1. NAME OF THE MEDICINAL PRODUCT

BROMO-BILIARON 5.0 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 5.0 mg active ingredient:
N-(3-bromo-2,4,6-trimethylphenylcarbamoil-methyl)- iminodiacetic acid 5.00 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for preparation of technetium Tc-^{99m} mebrofenin radiopharmaceutical.

The BROMO-BILIARON kit content:

Powder for solution for injection.

^{99m}Tc- BROMO-BILIARON pharmaceutical form: injection

Sterile, pyrogen free lyophilised white powder, sealed in nitrogen atmosphere. It can be labellled with oxidising agent free sodium pertechnetate (^{99m}Tc)injection (Ph.Eur), to carry out hepatobiliary scintigraphic imaging.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.
After radiolabelling with sodium (99mTc) pertechnetate sterile solution, the solution obtained is indicated in Hepatobiliary imaging.

- Hepatobiliary function studies.
- Evaluation of bile flow, and diagnosis of extrahepatic biliary obstruction, malfunctioning gall-bladder, gall-bladder inflammation, biliary duct artresia, biliary cysts or similar pathologic alterations of the biliary duct.

The preparation can be used in case of hyperbilirubinemia

4.2 Posology and Method of Administration

Posology: One vial content can be labelled with activity of maximum of 6 GBq in 2-5 ml sterile ^{99m}Tc-sodium pertechnetate solution. In case of the highest activity (6GBq) the recommended minimum volume is 5 ml.
Other activities may be justifiable. Radiochemical purity must be verified administration.

Method of administration: The solution is administered intravenously to patients fasting for 6 hours prior to examination.

Adult doses: 150 – 300 MBq
In case of normal bilirubin level: 1,1-1,5 MBq/kg body weight
In case of increased bilirubin level 2-3 MBq/kg body weight

In case of a sequential scintigraphic examination the first image should be taken within 5-10 minutes after i.v. injection, then in 5 min intervals until minute 45. Late image acquisition is recommended after 2, 6, or 24 hours.

Gall-bladder is tested within 25-60 minutes.

Late images can be taken 24 hours after administration to detect biliary duct obstruction. Visualizations: maximal hepatocyte uptake within 5-10 minutes; gall bladder accumulation within 10-30 minutes; biliary duct, duodenum and the jejunum within 20-45 minutes.
In case of an elevated serum bilirubin level the Tmax is 15-60 minutes, and the activity appears in the duodenum and in the jejunum after 100-120 minutes.
Cholecystokinins or a fatty meal can be given to contract the gall bladder.

Paediatric doses

The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight. The Paediatric Task Group of EANM recommends calculating the administered activity from the body weight according to the following table:

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

Fraction of adult dose:

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

The use in paediatric children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group.

In case of administration in children and adolescents under 18 no safety or efficacy data are available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy, lactation (see section 4.6), unless the likely benefit exceeds the risk.
- Age under 18 (see section 4.2) unless the likely benefit exceeds the risk.

There are no special contraindications for this product. No side effects or hypersensitivity reactions have been reported to date.

4.4 Special warnings and precautions for use

The biliary tree may not be adequately visualized in the following circumstances:
- Parenteral nutrition.
- Prolonged dieting.
- After a meal: the test should be performed with the patient fasted for six hours.
- Hepatocellular insufficiency.
- Hepatitis.

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.

For most diagnostic investigations using a nuclear medicine procedure the effective dose is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

The content of the vial is for preparation of Technetium Tc-^{99m} mebrofenin, and it must not be administered directly without labeling.

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local 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, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.
During labelling and use the compliance with radiation protection regulation is mandatory.

There are no data available on the diagnostic efficacy of the drug in the case of recurrence of the disease or when a disease is suspected to have developed as a metastasis.

IN ORDER TO MITIGATE BLADDER-IRRITATION ADEQUATE FLUID INTAKE AND FREQUENT URINATION IS NECESSARY.

IN CASE OF RENAL FAILURE, EXPOSURE TO IONIZING RADIATION MAY INCREASE, AND THIS SHOULD BE CONSIDERED DURING ACTIVITY CALCULATION.

4.5 Interaction with other medicinal products and other forms of interaction

Some drugs may influence the functioning of tested organs and ^{99m}Tc-BROMO-BILIARON binding e.g.:

Cholecystokinin and analogues	Enhance gall-bladder contraction and radioisotope excretion into the duodenum
Opioid pain killers and barbiturates	May cause spasm at the sphincter muscle of the common biliary duct and increase pressure in the bile. This increases the transfer time between bile and intestines and may improve gall bladder activity.
Morphine	Causes Oddi sphincter spasm.
Pain killers	Increase liver-duodenum transfer time
Neostigmin	Mimics choledocus obstruction
Atropin and somatostatin	Decreases the maximal reaction of the gall bladder to the standard meal
Phenobarbital	Accelerates biliar excretion
Nicotinic acid	Induces hepatotoxicity, may decrease biliar [99mTc]-Technetium-mebrofenin uptake and excretion
Chemotherapeutic treatment for which arterial liver-catheter is used	Negatively influences gall bladder mapping, since chemical gall bladder inflammation may develop

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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 always be considered.

Pregnancy

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 the mother and the foetus.

Lactation

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 and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of radioactivity in breast milk. If the administration is considered necessary, breast feeding should be interrupted for 12 hours and the expressed feeds discarded.
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.

4.7 Effects on ability to drive and use machines

Administration of the radiopharmacon does not influence the ability to drive or use machines.
In case of unexpected adverse events the ability to drive and use of machine should be considered.

4.8 Undesirable effects

No adverse events have been reported since the first marketing (1998).
Sporadic “allergic reactions” are noted in the literature, but these are inadequately evidenced and described. Based on the number of diagnostic studies performed during this time period, such symptoms and side effects should not be expected, and the frequency is lower than 1/10000.

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 suggest that these adverse effects will occur with low frequency because of the low radiation doses incurred.
For most diagnostic investigation using a nuclear medicine procedure the radiation dose delivered (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

No overdosing has been reported yet. Should this happen however, activities should primarily aim at maintaining the patient's vital functions.

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 this technetium-99m labelled compound, laxatives to aid faecal clearance is 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.

The administration of radioactive amounts higher than required causes unnecessary radiation exposure for the patient and his/her environment, thus it should be avoided. Should this still happen by mistake that is attributable to the medical staff, the actually administered value of ^{99m}Tc activity should be established in MBq, and the absorbed dose corresponding to the individual organs and the whole body must be calculated based on the dosimetric table provided. Based on the values obtained, a decision should be made whether the patient should be assigned to radiomedical procedure-treatment. The table includes absorbed dose values expressed in mGy caused during the intravenous administration of 1 MBq ^{99m}Tc-BROMO-BILIARON; and these should be multiplied by the administered activity expressed in MBq to obtain the absorbed dose values in mGy.

When dosaging follows prescriptions, a patient will receive a maximum of 2.5 mg ^{99m}Tc-BROMO-BILIARON. If by mistake or due to negligence of the medical staff the contents of a complete labeled injection vial are injected into a single patient, means administration of 5.0 mg ^{99m}Tc-BROMO-BILIARON. According to acute intravenous toxicity studies performed on mice, ^{99m}Tc-BROMO-BILIARON applied in 5 mg/body weight dose does not cause any clinical symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Technetium (^{99m}Tc) compounds
ATC-code: V09DA04.

Hepatobiliar scintigraphy is an imaging method that examines hepatic functions and the biliary system by imaging bile production and secretion, following bile pathways through the liver-gall bladder-small intestine. One of the most sensitive imaging diagnostic method to detect limited biliary flow.
The principle of hepatobiliar scintigraphic tests is that hepatocytes excrete various alkylated derivatives of iminodiacetate (IDA) labeled with Tc-99m.

At doses used for diagnostic procedures, technetium-99m mebrofenin injection does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Following intravenous injection, technetium-99m mebrofenin injection is bound to plasma proteins and carried to the liver.

Technetium-99m mebrofenin injection is taken up by active transport into hepatocytes in a manner similar to bilirubin.

Rate and extent of uptake depends on hepatic function: in case of high serum bilirubin levels the liver is not able to completely excrete [^{99m}Tc] –Technetium-mebrofenin, and in this case the amount of activity is excreted through the kidneys to a little extent (1.5-5%). In this case the kidneys, and then the bladder can be seen on the images.

[^{99m}Tc] –Technetium-mebrofenin is rapidly excreted from the blood, 1 hour after administration the residual activity in the blood is less than 1%. [^{99m}Tc] –Technetium-mebrofenin is detected in the liver already during the first minute after administration, but maximum activity can be detected only after 5-15 minutes. Hepatic excretion is characterized by a 20-25 minute half-life in normal cases.

Hepatic excretion of [^{99m}Tc] –Technetium-mebrofenin is significantly influenced by the following 3 factors: plasma albumin concentration, rate of blood circulation through the liver, and hepatocyte function. [^{99m}Tc] –Technetium-mebrofenin is excreted in an unchanged form or as bound to biliary acids. Only a small amount is excreted through the urine, if biliary ducts are not obstructed. Normal elimination route: liver - gall bladder - duodenum - intestines.
In healthy subjects, the biliary tree is visualized within 5 - 20 minutes of injection and the gall bladder within 10 - 40 minutes.

5.3 Preclinical safety data

Toxicity after single administration:
acute LD50 value of mebrofenin after intravenous injection:

LD50: 285 mg/kg body weight in mice
LD50: 250 mg/kg body weight in rats.

The maximum amount of technetium-99m mebrofenin injection given to patients is approximately 2.5 mg, and it is therefore unlikely to be toxic.

Toxicity after repeated administrations:
Non-clinical data from repeated dose-toxicity tests verified that the preparation does not pose any particular harm for humans.
No significant variations were observed in blood tests or histological studies of the major organs after the daily injection of mebrofenin for 14 consecutive days in rats.
Mutagenicity or reproduction studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tin(II)-chloride-dihydrate
Sodium-acetate trihydrate
L-ascorbic acid

6.2 Incompatibilities

The labeling reaction performed with sodium pertechnetate ^{99m}Tc sterile injection depends on the of tin level in reduced state. Thus, oxidant containing sodium pertechnetate Tc-^{99m} injection (Ph.Eur.) should not be used.

Tin(II)-chloride reduces technetium in free pertechnate (+7) to oxidation state (+4) capable for complex formation. The content of the injection vials is therefore incompatible with humidity and oxidizing media (chemical oxidizers, oxygen content in the air, etc). The substance is incompatible with any alkali, since the alkaline media facilitates tin(II) oxydation before the radioactive labeling process is executed. Therefore, the protecting cap of the injection vial should be opened only directly before the radioactive labeling process, and radioactive labeling should be performed according to the specifications prescribed in section 12.

6.3 Shelf life

Kit before reconstitution:12 months
Reconstituted product: should be used within 6 hours after preparation.

6.4 Special precautions for storage

The kit should be stored below 25ºC in the original packaging in order to ensure protection from light. Keep protected from oxidizers.
The labeled product should be stored below 25ºC and protected from light.
During storage of the labeled product effective protection and safety regulations should be adhered to.
The contents of the bottle included in the kit may only be used for the production of ^{99m}Tc-technetium labeled injection, according to the summary of product characteristics.
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings.

6.5 Nature and contents of container

Sterile, Type I glass injection vials, closed with rubber stoppers and grey plastic-aluminium flip off caps.

Pack size: kit contains 6 vials.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements for radioactive materials.
Note: ✠ (one cross)
Classification: **Group II / 3**
In accordance with 1997 CLIV Act on Health Care, (I), which is applicable under the conditions provided by providers of outpatient care or inpatient services provided by the outpatient clinic under section 3 (ga) of the Act.

7. MARKETING AUTHORISATION HOLDER

MEDI-RADIOPHARMA Ltd.
2030 Érd, Szamos u. 10-12.
Tel.: 06-23-521-261
Fax: 06 23-521-260
e-mail: mediradiopharma-ltd@mediradiopharma.hu

8. MARKETING AUTHORISATION NUMBER

OGYI-T-9941/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1998. January / 2010. April 1.

10. DATE OF REVISION OF THE TEXT

06. April 2021

11. DOSIMETRY

The table below shows the dosimetry as calculated according to publication No. 53 by the ICRP (International Commission of Radiological Protection).

	Absorbed dose mGy/MBq
Liver	$1{,}5\times10^{-2}$
Gall bladder	1.1×10^{-1}
Kidneys	6.3×10^{-3}
Hematopoetic tissue	7.0×10^{-3}

The radioactive [^{99m}Tc]-technetium is transformed into [^{99}Tc]-technetium isotope, which is practically stabile.

Radiation physical characteristics

Physical half life: 6.02 hours
Energy and yield of emitted gamma-photons: 140 keV 100%
Energy and yield of emitted beta-particles: -

^{99m}Tc-BROMO-BILIARON
HEALTHY INDIVIDUAL

Organs	Absorbed dose per unit activity administered (mGy/MBq)				
	adult	15 years old	10 years old	5 years old	1 year old
adrenals	0.0032	0.0047	0.0074	0.011	0.018
bladder wall	0.023	0.028	0.042	0.063	0.11
bone surfaces	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 intestines	0.052	0.065	0.11	0.16	0.29
ULI wall	0.092	0.11	0.19	0.29	0.55
LLI 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	0.0016	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 bone 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 tissues	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 70 kg individual).

PARENCHYMAL LIVER DISEASE

Organs	Absorbed dose per unit activity administered (mGy/MBq)				
	adult	15 years old	10 years old	5 years old	1 year old
adrenals	0.0021	0.0030	0.0046	0.0067	0.011
bladder wall	0.069	0.085	0.12	0.19	0.32
bone surfaces	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 intestines	0.019	0.024	0.039	0.060	0.11
ULI wall	0.033	0.040	0.066	0.10	0.19
LLI 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 bone 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 tissues	0.0021	0.0025	0.0036	0.0055	0.0095
Effective dose equivalent (mSv/MBq)	**0.013**	**0.016**	**0.024**	**0.037**	**0.075**

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

OCLUSION OF THE CYSTIC DUCT

Organs	Absorbed dose per unit activity administered (mGy/MBq)				
	adult	15 years old	10 years old	5 years old	1 year old
adrenals	0.0022	0.0033	0.0052	0.0079	0.013
bladder wall	0.039	0.048	0.070	0.10	0.19
bone surfaces	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
ULI wall	0.084	0.10	0.17	0.27	0.50
LLI 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
lung	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 bone marrow	0.0066	0.0075	0.0098	0.012	0.014
spleen	0.0022	0.0027	0.0046	0.0074	0.013
testis	0.0019	0.0030	0.0054	0.0086	0.016
thyroid gland	0.00015	0.00022	0.00042	0.00077	0.0017
uterus	0.013	0.017	0.027	0.040	0.066
other tissues	0.0027	0.0033	0.0048	0.0073	0.013
Effective Dose Equivalent (mSv/MBq)	**0.018**	**0.022**	**0.035**	**0.054**	**0.098**

For this product the effective dose equivalent resulting from an administered activity of 300 MBq is typically 5.4 mSv (per 70 kg individual).

OCLUSION OF THE COMMON BILE DUCT

Organs	Absorbed dose per unit activity administered (mGy/MBq)				
	adult	15 years old	10 years old	5 years old	1 year old
adrenals	0.0032	0.0047	0.0074	0.011	0.018
bladder wall	0.023	0.028	0.042	0.063	0.11
bone surfaces	0.0026	0.0033	0.0047	0.0071	0.014
breast	0.00061	0.00064	0.0013	0.0025	0.0048
gastrointestinal tract	0.11	0.12	0.16	0.28	0.96
stomach wall					
small intestine	0.0061	0.0077	0.013	0.021	0.034
ULI wall	0.052	0.065	0.11	0.16	0.29
LLI wall	0.092	0.11	0.19	0.29	0.55
kidneys	0.062	0.077	0.13	0.21	0.39
liver	0.0063	0.0074	0.011	0.016	0.025
lung	0.015	0.018	0.027	0.040	0.072
ovaries	0.0011	0.0016	0.0025	0.0040	0.0075
pancreas	0.020	0.024	0.036	0.052	0.084
red bone marrow	0.0057	0.0075	0.014	0.022	0.034
spleen	0.0070	0.0080	0.010	0.013	0.015
testis	0.0026	0.0034	0.0059	0.0096	0.016
thyroid gland	0.0015	0.0023	0.0042	0.0070	0.013
uterus	0.00012	0.00018	0.00037	0.00073	0.0017
other tissues	0.013	0.017	0.027	0.040	0.065
adrenals	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 2.9 mSv (per 70 kg individual).
Radiation exposures (newborns, congenital biliary atresia) as absorbed dose/injected activity (mGy/MBq).

Organs	Absorbed dose referred to a unit of administered activity (mGy/MBq)
Adrenals	0.033
Bladder wall	0.26
Bone surface	0.026
GI-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**

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Prior to preparation the kit is not radioactive.
BROMO-BILIARON kit and its components cannot be used directly; only the ^{99m}Tc-BROMO-BILIARON formed after labeling with ^{99m}Tc radionuclide can be administered as intravenous injection.
This radiopharmaceutical may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulation and/or appropriate licences of local competent official organisations (see section 6.6).
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.
The preparation does not contain any bacteriostatic agent.
Technetium Tc-^{99m} mebrofenin should be used within 6 hours after labeling.
The pharmaceutical preparation should be dissolved in oxidant-free sodium-pertechnetate Tc-^{99m} injection (Ph.Eur.). The solution produced is clean and colourless.
Like in the case of any other pharmaceutical preparation, if the vial is damaged during the preparation, the product must not be used.

Method of preparation of technetium Tc-^{99m} mebrofenin

Technetium Tc-^{99m} mebrofenin is prepared from the BROMO-BILIARON kit as follows:

1. During the preparation procedure a pair of waterproof gloves should be worn. Remove the plastic cap from the BROMO-BILIARON kit vial, then wipe the closing part of the bottle with alcohol to disinfect the surface.
2. Place the vial in an adequate lead shielding, and indicate date, preparation time, volume and activity appropriately.
3. Take 2-5 ml of sterile, pyrogen free, sodium-pertechnetate Tc-^{99m} solution (max 6 GBq) aseptically, with a sterile syringe protected by lead shield.
4. Aseptically add the sodium-pertechnetate Tc-^{99m} solution to the vial behind the lead-shield. Without removing the needle remove an amount of air from the vial that is necessary to maintain atmospheric pressure within the vial.
5. Shake the vial strongly 5-10 times, with upwards-downwards movements. Afterwards leave the preparation to rest at room temperature for 5 minutes.
6. Before use, visually inspect the vial for signs of solid particles and discolouration.
7. Use a sterile, radioprotected syringe aseptically. Use within 6 hours after preparation.
8. Before administration to patients, radiochemical purity must be verified according to the Radio TLC method as detailed below.

Radio-TLC method for the quantitative determination of Technetium Tc-^{99m} mebrofenin

Materials and reagents:

1. Solid phase (adsorbent): ITLC –SG (Gelman Sciences) (Label the start line 1.5 cm away from the bottom)
2. Eluent: 20% sodium chloride solution
3. Developing container: adequate chromatographic equipment, e.g. tank, Erlenmeyer flask.
4. Other: forceps, scissors, syringe, injection needle, adequate counter device

Procedure:

No air can penetrate the bottle containing the labeled product. The bottle – as it contains radioactive solution – should be kept in a lead shielding.

1. Drop 5-5 µl (approx. 1MBq/µ) of the test solution with a syringe and needle at 1.5 cm distance from one end of the 1.5 x20 cm ITLC-SG plate (3 plates)
2. Using forceps place the plate vertically in the chromatographic tank so that the starting line is in the vicinity of the running solution. Cover the chromatographic tank.
3. Develop chromatograms with 20% sodium-chloride eluent to an approx. 15 cm front distance.
4. After development chromatograms are dried. Detection of radioactivity distribution is performed with an appropriate gamma-scanner.
5. Reference R_f values:
   labeled colloid (reduced, hydrolized ^{99m}TC) R_f=0.0
   labeled compound: R_f = 0.4 – 0.5
   free pertechnate: R_f = 0.9 – 1.0
6. The % ratio of the labeled preparation is calculated as % of total activity.

The amount of ^{99m}Tc-mebrofenin complex should not be less than 94% within 6 hours.