February 9, 2010

SUMMARY OF PRODUCT CHARACTERISTICS

for

BRIDATEC, kit for radiopharmaceutical preparation

1. NAME OF THE MEDICINAL PRODUCT

BRIDATEC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

N-(3-bromo-2,4,6-trimethylphenylcarbamoyl methyl)-iminodiacetic acid (Mebrofenin), as sodium salt 40.0 mg/vial

BRIDATEC is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection (not included in this kit) to prepare technetium-99m mebrofenin 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 (^{99}Tc) which can be regarded as quasi stable.

Excipients:
This medicinal product contains sodium: 0.30 mg/ml.

For a full list of excipients, see section 6.1.

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 according to the following table:

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

(Paediatric Task Group, European Association of Nuclear Medicines)

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.

The instructions for preparation of radiopharmaceuticals are given in section 12.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

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 mebrofenin 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.

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

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.
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.

Lactation

If the administration is considered necessary the 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.
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.

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.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation 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
ATC-code: V09DA04.

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. It is cleared rapidly from the plasma, less than 1% of administered activity remaining 1 hour after injection.

Technetium-99m mebrofenin injection is taken up byactive 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 mebrofenin 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 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

Stannous chloride dihydrate 0.3 mg
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 before reconstitution:12 months

Reconstituted product: should be used within 6 hours after preparation.
Store below 25ºC. Do not refrigerate or freeze.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).

The reconstituted product should be stored in agreement with national regulations for radioactive materials.
For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

10 ml, (Ph.Eur. Type I) glass vials sealed by chlorobutyl rubber stoppers and metal flip-off caps.

Pack size: kit contains 5 vials.

6.6 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. MARKETING AUTHORISATION HOLDER

GE Healthcare Srl
Via Galeno, 36
20126 - Milan – Italy

Representative
GE Healthcare A/S
Park Allé 295
2605 Brøndby

8. MARKETING AUTHORISATION NUMBER

DK R 1099

9. DATE OF FIRST AUTHORISATION

13. February 1995

10. DATE OF REVISION OF THE TEXT

February 9, 2010

11. DOSIMETRY

The table below shows the shows the dosimetry as calculated according to publication No. 53 by the ICRP (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1987.).
The radiation doses absorbed, compared with the doses of technetium (^{99m}Tc) mebrofenin 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).

PARENCHYMAL LIVER DISEASE

	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 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 equivalent (mSv/MBq)	**0.85**

11. 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 (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.

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 Ph. Eur. 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.

Quality control

Radiochemical purity at 20 min. after labelling.

Free ^{99m}Tc by ascending paper chromatography:

Support	Paper No. 1
Eluent	Methylethylketone
Time	1 hour
Free ^{99m}Tc	≤ 5.0%
Rf	0.9 ± 10%