Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CHOLEDIAM Kit for radiopharmaceutical preparation of technetium [^{99m}Tc] mebrofenin injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mebrofenin 40.00 mg

The product contains no antimicrobial preservative.

3 PHARMACEUTICAL FORM

Powder for solution for injection. Kit for radiopharmaceutical preparations.

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

The product is to be used after reconstitution by the addition of sterile, pyrogen-free, isotonic sodium pertechnetate [^{99m}Tc] injection, allowing the preparation of technetium [^{99m}Tc] mebrofenin injection (technetium [^{99m}Tc] N-2,4,6 trimethyl 3 bromophenylcarbamoylmethyl) iminodiacetic acid, i.e. technetium [^{99m}Tc] trimethyl-bromo-IDA).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

After reconstitution with sodium pertechnetate [^{99m}Tc] solution for injection:

- Hepatobiliary imaging.
- Hepatobiliary function studies.

4.2 Posology and method of administration

The solution is administered intravenously, to patients fasting for 6 hours prior to examination.

In adults, the dose is 150 to 300 MBq (4.1 to 8.1 mCi), other doses may be justifiable.

The dose to be administered in a child should be a fraction of the adult dose calculated from the body weight according to the following table:

Fraction of adult dose:

3 k	= 0.1	22 kg= 0.50	42 kg= 0.78
4 k	= 0.14	24 kg= 0.53	44 kg= 0.80
6 k	= 0.19	26 kg= 0.56	46 kg= 0.82
8 k	= 0.23	28 kg= 0.58	48 kg= 0.85
10 k	= 0.27	30 kg= 0.62	50 kg= 0.88
12 k	= 0.32	32 kg= 0.65	52-54 kg= 0.90
14 k	= 0.36	34 kg= 0.68	56-58 kg= 0.92
16 k	= 0.40	36 kg= 0.71	60-62 kg= 0.96
18 k	= 0.44	38 kg= 0.73	64-66 kg= 0.98
20 k	= 0.46	40 kg= 0.76	68 kg= 0.99

(Paediatric Task Group, EANM)

In very young children (up to 1 year) a minimum dose of 20 MBq (0.5 mCi) is necessary to obtain images of sufficient quality.

The examination as sequential or functional scintigraphy may be started immediately after injection.

Cholecystokinins or a fatty meal may be used to contract the gall bladder.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

This radiopharmaceutical may be used and administered only by authorized persons.

Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.

The biliary tree may not be adequately visualised in the following circumstances:

- Parenteral nutrition
- Prolonged dieting
- After a meal: the test should be performed with the patient fasting for six hours
- Hepatocellular insufficiency
- Hepatitis

4.5 Interaction with other medicinal products and other forms of interaction

Opiate analgesics and barbiturates cause spasm in the Sphincter of Oddi and increased intrabiliary pressure. This increases biliary- bowel transit time and may enhance activity in the gall bladder.

Nicotinic acid is toxic to hepatocytes and may impair uptake and excretion of technetium [^{99m}Tc] mebrofenin in bile.

Gall bladder visualisation may be adversely affected in patients receiving chemotherapy via an indwelling hepatic artery catheter as a chemical cholecystitis has been described.

Cholecystokinin and sincalide stimulate gall bladder emptying and secretion of the radiotracer into the duodenum.

Atropine and somatostatin may impair gall bladder emptying.

4.6 Fertility, pregnancy and lactation

When it is necessary to administer radioactive medicinal products to a woman 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.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and operate machines are to be expected after use of this product.

4.8 Undesirable effects

Very rare cases of allergic type reactions may appear after administration of Mebrofenin.

- 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 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 dose incurred.

- For most diagnostic investigations using a nuclear medicine procedure, the radiation dose delivered (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In the event of the administration of an overdose of a radiopharmaceutical, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body.

In the event of an overdose of technetium [^{99m}Tc] labelled compound, laxatives to aid faecal clearance are recommended.

In the event of biliary obstruction or significant parenchymal liver disease, overall tissue radiation may be reduced by implementing a regime of forced diuresis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

At doses used for diagnostic procedures, technetium [^{99m}Tc] mebrofenin does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

At doses used for diagnostic procedures, technetium [^{99m}Tc] mebrofenin does not appear to exert any pharmacodynamic effects.

5.3 Preclinical safety data

5.3.1. Toxicity after single administration.

Trials of the acute intravenous tolerance of trimethyl-bromo-iminodiacetic acid have demonstrated:

- LD_{50} of 285 mg/kg body weight in mice.
- LD_{50} of 250 mg/kg body weight in rats.

The maximum amount of technetium [^{99m}Tc] mebrofenin given to patients is approximately 0.6 mg/kg. This is a factor 500 lower than the animal LD_{50}.

5.3.2. Toxicity after repeated administrations.

No significant variations were observed in blood tests or histological studies of the major organs after daily injection of mebrofenin for 14 consecutive days in rats.

Mutagenicity or reproduction studies and long-term carcinogenicity studies have not been carried out.

5.4 Radiation dosimetry

According to publication N^{o} 53 by the ICRP (International Commission on Radiological Protection), the radiation doses absorbed, compared with the doses of technetium [^{99m}Tc] mebrofenin administered are the following in healthy adults:

- Gallbladder : 1.1×10^{-1} mGy/MBq
- Liver : 1.5×10^{-2} mGy/MBq
- Haematopoietic tissue : 7×10^{-3} mGy/MBq
- Kidneys : 6.3×10^{-3} mGy/MBq

Technetium [^{99m}Tc] disintegrates with the emission of gamma radiation with an energy of 140 KeV and a half life of 6.02 hours to technetium

[^{99}Tc] which can be regarded as quasi stable.

Tc- LABELLED IMINODIACETIC ACID (IDA) DERIVATIVES

^{99m}Tc $T_{1/2}$ = 6.02 hours

Healthy subject

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0032	0.0047	0.0074	0.011	0.018
Bladder wall	0.023	0.028	0.042	0.063	0.11
Bone surface	0.0026	0.0033	0.0047	0.0071	0.014
Breast	0.00061	0.00064	0.0013	0.0025	0.0048
Gall Bladder Wall	0.11	0.12	0.16	0.28	0.96
Gastrointestinal tract					
Stomach wall	0.0061	0.0077	0.013	0.021	0.034
Small intestine	0.052	0.065	0.11	0.16	0.29
Upper large intestine wall	0.092	0.11	0.19	0.29	0.55
Lower large intestine wall	0.062	0.077	0.13	0.21	0.39
Kidneys	0.0063	0.0074	0.011	0.016	0.025
Liver	0.015	0.018	0.027	0.040	0.072
Lungs	0.0011	0.016	0.0025	0.0040	0.0075

Ovaries	0.020	0.024	0.036	0.052	0.084
Pancreas	0.0057	0.0075	0.014	0.022	0.034
Red marrow	0.0070	0.0080	0.010	0.013	0.015
Spleen	0.0026	0.0034	0.0059	0.0096	0.016
Testes	0.0015	0.0023	0.0042	0.0070	0.013
Thyroid	0.00012	0.00018	0.00037	0.00073	0.0017
Uterus	0.013	0.017	0.027	0.040	0.065
Other tissue	0.0030	0.0036	0.0053	0.0080	0.014
Effective dose equivalent (mSv/MBq)	**0.024**	**0.029**	**0.044**	**0.070**	**0.15**

For this product, the effective dose equivalent resulting from an administered activity of 300 MBq is typically 7.2 mSv (per 70kg individual).

Parenchymal Liver Disease

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 years**
Adrenals	0.0021	0.0030	0.0046	0.0067	0.011
Bladder wall	0.069	0.085	0.12	0.19	0.34
Bone surface	0.0017	0.0021	0.0030	0.0046	0.0087
Breast	0.00056	0.00057	0.0010	0.0018	0.0035
Gall Bladder Wall	0.035	0.040	0.053	0.092	0.30
Gastrointestinal tract					
Stomach wall	0.0027	0.0034	0.0058	0.0094	0.016
Small intestine wall	0.019	0.024	0.039	0.060	0.11
Upper large intestine wall	0.033	0.040	0.066	0.10	0.19
Lower large intestine wall	0.024	0.030	0.050	0.079	0.15
Kidneys	0.0066	0.0079	0.011	0.017	0.027
Liver	0.010	0.013	0.020	0.028	0.050
Lungs	0.00092	0.0013	0.0019	0.0029	0.0054
Ovaries	0.0099	0.012	0.018	0.026	0.042
Pancreas	0.0028	0.0038	0.0066	0.010	0.017
Red marrow	0.0038	0.0045	0.0060	0.0074	0.0094
Spleen	0.0015	0.0019	0.0032	0.0052	0.0090
Testes	0.0025	0.0038	0.0067	0.011	0.020
Thyroid	0.00023	0.00037	0.00064	0.0011	0.0022
Uterus	0.011	0.014	0.022	0.031	0.051
Other tissue	0.0021	0.0025	0.0036	0.0055	0.0095
Effective dose equivalent (ms/MBq)	**0.013**	**0.016**	**0.024**	**0.037**	**0.075**

For this product, in case of parenchymal liver disease, the effective dose equivalent resulting from an administered activity of 300 MBq is typically 3.9 mSv (per 70 kg individual).

Occlusion of the Cystic Duct

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0022	0.0033	0.0052	0.0079	0.013
Bladder wall	0.039	0.048	0.070	0.10	0.19
Bone surface	0.0023	0.0028	0.0041	0.0061	0.012
Breast	0.00051	0.00051	0.00099	0.0019	0.0037
Gastrointestinal tract					
Stomach wall	0.0050	0.0062	0.0093	0.015	0.025
Small intestine	0.047	0.059	0.096	0.15	0.26
Upper large intestine wall	0.084	0.10	0.17	0.27	0.50
Lower large intestine wall	0.058	0.072	0.12	0.19	0.37
Kidneys	0.0055	0.0065	0.0097	0.014	0.023
Liver	0.010	0.013	0.020	0.030	0.054
Lungs	0.00086	0.0012	0.0019	0.0031	0.0058
Ovaries	0.019	0.023	0.034	0.049	0.079
Pancreas	0.0035	0.0047	0.0076	0.012	0.021
Red marrow	0.0066	0.0075	0.0098	0.012	0.014
Spleen	0.0022	0.0027	0.0046	0.0074	0.013
Testes	0.0019	0.0030	0.0054	0.0086	0.016
Thyroid	0.00015	0.00022	0.00042	0.00077	0.0017
Uterus	0.013	0.017	0.027	0.040	0.066
Other tissue	0.0027	0.0033	0.0048	0.0073	0.013
Effective dose equivalent (ms/MBq)	**0.018**	**0.022**	**0.035**	**0.054**	**0.098**

For this product, in case of occlusion of the cystic duct, the effective dose equivalent resulting from an administered activity of 300 MBq is typically 5.4 mSv [per 70 kg individual].

Occlusion of the Common Bile Duct

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0088	0.013	0.019	0.024	0.036
Bladder wall	0.020	0.024	0.036	0.056	0.10
Bone surface	0.0024	0.0030	0.0042	0.0065	0.013
Breast	0.0023	0.0023	0.0040	0.0064	0.012
Gastrointestinal tract					

Stomach wall	0.0037	0.0056	0.010	0.017	0.030
Small intestine	0.0036	0.0044	0.0083	0.014	0.024
Upper large intestine wall	0.0052	0.0064	0.012	0.021	0.035
Lower large intestine wall	0.0015	0.0018	0.0033	0.0057	0.010
Kidneys	0.0084	0.0099	0.015	0.021	0.031
Liver	0.085	0.11	0.16	0.22	0.39
Lungs	0.0049	0.0068	0.0093	0.013	0.022
Ovaries	0.0019	0.0026	0.0047	0.0078	0.014
Pancreas	0.0083	0.013	0.020	0.030	0.049
Red marrow	0.0035	0.0049	0.0066	0.0085	0.012
Spleen	0.0019	0.0029	0.0052	0.0085	0.014
Testes	0.00076	0.0011	0.0019	0.0033	0.0065
Thyroid	0.00034	0.00046	0.00091	0.0018	0.0035
Uterus	0.0028	0.0037	0.0066	0.011	0.019
Other tissue	0.0023	0.0028	0.0040	0.0060	0.011
Effective dose equivalent (ms/MBq)	**0.0096**	**0.012**	**0.018**	**0.026**	**0.046**

For this product, in case of occlusion of the common bile duct, the effective dose equivalent resulting from an administered activity of 300 MBq is typically 2.9 mSv (per 70 kg individual).

Newborns, congenital biliary atresia

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**
Adrenals	0.033
Bladder wall	0.26
Bone surface	0.026
Gastrointestinal tract	
Stomach wall	0.036
Small intestine	0.070
Upper large intestine wall	12
Lower large intestine wall	0.023
Kidneys	0.15
Liver	0.90
Lungs	0.044
Ovaries	0.045
Pancreas	0.057
Red marrow	0.047
Spleen	0.019
Testes	0.035

Thyroid	0.012
Uterus	0.037
Other tissue	0.021
Effective dose equivalent (mSv/MBq)	**0.85**

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous Chloride dihydrate
Hydrochloric acid, sodium hydroxide

6.2 Incompatibilities

None known.

6.3 Shelf life

12 months.

The labelled product must be injected within 4 hours after reconstitution.

6.4 Special precautions for storage

Store at 2°C to 8°C (in a refrigerator)

Reconstituted product: Do not store above 25°C. Do not refrigerate. Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of container

15 ml, colourless, Ph. Eur. type I, drawn glass vials, closed with chlorobutyl rubber stoppers and aluminium capsules.

Pack sizes: Kit of 5 multidose vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See Section 12.

7 MARKETING AUTHORISATION HOLDER

Mediam
21 Avenue de Verdun
59700 Marcq en Baroeul
France

8 MARKETING AUTHORISATION NUMBER

PA 1229/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2001

Date of last renewal: 13 July 2006

10 DATE OF REVISION OF THE TEXT

January 2018

11 DOSIMETRY

{For radiopharmaceuticals}

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

o Method of preparation

(An aseptic technique should be used throughout)

Usual precautions regarding sterility and radioprotection should be respected.

Take a vial from the kit and put it in an appropriate lead shielding.

Using a hypodermic syringe, introduce through the rubber stopper 1 to 5 ml of sterile and pyrogen-free sodium pertechnetate [^{99m}Tc] injection, activity varying as a function of the volume from 0.74 to maximum 3.7 GBq (from 20 to maximum 100 mCi). Sodium pertechnetate [^{99m}Tc] injection should comply with European Pharmacopoia 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, let the piston rise into the syringe so as to reduce the excess of pressure.

Invert a few times the vial to dissolve the freeze-dried product, and then allow to stand for about 30 minutes at ambient temperature.

The obtained preparation is a clear and colourless solution, with a pH ranging between 4.0 and 6.0.

Limpidity of the solution after preparation, pH, radioactivity and gamma spectrum should be checked before use.

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.

o Quality control

The quality of labelling (radiochemical purity) may be checked according to the following procedure.

Method

Paper chromatography

Materials and reagents

1. Adsorbent

Whatman paper N^{o}1. Trace a starting line 2.5 cm from the bottom of the paper strip.

2. Solvent
   Methylethylketone.
3. Containers
   Appropriate containers such as chromatography tank, Erlenmeyer flasks.
4. Miscellaneous
   Foreceps, scissors, syringes, needles, appropriate counting assembly.

Procedure
Do not let air enter the vial to be tested and store all vials containing radioactive solution in lead shieldings.

1. Apply a spot of the preparation to the starting line of the paper strip using a syringe and needle.
2. Using forceps, introduce the paper strip vertically into the chromatography tank for development with the starting line downward. Stopper the chromatography tank.
3. When the solvent has reached the top of the strip, use the forceps to remove the strip and dry in the air.
4. Cut the strip at Rf = 0.5.
5. Separately count each section of the strip and record the obtained values (use an appropriate detection apparatus with a constant counting time, and known geometry and background noise).
6. Calculations
   Correct the counting data for background noise.Calculate the percentage of free technetium [^{99m}Tc] :

$$\% \text{ free } ^{99m}\text{Tc} = \frac{\text{Activity of strip for Rf 0.5-1.0}}{\text{Total activity of strip}} \times 100$$

Calculate the percentage of bound technetium [^{99m}Tc] (radiochemical purity) :

$$\% \text{ bound } ^{99m}\text{Tc} = 100\ \% - \% \text{ free } ^{99m}\text{Tc}$$

7. The percentage of bound ^{99m}Tc (radiochemical purity) should be more than 95 %.

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.

Radioactive waste must be disposed of in conformity with the relevant national and international regulations.