The effective dose equivalent resulting from an administered activity of 185 MBq to a patient of 70 kg body weight is 2.4 mSv.

Patients with 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	0.07	0.1	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
GI tract:					
Stomach wall	0.005	0.0062	0.0093	0.015	0.025
Small intestine	0.047	0.059	0.096	0.15	0.26
ULI wall	0.084	0.1	0.17	0.27	0.5
LLI wall	0.058	0.072	0.12	0.19	0.37
Kidneys	0.0055	0.0065	0.0097	0.014	0.023
Liver	0.01	0.013	0.02	0.03	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	0.003	0.0054	0.0086	0.016
Thyroid	0.00015	0.00022	0.00042	0.00077	0.0017
Uterus	0.013	0.017	0.027	0.04	0.066
Other tissues	0.0027	0.0033	0.0048	0.0073	0.013
Effective dose [mSv/MBq]	**0.018**	**0.022**	**0.035**	**0.054**	**0.098**

The effective dose equivalent resulting from an administered activity of 185 MBq to a patient of 70 kg body weight is 3.3 mSv.

Patients with 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	0.02	0.024	0.036	0.056	0.1
Bone surfaces	0.0024	0.003	0.0042	0.0065	0.013
Breast	0.0023	0.0023	0.004	0.0064	0.012
GI tract:					
Stomach wall	0.0037	0.0056	0.01	0.017	0.03
Small intestine	0.0036	0.0044	0.0083	0.014	0.024
ULI wall	0.0052	0.0064	0.012	0.021	0.035
LLI wall	0.0015	0.0018	0.0033	0.0057	0.01
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	0.02	0.03	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 tissues	0.0023	0.0028	0.004	0.006	0.011
Effective dose [mSv/MBq]	**0.0096**	**0.012**	**0.018**	**0.026**	**0.046**

The effective dose equivalent resulting from an administered activity of 185 MBq to a patient of 70 kg body weight is 1.8 mSv.

Congenital biliary atresia in newborns

Adrenals	0.033
Bladder wall	0.26
Bone surface	0.026
GI-tract Stomach wall Small intestine Upper large intestine wall Lower large intestine wall	 0.036 0.070 12 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 [mSv/MBq]	**0.85**

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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.
As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised, the product should not be used. Therefore, prior to the radiolabelling procedure carefully inspect the vial for the presence of damage, in particular cracks.
PoltechMBrIDA is designed for labelling with technetium-99m as eluate of sodium pertechnetate-^{99m}Tc obtained from the ^{99}Mo/^{99m}Tc radionuclide generator. The labeling procedure should ensure sterility of the preparation.

Labelling procedure:
- Place the kit vial containing the lyophilisate in an appropriate radioprotective shield.
- Using a syringe inject (by piercing the rubber stopper) about 5 ml of eluate of sodium pertechnetate-^{99m}Tc (or eluate with activity 370 – 1500 MBq pre-diluted with sterile saline) into the vial.
- Using the same syringe relieve the excess of pressure in the vial by withdrawing the equivalent volume of gas.
- Shake the contents of the vial until complete dissolution of the powder (about 2 min.). Keep the vial in the shield all the time.
- Incubate the vial at the room temperature for not less than 30 min.
- The resultant solution is a ready-to-use solution for injection.

^{99m}Tc-MBrIDA preparation should be used within 5 hours after completing the labelling procedure.

Quality control of ^{99m}Tc-MBrIDA:
Radiochemical purity measurement by chromatography in two systems:
1. ITLC-SG plates, mixture of acetonitrile: water (3:1 v/v) as developing solution.
   Under these conditions:
   - free pertechnetate ion, $^{99m}TcO_4^-$ and ^{99m}Tc-MBrIDA complex migrates with the solvent front (R_f = 0.8 - 1.0)
   - non-bound reduced ^{99m}Tc remains at the origin (R_f = 0.0)

2. ITLC-SG plates (impregnated with 10% NaCl solution, dried at 80°C), saturated sodium chloride as developing solution.
   Under this conditions:
   - non-bound, reduced ^{99m}Tc and ^{99m}Tc-MBrIDA complex remain at the origin (R_f = 0.0)
   - free pertechnetate ion $^{99m}TcO_4^-$ migrates with the solvent front (R_f = 0.9 – 1.0)

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POLATOM

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PoltechMBrIDA, 20 mg,
kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 vial contains:
N-[2,4,6-trimethyl-3-bromacetanilid] iminodiacetic acid sodium salt, 20 mg
The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Kit for radiopharmaceutical preparation
Lyophilisate for solution for injection

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.

The radiopharmaceutical ^{99m}Tc-MBrIDA is intended for hepatobiliary imaging and for hepatobiliary function studies.

4.2 Posology and method of administration
Product intended for intravenous administration.
This radiopharmaceutical may be used only by authorized persons. Safety precautions for careful handling this radiopharmaceutical should be observed.

The radiopharmaceutical ^{99m}Tc-MBrIDA is administered intravenously after labelling with sterile, oxidant-free eluate of sodium pertechnetate (^{99m}Tc) solution from a radionuclide generator ^{99}Mo/^{99m}Tc, in accordance with the labelling instructions – see section 12.

For patient preparation – see section 4.4.

For radiolabelling of one kit vial the sodium pertechnetate (^{99m}Tc) solution with activity of 370 - 1500 MBq should be used. This amount is sufficient to perform the examination in several (1-10) adult patients.

Posology
Adults
The activity recommended for a single examination in adult patient ranges from 111 to185 MBq. Higher administered activity may be justifiable in hyperbilirubinaemia.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activity for children is adjusted according to body weight or surface area.

The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below:

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

(Paediatric Task Group, EANM)

In very young children (up to 1 year) a minimum dose of 20 MBq is necessary in order to obtain images of sufficient quality. In neonates with hyperbilirubinaemia a minimum administered activity of 37 MBq ^{99m}Tc-MBrIDA is recommended as up to 24 h delayed images are often necessary.
The examination can be started immediately after injection.
In several cases for improving the diagnostic value of examination (gall bladder contraction) there are used some physiological (fatty meal) or pharmacological stimuli (cholecystokinin analogues, morphine sulphate, phenobarbital).

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
Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Pregnancy, see section 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.

Paediatric population
For information on the use in paediatric population, see section 4.2.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults – see section 11.

Patient preparation
Depending on indications an adult patient must have fasted for 6 – 24 h before administration of the radiopharmaceutical and avoid the products which may affect the examination result.

The biliary tree may not be adequately visualized in the following circumstances:
- parenteral nutrition,
- prolonged dieting (more than 24 h),
- after a meal (the test should be performed at least 2 h and more preferably 6 h after the last meal),
- hepatocellular insufficiency,
- hepatitis.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium free”.

4.5 Interactions 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. Morphine sulphate is commonly used to augment the bile flow into the gall bladder.
Cholecystokinin and its analogs cause the gall bladder to contract, thereby reducing the radiotracer flow into it. Fat meals and some food supplements may also stimulate gall bladder contraction.
In patients parenterally feeding or fasting for 24 – 48 h intraluminal pressure in the gall bladder may rise, which prevents entry of the radiopharmaceutical.
Phenobarbital and ursodeoxycholic acid enhance biliary excretion of the radiotracer.

Other pharmaceuticals and substances known to affect gall bladder, sphincter of Oddi or to change ^{99m}Tc-iminodiacetates biodistribution are listed below:

Atropine
Benzodiazepine
Erythromycin
Estrogen
Ethanol
Glyceryl trinitrate
Glucagon
Naloxone
Nicotine
Nifedipine
Nicardipine
Nitric oxide
Pancreatic enzymes
Pirenzepine
Progesterone
Prostigmine
Somatostatine analogs
Theophylline

Gall bladder visualization may be adversely affected in patients receiving chemotherapy via an indwelling hepatic artery catheter as a chemical cholecystitis has been described as a consequence of the chemotherapy and its route of administration.

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.
Where uncertainly exists it is important that the radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

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

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 4 hours and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Tabulated list of adverse reactions
The frequencies of undesirable effects are defined as follows:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data)

Immune system disorders Not known	Hypersensitivity

For each patient, exposure to ionising radiation must be justified 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 reactions are expected to occur with a low probability.

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.

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.

Adverse reactions may be reported to Marketing Authorisation Holder.

4.9 Overdose

In the event of the administration of a radiation overdose with ^{99m}Tc-MBrIDA injection, 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 ^{99m}Tc-MBrIDA injection, laxatives to aid faecal clearance is recommended.

In patients with severe jaundice, when significant fraction of injected activity is excreted through kidneys overall tissue radiation may be reduced by implementing a regime of forced diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical, technetium (^{99m}Tc) compounds, ATC code: V09DA04

At the chemical concentrations of radiopharmaceutical and excipients used for diagnostic procedures ^{99m}Tc-MBrIDA does not appear to exert any pharmacodynamic effect.

5.2 Pharmacokinetic properties

Distribution

Following intravenous injection, ^{99m}Tc-MBrIDA is bound to plasma proteins and carried to the liver, where it is rapidly extracted from the plasma by the hepatocytes, through which it is transported and secreted unchanged into the biliary canaliculi.

Organ uptake

Less than 1% of administered activity remains in plasma 1 hour after injection. In healthy subjects the liver is typically seen within the first minute after injection and hepatic activity peaks at approximately 11-12 minutes.

The liver $T_{1/2}$ is 25 - 30 minutes in health, but this may be influenced by plasma albumin concentration, hepatic blood flow and hepatocyte function. In healthy subjects, the biliary tree is visualized within 5 - 20 minutes of injection and the gall bladder within 10 - 40 minutes. The intestinal activity is visualized by 30 to 60 minutes.

Elimination

In healthy individuals the mean percent injected dose excreted in the urine during the first 3 hours is 1% (0.4 to 2.0%) but elevated serum bilirubin levels increase renal excretion of ^{99m}Tc-MBrIDA.

In patients with hyperbilirubinaemia, the percent injected dose remaining in the blood at 10 minutes may be twice as high (or more) than the level in health and hepatobiliary transit may be delayed.

5.3 Preclinical safety data

This product is not intended for regular or continuous administration.
Very low toxicity of the complex (LD_{50} = 250 mg/kg) allows safe administration of diagnostic doses. No immunization effects have been observed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride dihydrate
Nitrogen

6.2 Incompatibilities

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

6.3 Shelf life

Kit - 1 year.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution: 5 hours. Store below 25°C in a suitable radiation lead shield.

6.4 Special precautions for storage

Store in a refrigerator (2°C- 8°C).
During transportation (not longer than 7 days) up to 35°C.
For storage conditions after radiolabelling 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

10 ml glass vials sealed with a rubber stopper and aluminium cap in cardboard box.
3 vials
6 vials
Not all pack sizes may be marketed.

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 licenses 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.
Contents of the vial are intended only for use in the preparation of medicinal product and are not to be administered directly to the patient without first undergoing the preparative procedure.
For instructions on extemporary preparation of the medicinal product before administration, see section 12.
If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.
Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.
The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc) is added, adequate shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting or any other biological fluids. 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

Narodowe Centrum Badań Jądrowych
ul. Andrzeja Sołtana 7
05-400 Otwock, Poland
Phone: +48 22 7180700
Fax: +48 22 7180350
e-mail: polatom@polatom.pl

8. MARKETING AUTHORISATION NUMBER

Marketing authorization number: R/3270

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 22.04.1991
Date of latest renewal: 27.08.2013

10. DATE REVISION OF THE TEXT

27.04.2017

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) radionuclide generator and decays 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, in view of its long half-life of 2.13 x 10^5 years, can be regarded as quasi stable.
The projected radiation doses to organs and tissues of a patient after intravenous injection of ^{99m}Tc-IDA-iminodiacetic acid derivatives labelled with technetium are given in the table below. These data are adopted from ICRP 53 and 80 *(International Commission of Radiological Protection)*.

Organ	**Absorbed dose per unit activity administered [mGy/MBq]**				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.0037	0.0048	0.0075	0.011	0.018
Bladder wall	0.022	0.028	0.037	0.043	0.076
Bone surfaces	0.0038	0.0047	0.0068	0.01	0.019
Brain	0.000034	0.00004	0.000079	0.00014	0.00026
Breast	0.00048	0.00065	0.0014	0.0025	0.0048
Gall bladder wall	0.11	0.12	0.16	0.28	0.95
GI tract:					
Stomach wall	0.0056	0.0078	0.013	0.021	0.034
Small intestine	0.044	0.055	0.09	0.14	0.25
Colon	0.074	0.095	0.15	0.25	0.47
Upper low int.	0.086	0.11	0.18	0.29	0.54
Lower low int.	0.059	0.075	0.12	0.2	0.38
Heart	0.0018	0.0024	0.004	0.0063	0.012
Kidneys	0.0061	0.0075	0.011	0.016	0.025
Liver	0.014	0.018	0.027	0.04	0.071
Lungs	0.0013	0.0019	0.0028	0.0046	0.0086
Muscles	0.0029	0.0036	0.0053	0.0078	0.014
Oesophagus	0.00041	0.0006	0.00091	0.0017	0.0032
Ovaries	0.019	0.024	0.035	0.05	0.083
Pancreas	0.0056	0.0076	0.014	0.022	0.034
Red marrow	0.0039	0.0047	0.0063	0.0077	0.01
Skin	0.00089	0.0011	0.0017	0.0027	0.005
Spleen	0.0027	0.0036	0.0063	0.01	0.017
Testes	0.0015	0.0023	0.0041	0.0062	0.012
Thymus	0.00041	0.0006	0.00091	0.0017	0.0032
Thyroid	0.00014	0.00023	0.00042	0.00077	0.0019
Uterus	0.013	0.017	0.026	0.038	0.061
Other organs	0.0037	0.0046	0.0066	0.0097	0.016
Effective dose [mSv/MBq]	**0.017**	**0.021**	**0.029**	**0.045**	**0.1**

The effective dose equivalent resulting from an administered activity of 185 MBq to a patient of 70 kg body weight is 3.15 mSv.

Patients with parenchymal liver disease

Organ	**Absorbed dose per unit activity administered [mGy/MBq]**				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.0021	0.003	0.0046	0.0067	0.011
Bladder wall	0.069	0.085	0.12	0.19	0.34
Bone surfaces	0.0017	0.0021	0.003	0.0046	0.0087
Breast	0.00056	0.00057	0.001	0.0018	0.0035
Gall bladder wall	0.035	0.04	0.053	0.092	0.3
GI tract:					
Stomach wall	0.0027	0.0034	0.0058	0.0094	0.016
Small intestine	0.019	0.024	0.039	0.06	0.11
ULI wall	0.033	0.04	0.066	0.1	0.19
LLI wall	0.024	0.03	0.05	0.079	0.15
Kidneys	0.0066	0.0079	0.011	0.017	0.027
Liver	0.01	0.013	0.02	0.028	0.05
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	0.01	0.017
Red marrow	0.0038	0.0045	0.006	0.0074	0.0094
Spleen	0.0015	0.0019	0.0032	0.0052	0.009
Testes	0.0025	0.0038	0.0067	0.011	0.02
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 [mSv/MBq]	**0.013**	**0.016**	**0.024**	**0.037**	**0.075**