PHYTACIS®

Kit for the preparation of technetium [^{99m}Tc] phytate injection

USER PACKAGE LEAFLET

CIS bio international, member of IBA Molecular group of companies

T1800nH
(T1800- T1817)

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IDENTIFICATION OF THE MEDICINAL PRODUCT

Trade name of the medicinal product

PHYTACIS®
Kit for the preparation of technetium [^{99m}Tc] phytate injection

Qualitative and quantitative composition

The kit for the preparation of technetium [^{99m}Tc] phytate injection consists of 5 multidose vials containing under nitrogen atmosphere the sterile, pyrogen-free, freeze-dried product with the following composition:

Active substance

Anhydrous sodium phytate.

Quantitative composition

Anhydrous sodium phytate ..... 20 mg
Stannous chloride dihydrate..... 1 mg
Sodium chloride.....1.46 mg

The product contains no antimicrobial preservative.

After the addition of sterile, pyrogen-free sodium pertechnetate [^{99m}Tc] injection, 5 preparations of technetium [^{99m}Tc] phytate injection are obtained.

Nature and contents of the container

15 ml colourless, European Pharmacopoeia type I, drawn glass vial, closed with a grey chlorobutyl rubber stopper and an aluminium capsule.

Pharmaceutical form

Powder for injection.

Pharmaco-therapeutic group

Radiopharmaceutical preparation for diagnostic use.
ATC code: V09DB07

Name and address of the marketing authorization holder

Country specific.

Name and address of the manufacturer

CIS bio international
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91192 GIF-SUR-YVETTE CEDEX
FRANCE

PHARMACODYNAMIC PROPERTIES

At the chemical concentrations and activities used for diagnostic procedures technetium [^{99m}Tc] phytate does not appear to exert any pharmacodynamic effects.

PHARMACOKINETIC PROPERTIES

Technetium [^{99m}Tc] phytate, a complex of the mesoinositol hexaphosphoric acid, forms a colloid with serum calcium in vivo which is trapped by the reticuloendothelial system.

The process of uptake of foreign materials including particular matter by the cells of the reticuloendothelial system is well documented.

Various factors such as liver and spleen mass, hepatic blood flow, reticuloendothelial system integrity, the physical characteristics of particles and the size and the number of particles affect the in vivo distribution of the colloid. Large particles (> 8 µm) are trapped in the lungs, particles in the range of 300 to 1000 nm are taken up preferentially by the liver and spleen, particles ≤ 100 nm by red marrow and particles in the range 5 to 50 nm by lymphatic system. The particle size of technetium [^{99m}Tc] phytate ranges from 5 to 1000 nm, the fraction of free technetium [^{99m}Tc] phytate is about 5%.

Uptake fractions of technetium [^{99m}Tc] phytate have been estimated in healthy volunteers over a period of 24 hours. Maximum uptake occurs 10 minutes after intravenous injection (liver 75%, spleen 4%, blood 6% of dose).

Five per cent of the injected activity is excreted by the kidney after 2 hours and 14% after 24 hours. In this period, liver retention decreases from 75% (2 hours) to 71% of activity (24 hours). The uptake in bone marrow is 5-10%.

In decreased hepatocellular function the colloid uptake is shifted toward the spleen and bone marrow.
Liver uptake decreases up to 50% in patients with early to intermediate diffuse parenchymal liver disease and up to 30% in patients with advanced diffuse parenchymal liver disease. In these cases, uptake in spleen increases respectively up to 20 and 30%, in bone marrow respectively up to 15 and 25%. In experimentally induced vitamin D deficient rachitic rats, technetium [^{99m}Tc] phytate showed abnormal uptake in the bone matrix.

PRECLINICAL SAFETY DATA

In toxicological studies, phytic acid was investigated in a buffered calcium chloride solution in mice, rats and dogs (beagles). The doses administered were a factor of 30-70 times higher than maximum dose used in man. After the intravenous injection of 10 mg/kg body weight of unlabelled phytic acid to mice and rats and 5 mg/kg body weight to dogs, no evidence of toxic effects was found within 24 hours or at autopsy.

In rats, unlabelled phytic acid showed no teratogenic effects. No studies on reproductive toxicity or placental transfer and excretion into milk were performed with the labelled product.

No animal studies regarding fertility or peri-postnatal development were performed. This agent is not intended for regular or continuous administration. Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

Toxicological studies with tin chloride and tin chloride dihydrate were carried out in mouse, rats and dogs. In dogs the minimum toxic dose (intravenous injection) was found to be 20 mg/kg body weight.

Limited studies on tin salts demonstrate a weak potential for mutagenicity.

At the amounts used for diagnostic procedures (about 1 mg) toxic effects are not to be expected.

DOSIMETRY

Technetium [^{99m}Tc] is produced by means of a [^{99}Mo/^{99m}Tc] generator and decays with emission of gamma-radiation with an energy of 140 keV and a half-life of 6.02 hours to technetium [^{99}Tc] which, in view of its long half-life of 2.14×10^5 years, can be regarded as quasi stable.

The dosimetry data were quoted from ICRP publication 53 for large colloids (100-1000 nm).

Normal liver function

Absorbed dose per unit activity administered (mGy/MBq)					
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals *	1.0E-02	1.5E-02	2.1E-02	2.8E-02	4.2E-02
Bladder wall	1.1E-03	1.6E-03	2.8E-03	5.7E-03	9.5E-03
Bone surfaces	6.4E-03	8.4E-03	1.3E-02	2.2E-02	4.6E-02
Breast	2.7E-03	2.7E-03	4.6E-03	7.3E-03	1.3E-02
Gl-tract					
Stomach wall	6.2E-03	8.3E-03	1.3E-02	2.1E-02	3.5E-02
Small intest	4.3E-03	5.1E-03	9.0E-03	1.4E-02	2.5E-02
ULI wall	5.6E-03	6.9E-03	1.2E-02	2.1E-02	3.4E-02
LLI wall	1.8E-03	2.2E-03	3.8E-03	6.1E-03	1.1E-02
Kidneys *	9.7E-03	1.1E-02	1.7E-02	2.4E-02	3.5E-02
Liver *	7.4E-02	9.2E-02	1.4E-01	1.9E-01	3.4E-01
Lungs	5.5E-03	7.5E-03	1.0E-02	1.5E-02	2.5E-02
Ovaries	2.2E-03	2.9E-03	4.9E-03	7.9E-03	1.4E-02
Pancreas *	1.2E-02	1.7E-02	2.5E-02	3.7E-02	5.9E-02
Red marrow	1.1E-02	1.5E-02	2.3E-02	3.8E-02	7.2E-02
Spleen *	7.7E-02	1.1E-01	1.6E-01	2.5E-01	4.5E-01
Testes	6.2E-04	7.6E-04	1.3E-03	2.2E-03	4.5E-03
Thyroid	7.9E-04	1.2E-03	2.0E-03	3.5E-03	6.5E-03
Uterus	1.9E-03	2.5E-03	4.4E-03	7.4E-03	1.3E-02
Other tissues	2.8E-03	3.4E-03	4.9E-03	7.3E-03	1.3E-02
Effective dose equivalent (mSv/MBq)	1.4E-02	1.8E-02	2.8E-02	4.1E-02	7.3E-02

The effective dose equivalent resulting from an administered activity of 100 MBq is typically 1.4 mSv (per 70 kg individual).

Diffuse parenchymal liver disease

Absorbed dose per unit activity administered (mGy/MBq)		
Organ	**Early to intermediate**	**Intermediate to advanced**
Adrenals *	9.9E-03	9.8E-03
Bladder wall	1.4E-03	1.6E-03
Bone surfaces	8.2E-03	1.2E-02
Breast	2.6E-03	2.4E-03
Gl-tract		
- Stomach wall	8.1E-03	9.8E-03
- Small intest	4.4E-03	4.6E-03
- ULI wall	5.3E-03	4.9E-03
- LLI wall	2.4E-03	3.1E-03
Kidneys *	1.1E-02	1.1E-02
Liver *	4.0E-02	4.2E-02
Lungs	5.2E-03	4.8E-03
Ovaries	2.7E-03	3.3E-03
Pancreas *	1.5E-02	1.8E-02
Red marrow	1.5E-02	2.3E-02
Spleen *	1.0E-01	1.4E-01
Testes	8.6E-04	9.5E-04
Thyroid	1.0E-03	1.1E-03
Uterus	2.4E-03	2.8E-03
Other tissues	3.0E-03	3.1E-03
Effective dose equivalent (mSv/MBq)	1.4E-02	1.7E-02

If liver is impaired the effective dose equivalent resulting from an administered activity of 100 MBq is typically 1.4 mSv (early to intermediate parenchymal liver disease) and 1.7 mSv (intermediate to advanced parenchymal liver disease) per 70 kg individual.

DIAGNOSTIC INDICATIONS

After reconstitution with sodium pertechnetate [^{99m}Tc] solution the injection is used for liver scintigraphy.

NECESSARY INFORMATION BEFORE TAKING THE MEDICINAL PRODUCT

Contra-indications

There are no specific contra-indications.

Special warnings and special precautions for use

This radiopharmaceutical may be used only by qualified personnel with the government authorisation for the use and manipulation or radionuclides.

To avoid any influence on the stability of the technetium [^{99m}Tc] labelled complexes, technetium [^{99m}Tc] preparations should not be mixed or applied together with other pharmaceuticals or components.

Interactions with other medicaments and other forms of interactions

Liver uptake may also decrease after therapy with general anaesthetic agents, e.g. halothane, due to decrease of hepatic blood flow.

Drugs known to be associated with short-term or long-term hepatotoxicity, such as cancer therapeutic agents, notably the nitrosoureas may affect the biodistribution pattern of radiolabelled colloids.

Pregnancy and lactation

When 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 to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by mother and foetus.

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk.

If the administration is considered necessary, breast feeding should be interrupted for 12 hours and the expressed feeds discarded. It is usual to advise that breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.

Effects on ability to drive and use machines

No effects are to be expected after administration of this diagnostic agent.

List of excipients

Stannous chloride dihydrate
Sodium chloride
Nitrogen

Incompatibilities

None known to date.

NECESSARY AND USUAL INSTRUCTIONS FOR PROPER USE

Posology and Method of Administration

The recommended activity by single intravenous injection for adults and the elderly is in the range of 37-100 MBq. Scanning can be started 10-60 minutes post-injection.

The activities to be administered to children should be a fraction of the adult dose. Body surface is the more usual prorata factor on which to base the adjustment of the administered activity according to the following formula :

$$\text{Paediatric dose (MBq)} = \frac{\text{adult dose (MBq)} \times \text{child surface } (m^2)}{1.73\ (m^2)}$$

In some cases relative body weight may be considered more appropriate:

$$\text{Paediatric dose (MBq)} = \frac{\text{adult dose (MBq) x child weight (kg)}}{\text{70 (kg)}}$$

3 kg = 0.10	22 kg = 0.50	42 kg = 0.78
4 kg = 0.14	24 kg = 0.53	44 kg = 0.80
6 kg = 0.19	26 kg = 0.56	46 kg = 0.82
8 kg = 0.23	28 kg = 0.58	48 kg = 0.85
10 kg = 0.27	30 kg = 0.62	50 kg = 0.88
12 kg = 0.32	32 kg = 0.65	52-54 kg = 0.90
14 kg = 0.36	34 kg = 0.68	56-58 kg = 0.92
16 kg = 0.40	36 kg = 0.71	60-62 kg = 0.96
18 kg = 0.44	38 kg = 0.73	64-66 kg = 0.98
20 kg = 0.46	40 kg = 0.76	68 kg = 0.99

In very-young children (up to 1 year) a minimum activity of 15 MBq is necessary in order to obtain images of sufficient quality.

Instructions for use

Method of preparation

Usual precautions regarding sterility and radioprotection should be respected.

- Put one vial from the kit in a lead shielding.

- Using a hypodermic syringe, introduce through the rubber stopper 10 ml maximum of sterile pyrogen-free sodium pertechnetate [^{99m}Tc] injection corresponding to maximum 9250 MBq. Sodium pertechnetate [^{99m}Tc] injection should comply with European Pharmacopoeia specifications. Do not use a breather needle as the contents are under nitrogen: after introduction of the volume of sodium pertechnetate [^{99m}Tc] injection, without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial.

- Shake during about 2 minutes.

- The obtained preparation is a clear and colorless solution, with a pH ranging between 6.0 and 7.0. Before use, limpidity of the solution after preparation, pH and radioactivity will be checked. The vial should never be opened and must be kept inside its lead shielding. The solution should be removed aseptically through the stopper with a sterile lead protected syringe.

Quality control

Method

Ascending paper chromatography.

Materials and reagents

- Whatman 1 paper
- Mobile phase : methanol/water (80/20)
- Chromatography tanks
- Berthold-type device for measuring the linear distribution of radioactivity.

Operating procedure

The test is performed on 1 vial.
- Apply a spot of the preparation to the deposit line of each strip.
- Place each support in the corresponding chromatography tanks containing the mobile phase.
- Allow to migrate to the solvent front at room temperature. Remove the paper strips and dry in air.
- Determine the distribution of radioactivity with an appropriate detector.
- Identify each radioactive spot by calculating the Rf value. The Rf for the complex is 0 and that of pertechnetate [TcO_4^-] is 0.6.
- Measure the radioactivity of each spot by integrating the peaks.

Specifications

Radioactivity due to the technetium [^{99m}Tc] phytate complex is not less than 95%.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills or urine, vomiting, etc. Suitable precautions should be taken concerning the radioactivity eliminated by the patients in order to avoid any contamination. Radiation protection precautions in accordance with national regulations must therefore be taken.

The residues may be put in an ordinary waste bin sofar as long as the activity of vials and syringes does not exceed that of background when measured with a low level radiation detector. Waste must be disposed of according to national regulations.

Overdose

No specific therapy is possible in the event of the administration of a radiation overdose with technetium [^{99m}Tc] phytate.

UNDESIRABLE EFFECTS

No adverse effects have been reported for this agent.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (effective dose/EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

SHELF-LIFE

The expiry date for this product is 6 months from the day of manufacture.

The labeled product should be used within 6 hours after labeling.

Special precautions for storage

Store the kit and the labeled product at 2°C - 8°C (in a refrigerator).

Storage should be in accordance with national regulations for radioactive materials.

DATE OF LAST REVISION OF THE TEXT

08/2008

FINLAND

Name and address of the marketing authorisation holder

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Marketing authorisation number: 11250

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