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SUMMARY OF PRODUCT CHARACTERISTICS
(Br-HIDA)

1. NAME OF THE MEDICINAL PRODUCT

BROMEZIDA **kit for radiopharmaceutical preparation (Br-HIDA)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

N-(3-bromo-2,4,6-trimethylphenylcarbamoyl methyl)-iminodiacetic acid (Br-HIDA), as sodium salt 41.5 mg/vial

BROMEZIDA is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection (not included in this kit) to prepare technetium-99m Br-HIDA injection.

Technetium (^{99m}Tc) disintegrates with the emission of gamma radiation with an energy of 140 keV and a half-life of 6 hours to technetium (^{99m}Tc) which can be regarded as quasi stable.

Excipients:

This medicinal product contains sodium: 0.30 mg/ml.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After reconstitution with Sodium Pertechnetate (^{99m}Tc) 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.

Adult doses

In adults, the dose is 150 to 300 MBq, other doses may be justifiable.

Paediatric doses

The dose to be administered in a child should be a fraction of the adult dose calculated from the body weight.

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

Commencement of the examination as sequential or functional scintigraphy immediately after injection.

Cholocystokinins 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.

4.4 Special warnings and precautions for use

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.

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.

Excipients:

Before reconstitution the vial contains sodium 0.30 mg mg/ml. This needs to be taken into considerations for patients on a controlled sodium diet.

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 Br-HIDA injection in bile.

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.

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 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 uncertainly exists it is important that the radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Pregnancy

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

Breastfeeding

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 activity in breast milk.

If the administration is considered necessary the breast feeding should be interrupted for 4 hours and the expressed feeds discarded. The interruption time is based such that the dose to the infant should be less than 1 mSv.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions have not been reported.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred.

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

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Technetium (^{99m}Tc) compounds.

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

5.2 Pharmacokinetic properties

Following intravenous injection, Technetium-99m Br-HIDA injection is bound to plasma proteins and carried to the liver. It is cleared rapidly from the plasma, less than 1% of administered activity remaining 1 hour after injection.

Technetium-99m Br-HIDA injection is taken up by active transport into hepatocytes in a manner similar to bilirubin, reaching peak activity in the liver in 12 minutes. The liver T1/2 is 25 - 30 minutes in health but this may be influenced by plasma albumin concentration, hepatic blood flow and hepatocyte functions. Tracer can be excreted unchanged into bile or bound to bile salts either within the hepatocyte or immediately after excretion. Small amounts only are excreted in the urine unless there is a significant biliary obstruction.

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:

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

LD50: 285 mg/kg body weight in mice

LD50: 250 mg/kg body weight in rats.

The maximum amount of technetium-99m Br-HIDA injection given to patients is approximately 0.6 mg/kg. This is a factor 500 lower than the animal LD50, and it is therefore unlikely to be toxic.

Toxicity after repeated administrations:

No significant variations were observed in blood tests or histological studies of the major organs after the daily injection of Br-HIDA 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

Stannous chloride dihydrate 0.52 mg

6.2 Shelf life

12 month

After radiolabeling: 5 hours. Do not store above 25°C after radiolabeling. Do not refrigerate or freeze.

6.3 Special precautions for storage

Store in a refrigerator (2°C-8°C). Keep the vials in the outer carton in order to protect from light.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.4 Nature and contents of container

The labelled 10 ml injection vials are closed with rubber stopper and aluminum cap. One box contains six (6) vials, one Instruction Manual and one Quality Certificate.

6.5 Special precautions for disposal and other handling

Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

Any unused product or waste material should be disposed of in accordance with local requirements for radioactive material.

7. DOSIMETRY

The table below shows the dosimetry of the radiation doses absorbed, compared with the doses of technetium (^{99m}Tc) Br-HIDA administered, are the following in healthy adults at $T_{1/2}$ (6.02 hours):

Gall bladder : 1.1 x 10-1 mGy/MBq
Liver : 1.5 x 10-2 mGy/MBq
Hematopoietic tissue: 7.0 x 10-3 mGy/MBq
Kidneys : 6.3 x 10-3 mGy/MBq

TECHNETIUM – LABELLED IMINODIACETIC ACID (IDA) DERIVATES

Technetium-99m 6.02 hours

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	3.2E-03	4.7E-03	7.4E-03	1.1E-02	1.8E-02
Bladder wall	2.3E-02	2.8E-02	4.2E-02	6.3E-02	1.1E-01
Bone surfaces	2.6E-03	3.3E-03	4.7E-03	7.1E-03	1.4E-02
Breast	6.1E-04	6.4E-04	1.3E-03	2.5E-03	4.8E-03
Gall bladder wall	1.1E-01	1.2E-01	1.6E-01	2.8E-01	9.6E-01
GI tract:					
– Stomach wall	6.1E-03	7.7E-03	1.3E-02	2.1E-02	3.4E-02
– Small intestine	5.2E-02	6.5E-02	1.1E-01	1.6E-01	2.9E-01
– ULI wall	9.2E-02	1.1E-01	1.9E-01	2.9E-01	5.5E-01
– LLI wall	6.2E-02	7.7E-02	1.3E-01	2.1E-01	3.9E-01
Kidneys	6.3E-03	7.4E-03	1.1E-02	1.6E-02	2.5E-02
Liver	1.5E-02	1.8E-02	2.7E-02	4.0E-02	7.2E-02
Lungs	1.1E-03	1.6E-03	2.5E-03	4.0E-03	7.5E-03
Ovaries	2.0E-02	2.4E-02	3.6E-02	5.2E-02	8.4E-02
Pancreas	5.7E-03	7.5E-03	1.4E-02	2.2E-02	3.4E-02
Red marrow	7.0E-03	8.0E-03	1.0E-02	1.3E-02	1.5E-02
Spleen	2.6E-03	3.4E-03	5.9E-03	9.6E-03	1.6E-02
Testes	1.5E-03	2.3E-03	4.2E-03	7.0E-03	1.3E-02
Thyroid	1.2E-04	1.8E-04	3.7E-04	7.3E-04	1.7E-03
Uterus	1.3E-02	1.7E-02	2.7E-02	4.0E-02	6.5E-02
Other tissues	3.0E-03	3.6E-03	5.3E-03	8.0E-03	1.4E-02
Effective Dose Equivalent mSv/MBq)	**2.4E-02**	**2.9E-02**	**4.4E-02**	**7.0E-02**	**1.5E-01**

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

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	2.1E-03	3.0E-03	4.6E-03	6.7E-03	1.1E-02
Bladder wall	6.9E-02	8.5E-02	1.2E-01	1.9E-01	3.4E-01
Bone surfaces	1.7E-03	2.1E-03	3.0E-03	4.6E-03	8.7E-03
Breast	5.6E-04	5.7E-04	1.0E-03	1.8E-03	3.5E-03
Gall bladder wall	3.5E-02	4.0E-02	5.3E-02	9.2E-02	3.0E-01
GI tract:					
– Stomach wall	2.7E-03	3.4E-03	5.8E-03	9.4E-03	1.6E-02
– Small intestine	1.9E-02	2.4E-02	3.9E-02	6.0E-02	1.1E-01
– ULI wall	3.3E-02	4.0E-02	6.6E-02	1.0E-01	1.9E-01
– LLI wall	2.4E-02	3.0E-02	5.0E-02	7.9E-02	1.5E-01
Kidneys	6.6E-03	7.9E-03	1.1E-02	1.7E-02	2.7E-02
Liver	1.0E-02	1.3E-02	2.0E-02	2.8E-02	5.0E-02
Lungs	9.2E-04	1.3E-03	1.9E-03	2.9E-03	5.4E-03
Ovaries	9.9E-03	1.2E-02	1.8E-02	2.6E-02	4.2E-02
Pancreas	2.8E-03	3.8E-03	6.6E-03	1.0E-02	1.7E-02
Red marrow	3.8E-03	4.5E-03	6.0E-03	7.4E-03	9.4E-03
Spleen	1.5E-03	1.9E-03	3.2E-03	5.2E-03	9.0E-03
Testes	2.5E-03	3.8E-03	6.7E-03	1.1E-02	2.0E-02
Thyroid	2.3E-04	3.7E-04	6.4E-04	1.1E-03	2.2E-03
Uterus	1.1E-02	1.4E-02	2.2E-02	3.1E-02	5.1E-02
Other tissues	2.1E-03	2.5E-03	3.6E-03	5.5E-03	9.5E-03
Effective Dose Equivalent (mSv/MBq)	**1.3E-02**	**1.6E-02**	**2.4E-02**	**3.7E-02**	**7.5E-02**

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

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	2.2E-03	3.3E-03	5.2E-03	7.9E-03	1.3E-02
Bladder wall	3.9E-02	4.8E-02	7.0E-02	1.0E-01	1.9E-01
Bone surfaces	2.3E-03	2.8E-03	4.1E-03	6.1E-03	1.2E-02
Breast	5.1E-04	5.1E-04	9.9E-04	1.9E-03	3.7E-03
GI tract:					
– Stomach wall	5.0E-03	6.2E-03	9.3E-03	1.5E-02	2.5E-02
– Small intestine	4.7E-02	5.9E-02	9.6E-02	1.5E-01	2.6E-01
– ULI wall	8.4E-02	1.0E-01	1.7E-01	2.7E-01	5.0E-01
– LLI wall	5.8E-02	7.2E-02	1.2E-01	1.9E-01	3.7E-01
Kidneys	5.5E-03	6.5E-03	9.7E-03	1.4E-02	2.3E-02
Liver	1.0E-02	1.3E-02	2.0E-02	3.0E-02	5.4E-02
Lungs	8.6E-04	1.2E-03	1.9E-03	3.1E-03	5.8E-03
Ovaries	1.9E-02	2.3E-02	3.4E-02	4.9E-02	7.9E-02
Pancreas	3.5E-03	4.7E-03	7.6E-03	1.2E-02	2.1E-02
Red marrow	6.6E-03	7.5E-03	9.8E-03	1.2E-02	1.4E-02
Spleen	2.2E-03	2.7E-03	4.6E-03	7.4E-03	1.3E-02
Testes	1.9E-03	3.0E-03	5.4E-03	8.6E-03	1.6E-02
Thyroid	1.5E-04	2.2E-04	4.2E-04	7.7E-04	1.7E-03
Uterus	1.3E-02	1.7E-02	2.7E-02	4.0E-02	6.6E-02
Other tissues	2.7E-03	3.3E-03	4.8E-03	7.3E-03	1.3E-02
Effective Dose Equivalent (mSv/MBq)	**1.8E-02**	**2.2E-02**	**3.5E-02**	**5.4E-02**	**9.8E-02**

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

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	8.8E-03	1.3E-02	1.9E-02	2.4E-02	3.6E-02
Bladder wall	2.0E-02	2.4E-02	3.6E-02	5.6E-02	1.0E-01
Bone surfaces	2.4E-03	3.0E-03	4.2E-03	6.5E-03	1.3E-02
Breast	2.3E-03	2.3E-03	4.0E-03	6.4E-03	1.2E-02
GI tract:					
– Stomach wall	3.7E-03	5.6E-03	1.0E-02	1.7E-02	3.0E-02
– Small intestine	3.6E-03	4.4E-03	8.3E-03	1.4E-02	2.4E-02
– ULI wall	5.2E-03	6.4E-03	1.2E-02	2.1E-02	3.5E-02
– LLI wall	1.5E-03	1.8E-03	3.3E-03	5.7E-03	1.0E-02
Kidneys	8.4E-03	9.9E-03	1.5E-02	2.1E-02	3.1E-02
Liver	8.5E-02	1.1E-01	1.6E-01	2.2E-01	3.9E-01
Lungs	4.9E-03	6.8E-03	9.3E-03	1.3E-02	2.2E-02
Ovaries	1.9E-03	2.6E-03	4.7E-03	7.8E-03	1.4E-02
Pancreas	8.3E-03	1.3E-02	2.0E-02	3.0E-02	4.9E-02
Red marrow	3.5E-03	4.9E-03	6.6E-03	8.5E-03	1.2E-02
Spleen	1.9E-03	2.9E-03	5.2E-03	8.5E-03	1.4E-02
Testes	7.6E-04	1.1E-03	1.9E-03	3.3E-03	6.5E-03
Thyroid	3.4E-04	4.6E-04	9.1E-04	1.8E-03	3.5E-03

Uterus	2.8E-03	3.7E-03	6.6E-03	1.1E-02	1.9E-02
Other tissues	2.3E-03	2.8E-03	4.0E-03	6.0E-03	1.1E-02
Effective Dose Equivalent (mSv/MBq)	**9.6E-03**	**1.2E-02**	**1.8E-02**	**2.6E-02**	**4.6E-02**

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).

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**

8. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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.

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.

Method of preparation

- Place a vial containing the freeze-dried mixture in a convenient lead shield.
- Aseptically introduce into the vial 1-8 ml ^{99m}Tc-sodium pertechnetate injection with a radioactivity ranging from 37 to 1480 MBq (1 to 40 mCi).
- Do not use a breather needle.
- Relieve the excess of pressure in the vial by simply withdrawing an equal volume of gas in the syringe.
- Invert carefully a few times to dissolve the contents of the vial.
- Then allow standing for about 15 min. at room temperature.
- Shake before withdrawing a dose.
- In no case should the preparation be left in contact with air.