PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

CHOLETEC®

45 milligram Kit for the Preparation of Technetium Tc 99m Mebrofenin for Injection

Diagnostic Radiopharmaceutical, V09DA04

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CHOLETEC® (Technetium Tc 99m Mebrofenin) is indicated for use as a hepatobiliary imaging agent.

1.1 Pediatrics

Pediatric (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Technetium Tc 99m Mebrofenin is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The patient should be in a fasting state, preferably for 4 hours prior to imaging. False positives (non-visualization) may result if the gallbladder has been emptied by ingestion of food.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

An interval of at least 24 hours should be allowed before repeat administration.

It is anticipated that any Tc-99m Generator approved in Canada would be suitable as a source of sodium pertechnetate Tc-99m, however, complete data is not available to confirm this. Bracco Imaging Canada should be contacted for any available information.

4.2 Recommended Dose and Dosage Adjustment

The suggested intravenous dose range of Technetium Tc 99m Mebrofenin in the average patient (70 kg) is:

- Non-jaundiced patient: 74 - 185 MBq (2 - 5 mCi)
- Patient with serum bilirubin level greater than 1.5 mg/dL: 111 - 370 MBq (3 - 10 mCi).

4.3 Reconstitution

Please refer to section 4.7 Instructions for Preparation and Use.

4.4 Administration

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

4.6 Image Acquisition and Interpretation

In jaundiced patients, the percent injected dose remaining in the blood at 10 minutes is at least twice as high compared to patients with normal bilirubin levels. Hepatobiliary transit may be delayed and visualization times increased. As a consequence, the quality of the images obtained is usually diminished.

4.7 Instructions for Preparation and Use

The CHOLETEC® kit is supplied as a multi-dose vial containing lyophilized sterile powder (with 45 mg mebrofenin per vial) which allows for preparation of Tc-99m Mebrofenin when combined with Tc-99m sodium pertechnetate eluate (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). The Tc-99m sodium pertechnetate eluate should be less than 2 hours old, and must be obtained from a generator eluted within the last 24 hours. The generator is not supplied with the kit.

Radiochemical purity of the reconstituted/labelled product should be checked prior to patient administration. At 15 minutes after sample preparation, determine the percent free pertechnetate Tc 99m and percent reduced hydrolyzed Tc 99m using the following or equivalent procedures.

INSTRUCTIONS FOR PREPARATION

Preparation of Technetium Tc 99m Mebrofenin is done by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.
2. Place reaction vial in an appropriate lead shield.
3. Swab the rubber closure of the reaction vial with a germicide.
4. Inject 1 to 5 mL sterile additive free sodium pertechnetate Tc 99m injection containing up to 3700 MBq (100 mCi) Tc 99m into the reaction vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution.

NOTE: if sodium pertechnetate Tc 99m injection must be diluted for use with CHOLETEC® (Kit for the Preparation of Technetium Tc 99m Mebrofenin), only Sodium Chloride Injection USP without preservatives should be used.

5. Secure the lead shield cover. Swirl the vial gently to mix contents and let stand for 15 minutes.
6. Record the date and time of preparation on pressure-sensitive label.
7. Affix pressure-sensitive label to shield.
8. Examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
9. Measure the radioactivity by a suitable calibration system and record on the shield of label prior to patient administration.
10. Withdraw material with a sterile lead shielded syringe for use within 18 hours of preparation.

Radiochemical Purity Determination:

Percent (%) Free Pertechnetate Tc 99m

Support Media: Varian/ANSYS Toxigram sheets (1.0 x 12.5 cm strips). Mark the origin at 1.5 cm from one end.

Developing solvent: Saturated sodium chloride solution.

Method:

1. Spot a sample (1 to 5 µL) of the preparation at the origin.
2. Immediately develop in NaCl chamber until solvent front reaches 10 to 12 cm (about 25 minutes).
3. Remove strip and dry.
4. Cut the strip into two segments halfway between the origin and solvent front.
5. Count each segment.

$$\% \text{ free pertechnetate Tc 99m} = \frac{A}{A+B} \times 100$$

Where, A = net counts of segment containing solvent front;
B = net counts of segment containing origin.

Percent (%) Reduced Hydrolyzed Tc 99m

Support media: Gelman ITLC-SG (1.0 x 12.5 cm strips). Mark the origin at 1.5 cm from one end.

Developing Solvent: Acetonitrile: water (3:1).

Method:

1. Spot a sample of the preparation at the origin.
2. Immediately develop in acetonitrile: water chamber until solvent front reaches 10 to 12 cm (about 10 minutes).
3. Remove strip and dry.
4. Cut the strip into two segments halfway between the origin and solvent front.
5. Count each segment.

$$\% \text{ reduced hydrolyzed Tc-99m} = \frac{C}{C+D} \times 100$$

Where, C = net counts of segment containing origin;
D = net counts of segment containing solvent front.

The total percent of free pertechnetate Tc 99m and percent reduced hydrolyzed Tc 99m should not exceed 10%.

4.8 Radiation Dosimetry

The estimated absorbed radiation doses[1,2] to organs and tissues of an average (70 kg) individual from an intravenous injection of 370 MBq (10 mCi) of Technetium Tc 99m Mebrofenin are shown in Table 1.

Table 1 - Estimated Absorbed Radiation Doses+

	Patients with Normal Bilirubin Levels* (bilirubin $\leq$ 1.5 mg/dL)		Severely Jaundiced Patients** (bilirubin $\geq$ 10 mg/dL)	
Tissue	mGy/370MBq	rads/10mCi	mGy/370MBq	rads/10mCi
Total Body	2.0	0.2	1.7	0.17
Liver	4.7	0.47	8.1	0.81
Gallbladder wall	13.7	1.37	12.5	1.25
Small intestine	29.9	2.99	16.1	1.61

[1] Loberg, M.D., Buddemeyer, E.V.: Application of pharmacokinetic modelling to the radiation dosimetry of hepatobiliary agents. In Third International Radiopharmaceutical Dosimetry Symposium, FDA No. 81-8166, U.S. Department of Health and Human Services, Public Health Service, FDA, Bureau of Radiological Health, Rockville, MD (1981) pp. 318-332.

[2] Values for S: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

	Patients with Normal Bilirubin Levels* (bilirubin $\leq$ 1.5 mg/dL)		Severely Jaundiced Patients** (bilirubin $\geq$ 10 mg/dL)	
Upper large intestinal wall	47.4	4.74	24.8	2.48
Lower large intestinal wall	36.4	3.64	19.7	1.97
Kidney	2.2	0.22	1.9	0.19
Urinary bladder wall	2.9	0.29	24.2	2.42
Ovaries	10.1	1.01	6.4	0.64
Testes	0.5	0.05	1.1	0.11
Red marrow	3.4	0.34	2.5	0.25

+ Method of Calculation:

*Bilirubin $\leq$ 1.5 mg/dL
Calculations assume that 98% of the injected activity is taken up by the liver, activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

**Bilirubin $\geq$ 10 mg/dL (mean 21.8 mg/dL)
Calculations assume that 66% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

Effective Dose Equivalent: unknown as the data on which the original indication was authorized is not available.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Lyophilized sterile powder /45 mg mebrofenin/vial	Hydrochloric acid, methylparaben, propylparaben, sodium hydroxide and stannous fluoride

CHOLETEC® (Kit for the Preparation of Technetium Tc 99M Mebrofenin) is supplied in kits of 10 reaction vials. Each vial contains a nonradioactive, sterile, non-pyrogenic lyophilized mixture of 45 mg mebrofenin, 0.73 mg stannous fluoride, 4.5 mg methylparaben, and 0.5 mg propylparaben. The pH has been adjusted with hydrochloric acid or sodium hydroxide prior to lyophilization. The lyophilized vial contents are sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 4.2 - 5.7.

When sterile, pyrogen-free sodium pertechnetate Tc 99m is added to the vial, the diagnostic agent Technetium Tc 99m Mebrofenin is formed and can be administered by intravenous injection. The structure of the complex is unknown.

Kit contents:
10 sterile multi-dose reaction vials, 20 pressure-sensitive labels for Technetium Tc 99m Mebrofenin; 1 package insert.

6.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principle photon that is useful for the detection and imaging studies is listed in Table 3.

Table 3 - Principal Radiation Emission Data

Radiation	Mean Disintegration (%)	Mean Energy (keV)
Gamma-2	89.07	140.5

6.2 External Radiation

The specific gamma ray constant for Tc 99m is 5.4 micro-coulombs/Kg-MBq-hour (0.78 R/hour-millicurie) at 1 cm. The first half value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of lead is shown in Table 4. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of lead with a 0.25 cm thickness will attenuate the radiation emitted by a factor of about 1,000.

Table 4 - Radiation Attenuation by Lead (Pb) Shielding

Pb Shield thickness (cm)	Coefficient of Attenuation
0.017	0.5
0.08	0.1
0.16	0.01
0.25	0.001
0.33	0.0001

To correct for physical decay of Technetium Tc 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 5.

Table 5 - Physical Decay Chart Tc 99m half-life 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501	13	0.126

* Calibration Time

7 WARNINGS AND PRECAUTIONS

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product 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 regulations and/or appropriate licenses of local competent official organizations.

The contents of this kit are not radioactive. However, following the addition of Tc99m radionuclide, adequate shielding of the final preparation should be maintained to minimize radiation exposure to occupational workers and patients.

Contents of this kit are intended for use in the preparation of Technetium Tc 99m Mebrofenin and are not to be directly administered to the patient.

The Tc 99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, sodium pertechnetate Tc 99m containing oxidants should not be used.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

The components of this kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the pertechnetate solution and the withdrawal of doses for patient administration.

Tc 99m Mebrofenin should be formulated no more than 18 hours prior to clinical use.

General

Delayed or non-visualization of the gallbladder may occur in the immediate post-prandial period or after prolonged fasting or parenteral feeding. Functional biliary obstruction may accompany chronic cholecystitis or pancreatitis. In addition, patients with hepatocellular disease may show non-visualization or delayed visualization of the gallbladder. Delayed intestinal transit may also be noted in such patients. Juvenile hepatitis may be associated with gallbladder non-visualization and the failure to visualize activity in the intestine. Administration of meperidine or morphine may delay intestinal transit of the imaging agent and may result in non-visualization. Septic patients may show absent or delayed hepatobiliary clearance. Thus, a positive finding does not of itself permit a differential diagnosis of any of the above conditions and should be evaluated in the context of the total clinical picture and results of other diagnostic modalities.

Carcinogenesis and Mutagenesis

No long-term animal studies have been performed to evaluate carcinogenic potential.

Contamination

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use. If blood or urine gets onto clothing such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Reproductive Health: Female and Male Potential

Animal reproduction studies have not been conducted with Technetium Tc 99m Mebrofenin.

- **Fertility**

  It is not known whether Technetium Tc 99m Mebrofenin can have an effect on reproductive capacity.

- **Teratogenic Risk**

  It is not known whether Technetium Tc 99m Mebrofenin can cause fetal harm when administered to a pregnant woman.

Sensitivity/Resistance

The theoretical possibility of allergic reactions should be considered in patients who receive multiple doses.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with Technetium Tc 99m Mebrofenin. It is also not known whether Technetium Tc 99m Mebrofenin can cause fetal harm when administered to a pregnant woman or can have an effect on reproductive capacity.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a person of childbearing capability, should be performed during the first 10 days following the onset of the menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

7.1.2 Breast-feeding

Technetium Tc 99m is excreted in human milk during lactation. Where an assessment of the risk to benefit ratio suggests the use of this product in nursing mothers, formula feeding should be substituted for breast feeding.

7.1.3 Pediatrics

Pediatric (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

There is no evidence to suggest that use in the geriatric population is associated with differences in the safety or effectiveness of this product.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Urticaria and rash have been reported but are uncommon. Although not specifically associated with Technetium Tc 99m Mebrofenin, cases of pruritic rash, chills and nausea have been reported with the use of related compounds but are uncommon. Infrequently, death has been reported in association with the use of this class of agents.

8.2 Clinical trial adverse reactions

The clinical trial data on which the original indication was authorized is not available.

9 DRUG INTERACTIONS

The drug interaction data on which the original indication was authorized is not available.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established as the data on which the original indication was authorized is not available.

9.5 Drug-Food Interactions

Interactions with food have not been established as the data on which the original indication was authorized is not available.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established as the data on which the original indication was authorized is not available.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established as the data on which the original indication was authorized is not available.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Mebrofenin is an iminodiacetic acid (HIDA) derivative with unknown pharmacologic action at the recommended doses.

10.2 Pharmacodynamics

The pharmacodynamic data on which the original indication was authorized is not available.

10.3 Pharmacokinetics

The absorption, distribution and metabolism data on which the original indication was authorized is not available.

Elimination

Following intravenous administration in subjects with normal bilirubin levels, Technetium Tc 99m Mebrofenin was rapidly cleared from the circulation. The mean percent injected dose remaining in the blood at 10 minutes was 17%. The injected activity was cleared through the hepatobiliary system with visualization of the liver by 5 minutes and maximum liver uptake occurring at 11 minutes post injection. Hepatic duct and gallbladder visualization occurred by 10 to 15 minutes and intestinal activity was visualized by 30 to 60 minutes in subjects with normal hepatobiliary function. The mean percent injected dose excreted in the urine during the first 3 hours was 1% (0.4 to 2.0%).

Elevated serum bilirubin levels increase renal excretion of Tc 99m HIDA agents. In two studies in which Tc 99m mebrofenin was administered to patients having elevated serum bilirubin levels 9.8 mg/dL (1.7 to 46.3 mg/dL), the mean percent injected dose excreted in the urine during the first 3 hours was 3% (0.2 to 11.5%). The mean percent injected dose excreted in the urine during 3-24 hours was 14.9% (0.4 to 34.8%).

In jaundiced patients, the percent injected dose remaining in the blood at 10 minutes is at least twice as high compared to patients with normal bilirubin levels. Hepatobiliary transit may be delayed and visualization times increased. As a consequence, the quality of the images obtained is usually diminished (see 4.6 Image Acquisition and Interpretation).

11 STORAGE, STABILITY AND DISPOSAL

Store the kit as supplied at 15 - 30°C prior to reconstitution. After preparation, CHOLETEC® should be stored at room temperature and used within 18 hours. Do not use the kit beyond the expiration date stamped on the box.

12 SPECIAL HANDLING INSTRUCTIONS

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

The receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent organization.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to ensure minimum radiation exposure to occupational workers.

It is recommended to use protective equipment (e.g. gloves, safety glasses, lab coat, tongs) and appropriate shielding to minimize radiation exposure.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

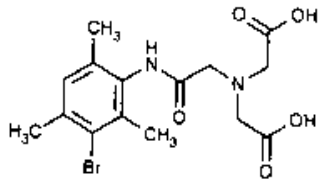
Drug Substance

Proper name: mebrofenin

Chemical name: (2,2' - [[2-[(3-Bromo-2,4,6-Trimethylphenyl)-amino]-2-oxoethyl]imino]bisacetic acid)

Molecular formula and molecular mass: $C_{15}H_{19}BrN_2O_5$ 387.226 g/mol

Structural formula:



14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether CHOLETEC® affects fertility in males or females.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if uptake into the cell nucleus occurs.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

CHOLETEC®

Kit for the Preparation of Technetium Tc 99m Mebrofenin

Read this carefully before you start taking **CHOLETEC®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CHOLETEC®**.

What is CHOLETEC® used for?

CHOLETEC® is indicated as a hepatobiliary imaging agent.

How does CHOLETEC® work?

CHOLETEC® is a radioactive diagnostic imaging agent used to examine the liver, hepatic duct and gallbladder.

What are the ingredients in CHOLETEC®?

Medicinal ingredients: mebrofenin

Non-medicinal ingredients: hydrochloric acid, methylparaben, propylparaben, sodium hydroxide and stannous fluoride.

CHOLETEC® comes in the following dosage forms:

Kit for the preparation of Technetium Tc 99m Mebrofenin for intravenous injection.

Do not use CHOLETEC® if:

- you are allergic to mebrofenin or any of the non-medicinal ingredients of CHOLETEC®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive CHOLETEC®. Talk about any health conditions or problems you may have, including if you:

- are pregnant, or planning to become pregnant;
- are breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CHOLETEC®:

- No interactions have been established as the data on which the original indication was authorized is not available.

How to take CHOLETEC®:

- CHOLETEC® will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.

Usual dose:

Your healthcare professional will decide on the dose that is right for you. The dose depends on your medical condition.

Overdose:

If you think you, or a person you are caring for, have received too much CHOLETEC®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using CHOLETEC®?

These are not all the possible side effects you may have when taking CHOLETEC®. If you experience any side effects not listed here, tell your healthcare professional.

- Rash
- Itching

In addition, chills and nausea have been reported with the use of similar products. Infrequently, death has been reported in association with the use of this class of agents.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

CHOLETEC® should be stored at 15 - 30°C before and after preparation.

Keep out of reach and sight of children.

If you want more information about CHOLETEC®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.braccoimaging.com, or by calling 1-800-465-5820.

This leaflet was prepared by Bracco Imaging Canada.

Last Revised May 31, 2022