ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Fluorocholine (^{18}F) CIS bio international 225 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL contains 225 MBq of fluorocholine (^{18}F) chloride, also known as fluoromethylcholine (^{18}F) chloride, at the date and time of calibration.
The activity per vial ranges from 112 MBq to 3375 MBq at the date and time of calibration.

Fluorine-18 decays to stable oxygen-18 with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of of 633 keV, followed by photonic annihilation radiations of 511 keV.

Excipient with known effect:
Each mL contains 3.54 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution with a pH between 4.5 and 7.5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is for diagnostic use only.

Fluorocholine (^{18}F) chloride is indicated for use with positron emission tomography (PET) in adult males.

Fluorocholine (^{18}F) CIS bio international is used for imaging in patients undergoing oncologic diagnostic procedures, describing function or diseases where enhanced choline influx of specific organs or tissues is the diagnostic target.
The following indications for PET with Fluorocholine (^{18}F) chloride have been particularly documented:

- Initial staging of prostate cancer in high-risk patients, a category defined according to professional guidelines.
- Localisation of local, regional or metastatic recurrence in case of rising serum concentration of prostate specific antigen (PSA)

4.2. Posology and method of administration

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

Posology

Adults and elderly
The recommended activity for an adult weighing 70 kg is 100 to 400 MBq according to the body weight of the patient, the type of camera used and acquisition mode.
The maximal volume of solution to be administered must not be greater than 10 mL.

Paediatric population
There is no relevant use of Fluorocholine (^{18}F) CIS bio international in the paediatric population.

Renal impairment
Formal studies of dose adjustment have not been performed in patients with renal impairment.
The pharmacokinetic profile of fluorocholine (^{18}F) chloride in renally impaired patients has not been characterised.

Method of administration
Multidose vial, ready to use for direct intravenous injection.

Precautions to be taken before handling or administering the medicinal product
The activity of fluorocholine (^{18}F) chloride has to be measured with a activimeter immediately prior to injection.
The injection must be strictly intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

For instructions on dilution of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.

Image acquisition
For prostate cancer it is recommended to perform a dynamic PET acquisition over the pelvis including the prostate bed during 8 minutes, starting 1 minute after injection, or if not feasible one 2-minute static acquisition starting 1 minute post injection.
For all other localisations, it is usually recommended to perform a static whole-body PET acquisition starting 10 to 20 minutes after injection.
If there is any doubt concerning potential lesions with a slow uptake (e.g. negative static images whereas serum PSA levels are increased), a second static acquisition may be performed starting 60 min post 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.

Renal impairment
In patients with reduced kidney function, a very careful consideration of the indication is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in paediatric population, see section 4.2.

Patient preparation
Fluorocholine (^{18}F) CIS bio international should be given to patients fasting for a minimum of 4 hours with no hydric restriction.
Patients should be encouraged to drink sufficient amounts and to empty the bladder especially between dynamic acquisition and whole-body static acquisition of images and frequently after the examination in order to reduce radiation exposure.

Interpretation of images
Benign or malignant conditions other than prostate cancer can result in a significant uptake of fluorocholine (^{18}F) and therefore lead to false positive results, when search for prostate cancer is the aim of the fluorocholine (^{18}F) PET. Additional diagnostic techniques for the determination of the causative pathologic alteration may be required to supplement the information obtained by PET with fluorocholine (^{18}F).

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

Specific warnings
The detection of bone, lymph node or lung metastases of prostate cancer by fluorocholine (^{18}F) PET/CT has been widely reported. However, less evidence has been obtained, in case of prostate cancer, on the significance and the nature of foci of fluorocholine (^{18}F) uptake in other organs.

In case of rising PSA serum levels after an initial radical treatment, the detection rate of recurrent sites of prostate cancer with fluorocholine (^{18}F) is overall positively linked with the PSA serum level of the patient; usually the examination is undertaken when PSA serum level is greater than or equal to 0.2 ng/mL, or its doubling time less than 6 months.

This medication contains 3.54 mg/mL of sodium. Depending on the volume of solution administered, 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.

For precautions with respect to environmental hazard, see section 6.6.

4.5. Interaction with other medicinal products and other forms of interaction

The indication of fluorocholine (^{18}F) CIS bio international PET must be particularly documented in patients receiving anti-androgen therapy. Any recent change in therapy must lead to the revision of the fluorocholine (^{18}F) CIS bio international PET indication.

Antimitotic drugs (vincristine, docetaxel, paclitaxel) and colchicine may impair uptake by prostate cancer cells and may lead to false negative results.

Colony stimulating factors (G-CSF or erythropoietin) may increase bone marrow uptake of fluorocholine (^{18}F) CIS bio international. This could affect the detection of metastatic osteomedullar foci.

Concomitant intake of choline in foodstuff may affect the quality of images. Therefore, patients have to be fasted for at least 4h before the fluorocholine (^{18}F) chloride administration.

4.6. Fertility, pregnancy and lactation

This product is contra-indicated during pregnancy (see section 4.3.).

4.7. Effects on ability to drive and use machines

Fluorocholine (^{18}F) CIS bio international has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

No undesirable effects have been observed to date.

Since the administered substance quantity is very low, the major risk is caused by the radiation.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 8.0 mSv when the maximal recommended activity of400 MBq is administered in a 70 kg-weighted patient, 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 national reporting system listed in Appendix V.

4.9. Overdose

In the event of administration of a radiation overdose with fluorocholine (^{18}F) chloride, 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: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX 07

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

5.2. Pharmacokinetic properties

Distribution
Fluorocholine (^{18}F) chloride is an analogue of choline (precursor of the biosynthesis of phospholipids), in which an hydrogen atom has been substituted by fluorine (^{18}F). Choline is transported via the cell membrane using a carrier system and is phosphorylated by choline kinase (CK). The next steps are the conversion of the phosphorylcholine to cytidine diphosphate choline [(CDP)-choline] and incorporation into phosphatidylcholine, a component of the cell membrane.

The CK activity is increased in malignant cells, which explains the intense accumulation of radiolabeled choline in cancer.

It was shown that the metabolism of the analogue fluorocholine (^{18}F) corresponded to that of choline for these steps, but in the short time (<1h), where PET images are acquired, the main radiolabeled metabolite is the phosphorylated fluorocholine (^{18}F).

Following intravenous injection, the pharmacokinetic profile of fluorocholine (^{18}F) fits to a model that has two rapid exponential components plus a constant. The 2 fast phases, which are almost complete by 3 min after administration, represent > 93% of the peak concentration of radioactivity. Thus, the tracer is largely cleared from the intravascular compartment in the first 5 min after administration.

Organ uptake
The concentration of radioactive fluorine (^{18}F) in the liver increases rapidly in the first 10 min and then increased slowly. The concentration of radioactive fluorine (^{18}F) in the lungs remains relatively low at all times. The highest activity is observed in the kidneys, followed by liver and spleen.

Elimination
Thirty minutes after the injection 4-16% of injected activity remains in intravascular compartment. Less than 9% of injected activity is excreted with the urine during the first 3.5 hours after injection. The mean activity in the bladder is 1.9% of the injected dose.

5.3. Preclinical safety data

No deaths have been observed during acute toxicity studies after a single intravenous injection of decayed fluorocholine (^{18}F) chloride solution overloaded with active substance and impurities at doses of 1.25 mL/kg and 5 mL/kg in mice and rats respectively. Similarly no deaths have been observed during repeated toxicity studies in dogs at 0.33 mL/kg/day during 28 days.

The same solution has not demonstrated any mutagenicity in rats, when using the in vivo micronucleus test.

Neither long-term toxicity studies nor carcinogenicity studies have been performed since this medicinal product is not intended for regular or continuous administration.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for injection

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products in absence of compatibility study.

6.3. Shelf life

13 hours from the end of manufacturing. Date and time of expiry are indicated on the labels.

After the first withdrawal, use before the expiry time.

6.4. Special precautions for storage

Store in the original lead shielding.
For storage conditions after first withdrawal 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 colourless glass vial, Type I, closed with a rubber stopper and an aluminium seal.

The vial is placed into a lead container for protective shielding and packed in a metallic box.

Packsize: one multidose vial contains 0.5 to 15 mL of solution, corresponding to 112 MBq to 3375 MBq at calibration time.

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.

Before use, the packaging must be checked and the activity must be measured using an activimeter. If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

The solution should be inspected visually prior to use. Only clear solution, free of visible particles should be used.
The vial must be kept within its lead protection.
The vial must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single-use syringe fitted with suitable protective shielding and a disposable sterile needle.

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 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
BP 32
91192 GIF-SUR-YVETTE CEDEX
FRANCE

In Italy
Curium Italy S.r.l.
Via Nicola Piccinni, 2
I-20131 Milano

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 2016

10. DATE OF REVISION OF THE TEXT

10/2021

11. DOSIMETRY

Data listed below are from fourth addendum to ICRP Publication 53 (International Commission on Radiological Protection) of May 2013.

ORGANS	ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (mGy/MBq)				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	0.02	0.024	0.038	0.059	0.1
Bladder	0.059	0.075	0.11	0.16	0.22
Bone surfaces	0.012	0.015	0.023	0.037	0.07
Brain	0.0087	0.011	0.018	0.03	0.056
Breast	0.0090	0.011	0.018	0.028	0.054
Gall bladder	0.021	0.025	0.035	0.054	0.1
GI tract					
Stomach	0.013	0.016	0.025	0.04	0.076
Small Intestine	0.013	0.017	0.027	0.042	0.077
Colon	0.013	0.016	0.026	0.04	0.072
Upper large intestine	0.014	0.017	0.027	0.043	0.078
Lower large intestine	0.012	0.015	0.024	0.037	0.064
Heart	0.020	0.026	0.041	0.063	0.11
Kidneys	0.097	0.12	0.16	0.24	0.43
Liver	0.061	0.08	0.12	0.18	0.33
Lungs	0.017	0.022	0.035	0.056	0.11
Muscles	0.011	0.013	0.021	0.033	0.061
Oesophagus	0.011	0.014	0.021	0.033	0.062
Ovaries	0.013	0.016	0.026	0.04	0.072
Pancreas	0.017	0.022	0.034	0.052	0.093
Red marrow	0.013	0.016	0.024	0.036	0.066
Skin	0.008	0.0098	0.016	0.025	0.049
Spleen	0.036	0.05	0.077	0.12	0.22
Testes	0.0098	0.013	0.02	0.031	0.057
Thymus	0.011	0.014	0.021	0.033	0.062
Thyroid	0.011	0.014	0.022	0.037	0.07
Uterus	0.015	0.018	0.029	0.044	0.076
Remaining organs	0.011	0.014	0.021	0.034	0.062
Effective dose (mSv/MBq)	**0.02**	**0.024**	**0.037**	**0.057**	**0.1**

The effective dose resulting from the administration of an activity of 400 MBq for an adult weighing 70 kg is about 8.0 mSv. For an administered activity of 400 MBq, the typical radiation doses to the critical organs (kidneys and bladder) are 38.8 mGy and 23.6 mGy respectively.

12. INTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

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

The medicinal product may be diluted with sodium chloride 9 mg/mL solution for injection.

Withdrawals of the appropriate volume should be performed under aseptic conditions. The vial 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.

The preparation of individual dosis per patient with an automated application system, should be performed with a qualified and authorised system.

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

Quality control

The solution should be inspected visually prior to use. Only clear solution, free of visible particles should be used.