IASOcholine® 1 GBq/mL, solution for injection

SUMMARY OF PRODUCT CHARACTERISTICS

Malta

MARKETING AUTHORISATION NUMBER(S)
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IASOcholine 1 GBq/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution for injection contains 1 GBq of fluoromethyl-(^{18}F)-dimethyl-2-hydroxyethyl-ammonium chloride (fluorocholine (^{18}F) chloride) at date and time of calibration.

The total activity of the vial at that time is between 0.5 GBq and 15.0 GBq.

The radionuclide fluoride (^{18}F) has a half-life of 109.8 minutes and emits positron radiation with a maximum energy of 0.633 MeV followed by photon annihilation radiation of 0.511 MeV.

Excipient with known effects : each mL of IASOcholine 1 GBq/mL, solution for injection, contains 3.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.

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).

IASOcholine 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 sufficiently documented:

<u>Prostate cancer</u>
Detection of bone metastases of prostate cancer in high risk patients.

<u>Hepatocellular carcinoma</u>
- Localisation of lesions of proven well-differentiated hepatocellular carcinoma
- In addition to FDG PET, characterisation of liver nodes and/or staging of proven or very likely hepatocellular carcinoma, when FDG PET is non conclusive or when surgery or grafting is scheduled.

4.2 Posology and method of administration

Posology

Adults and elderly
The recommended activity for an adult weighting 70 kg is 200 to 500 MBq administered by direct intravenous injection. This activity has to be adapted according to the body weight of the patient and the type of PET or PET/CT camera used.

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

Paediatric population
No clinical data are available for patients aged less than 18 years concerning safety and diagnostic efficacy of the product. Therefore, the use in oncologic paediatrics is not recommended.

Method of administration
For patient preparation, see section 4.4.
The activity of fluorocholine (^{18}F) chloride has to be measured with activimeter immediately prior to injection.
The injection of fluorocholine (^{18}F) chloride must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts. It should be administered by direct intravenous injection.

Image acquisition
For prostate cancer: dynamic PET acquisition over the pelvis including the prostate bed and the pelvic bones, during 8 min, starting 1 min after injection, or if not feasible one 2 min static acquisition starting 1 min post injection.
For all indications: “Static” whole-body PET acquisition started 10 to 20 min after injection. If there is doubt concerning lesions with a slow uptake (e.g. negative static images whereas serum PSA levels are increased), a second static acquisition may be performed after one hour.

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the excipients or to any of the components of the labelled radiopharmaceutical.
- Pregnancy.

4.4 Special warnings and precautions for use

Pregnancy, see section 4.3 and 4.6

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

Paediatric population
For information on the use in paediatric population, see section 4.2. or 5.1.

Patient preparation
IASOcholine should be given to patients fasting for a minimum of 4 hours.
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.

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, the content of sodium given to the patient may in some cases be greater than 1 mmol. This should be taken into account in patient on low sodium diet.

Precautions with respect to environmental hazard see section 6.6.

The maximum volume to be administered to a patient should not exceed 10 mL.

4.5 Interaction with other medicinal products and other forms of interaction

In patients receiving anti-androgen therapy, the indication of IASOcholine PET must be particularly documented by rising serum PSA levels. Any recent change in therapy must lead to the revision of the IASOcholine PET indication taking into consideration the expected impact on patient management.

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 IASOcholine is contraindicated in pregnant women due to the radiation doses to the foetus (see section 4.3)..
No data are available concerning the use of this product during pregnancy. No studies of reproductive function have been performed in animals.

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 the initial 12 hours following injection and the expressed feeds discarded.

Close contact with infants should be restricted during this period.

4.7 Effects on ability to drive and use machines

Not relevant.

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 5.6 mSv when the maximal recommended activity of 280 MBq (4 MBq/kg for a subject weighting 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 ADR Reporting website: www.medicinesauthority.gov.mt/adrportal.

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 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: other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX07

At the chemical concentrations and 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 for the biosynthesis of phospholipids) in which a hydrogen atom has been replaced by fluorine (^{18}F). After crossing the cell membrane by a carrier-mediated mechanism, choline is phosphorylated by choline kinase (CK). In the next step, phosphorylcholine is converted to cytidinediphosphatecholine [(CDP)-choline] and subsequently incorporated into phosphatidylcholine which is a component of the cell membrane.

Organ uptake
The activity of CK has been found to be upregulated in malignant cells, providing a mechanism for the enhanced accumulation of radiolabelled choline by neoplasms. Fluorocholine (^{18}F) chloride has been shown to closely follow the metabolism of choline through these steps, although within the short timeframes of the PET scan (<1 h) and the half-life of the fluorine-18

radionuclide (110 min), the major radiolabelled metabolite is phosphorylated fluorocholine (^{18}F).
The concentration of ^{18}F radioactivity in liver increases rapidly in the first 10 min and then increases slowly thereafter. The concentration of ^{18}F radioactivity in lung is relatively low at all times. The highest uptake is in the kidney followed by the liver and spleen.

Elimination
The pharmacokinetics fits to a model that has 2 rapid exponential components plus a constant. The 2 rapid phases, which are nearly complete by 3 min after administration, represent > 93 % of the peak radioactivity concentration. Thus, the tracer is extensively cleared in the first 5 min after administration.

5.3 Preclinical safety data

A single intravenous administration of the undiluted test item fluorocholine (^{18}F) chloride, under a dose-volume of 5 mL/kg, does not induce any signs of toxicity in rats.
Studies on the mutagenic potential of fluorocholine (^{18}F) chloride are not available.
Mutagenicity studies und long-term carcinogenicity studies have not been carried out.
No studies of reproductive function have been performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 and 12.

6.3 Shelf life

14 hours from the time of calibration (15 min after time of production). Do not refrigerate or freeze.

8 hours after first use without exceeding the expiry time. After fisrt use, store below 25° C. Do not refrigerate or freeze.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze. Store in the original package.

After first use, store below 25° C. Do not refrigerate or freeze.

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

6.5 Nature and contents of container

15 or 25 mL <u>multidose</u> glass vial, colourless Type I glass, closed with a rubber stopper and sealed with an aluminium cap. As a result of the production process IASOcholine might be delivered with a punctured rubber septum.
One vial contains **0.5** to **15.0** mL of solution, corresponding to **500** to **15 000** MBq at calibration time.

6.6 Special precautions for disposal and other handling

<u>General warning</u>
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.

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

If at any time in the preparation of this product the integrity of this container 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.

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)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26th April, 2013 / 6th August, 2015

10. DATE OF REVISION OF THE TEXT

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11. DOSIMETRY

The data Listed below are from fourth addendum to ICRP publication 53.

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.020	0.024	0.038	0.059	0.10
Bladder	0.059	0.075	0.11	0.16	0.22
Bone surfaces	0.012	0.015	0.023	0.037	0.070
Brain	0.0087	0.011	0.018	0.030	0.056
Breast	0.0090	0.011	0.018	0.028	0.054
Gall bladder	0.021	0.025	0.035	0.054	0.10
Gastrointestinal-tract					
Stomach	0.013	0.016	0.025	0.040	0.076
Small Intestine	0.013	0.017	0.027	0.042	0.077
Colon	0.013	0.016	0.026	0.040	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	0.080	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	0.040	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	0.0080	0.0098	0.016	0.025	0.049
Spleen	0.036	0.050	0.077	0.012	0.22
Testes	0.0098	0.013	0.020	0.031	0.057
Thymus	0.011	0.014	0.021	0.033	0.062
Thyroid	0.011	0.014	0.022	0.037	0.070
Uterus	0.015	0.018	0.029	0.044	0.076
Remaining organs	0.012	0.014	0.021	0.034	0.062
Effective dose (mSv/MBq)	0.020	0.024	0.037	0.057	0.10

The effective dose resulting from the administration of a maximal recommended activity of 500 MBq of fluorocholine (^{18}F) chloride for an adult is about 10 mSv.
For an administered activity of 500 MBq the typical radiation doses delivered to the critical organs, kidneys, liver and bladder are 49, 31 and 30 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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

IASOcholine contains no preservatives. Multidose vial.
The solution is to be inspected visually prior to use and only clear solutions free of visible particles should be used.

Handle multidose vial under aseptic conditions.

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.

In case of automated preparation of patient dose, use only qualified authorised automated dispensing system.

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 solution of fluorocholine (^{18}F) chloride can be diluted with water for injections (1:1) or saline (sodium chloride 9 mg/mL solution for injection) (1:40).