 6-fluoro-(^{18}F)-L-dopa focus is detected. The physiologic biodistribution must be taken into account in the interpretation; in particular uptake in the basal ganglia, diffuse uptake in the pancreas, uptake in the gallbladder leading to subsequent activity in the gut, and uptake in the kidney leading to “hot spots” aspect in the ureters and a high activity in the bladder.

After the procedure
Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Specific warnings
Depending on the time when you administer the injection prepared extemporaneously after pH adjustment, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg). This should be taken into account in patient on low sodium diet.

Precautions with respect to environmental hazard : see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Carbidopa
Prior to 6-fluoro-(^{18}F)-L-dopa administration, use of carbidopa may increase 6-fluoro-(^{18}F)-L-dopa bioavailability to the brain by inhibiting peripheral decarboxylase activity and restricting peripheral 6-fluoro-(^{18}F)-L-dopa metabolism with 3-*O*-methyl-6-fluoro-(^{18}F)-L-dopa formation.

Haloperidol
Increased intracerebral dopamine turnover caused by haloperidol may result in increased accumulation of 6-fluoro-(^{18}F)-L-dopa.

Monoamine oxidase (MAO) inhibitors
Concurrent use with MAO inhibitors may result in increased accumulation of 6-fluoro-(^{18}F)-L-dopa in the brain.

Reserpine
Reserpine-induced depletion of the contents of intraneuronal vesicles may prevent retention of 6-fluoro-(^{18}F)-L-dopa in the brain.

Paediatric population
Interaction studies have only been performed in adults.

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
The use of 6-fluoro-(^{18}F)-L-dopa is contraindicated in pregnant women due to preventive radiation protection 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 interrupted for 12 hours and the expressed feeds discarded.

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

Fertility
No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

No undesirable effects have been observed to date.
Pain at injection has been reported in rare cases which resolved within minutes without corrective measures.
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 is administered, these adverse reactions are expected to occur with a low probability.

Paediatric population
Not reported.

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.

4.9 Overdose

An overdose in the pharmacological sense is unlikely given with the doses used for diagnostic purposes.

In the event of administration of a radiation overdose with 6-fluoro-(^{18}F)-L-dopa 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 diagnostic radiopharmaceuticals for tumour detection.
ATC code: V09IX05

Mechanism of action
IASOdopa positron emission tomography (PET) reflects the uptake of 6-fluoro-(^{18}F)-L-dopa by the target cells and its conversion to fluorodopamine by aromatic aminoacid decarboxylase.

Pharmacodynamic effects
Adult, elderly and paediatric populations:

At the chemical concentrations and activities recommended for diagnostic examinations, 6-fluoro-(^{18}F)-L-dopa does not appear to have any pharmacodynamic activity.

Clinical efficacy and safety
The marketing authorisation for IASOdopa was granted in the context of a well-established use procedure supported by bibliographical data.
No pivotal clinical studies were conducted, which is acceptable for this kind of procedure with more than 10 years of experience.

5.2 Pharmacokinetic properties

Distribution
Studies in healthy humans after administration of 6-fluoro-(18F)-L-dopa have shown a ubiquitous distribution of the activity throughout the body tissues.

Organ uptake
The aromatic amino acid analogue 6-fluoro-(^{18}F)-L-dopa accumulates rapidly in the tissue, particularly the striatum of the human brain and is transformed into the catecholamine neurotransmitter dopamine.
Human studies have shown that the uptake of 6-fluoro-(^{18}F)-L-dopa in the striatum and cerebellum can be increased approximately two-fold by administration of the amino acid decarboxylase inhibitor carbidopa

Elimination
6-fluoro-(^{18}F)-L-dopa is removed according to a bi-exponential kinetic process with biological half-lives of 12 hours (67-94 %) and 1.7 - 3.9 hours (6-33 %). Both these half-lives appear to be age-dependent. The ^{18}F-activity is excreted through the kidneys, 50 % with a half-life of 0.7 hours and 50 % with a half-life of 12 hours.

Half-life
On basis of distribution, organ uptake and elimination data, a biokinetic model for 6-fluoro-(^{18}F)-L-dopa was developed. This model assumes that 100 % of the 18F activity is homogeneously distributed in the body and eliminated through the kidneys with biological half-lives of 1 hour (50 %) and 12 hours (50 %). This model was considered to be dependent of age.

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

Paediatric population

The available data on normal biodistribution in children showed that it is similar to that of adults. No further specific data on pharmacokinetics are available in children.

5.3 Preclinical safety data

Toxicological studies with rats have demonstrated that with a single intravenous injection of undiluted 6-fluoro-(^{18}F)-L-dopa at 5 mL/kg no deaths were observed.
This product is not intended for regular or continuous administration.
Toxicity studies with repeated administration, mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except with the sterile sodium bicarbonate concentration of 84 mg/mL for pH-adjustment (see section 12).

6.3 Shelf life

12 hours from the time of calibration and 8 hours after first withdrawal.

After pH-adjustment with sodium bicarbonate solution 84 mg/mL, the product should be stored below 25°C for no longer than 2 hours.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

15 or 25 mL multidose glass vial, colourless Type I glass, closed with a coated rubber stopper and sealed with an aluminium cap. As a result of the production process IASOdopa might be delivered with a punctured rubber septum.
One vial contains 0.5 to 20.0 mL of solution, corresponding to 0.15 to 6 GBq at calibration time.
Multidose vial.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warnings
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. Appropriate aseptic precautions should be taken.
For instructions on extemporary preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of the medicinal 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.

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 be taken.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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11. DOSIMETRY

The data listed below are from ICRP publication 106.

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					
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
Bladder wall contributes 51 % of the effective dose					

The effective dose resulting from the administration of a maximal recommended activity of 280 MBq of 6-fluoro-(^{18}F)-L-dopa for an adult weighing 70 kg is about 7 mSv
For an administered activity of 280 MBq, the typical radiation dose to the critical organs, bladder, uterus and kidney are: 84 mGy, 7.8 mGy, 8.7 mGy respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The packaging must be checked before use and the activity measured using an activimeter.

Withdrawals should be performed under aseptic conditions. The vials must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

Method of preparation
The packaging must be checked before use and the activity measured using an activimeter.
The solution is to be inspected visually prior to use and only clear solutions free of visible particles should be used.
IASOdopa with the active agent 6-fluoro-(^{18}F)-L-dopa is delivered in an aqueous solution of acetic acid (1.05 mg/mL) which has an acid pH between 2.3 and 3.0 to preserve the chemical stability of the radiopharmaceutical. At a pH over 4.5, a slow oxidation of 6-fluoro-(^{18}F)-L-dopa takes place.

For each single dose, the pH has to be adjusted separately.
Immediately before injection, the pH of IASOdopa has to be adjusted to 4.0 – 5.0 by the addition of a sterile solution of sodium bicarbonate (8.4 g/100 mL, i.e. 84 mg/mL). 100 µL of the sodium bicarbonate solution are added per mL of used IASOdopa solution to obtain a pH between 4.0 and 5.0.

Only the following sterile sodium bicarbonate solutions 84 mg/mL can be used:
- with marketing authorisation
- solutions produced in the pharmacy according to local law.

The pH adjustment is followed by the rise of some CO_2 bubbles. It should be ensured that the gas generation has ceased before administration.

Any pH-adjusted dose has to be injected within 2 hours.

Quality control
The solution is to be inspected visually prior to use and only clear solutions free of visible particles should be used.

Detailed information on this product is available on the website of the {name of the Member state Agency}.