

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Edicis 2mg kit for radiopharmaceutical preparation

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Edicis vial contains 2 mg of ethylenedicysteine.

The radionuclide is not part of the kit.

### Excipients with known effect

Each Edicis vial contains 3.5 mg of sodium.

Each buffer vial contains 5.2 mg of potassium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation

Edicis (red strip): White or slightly yellow powder

Reducing agent (yellow strip): White or slightly yellow powder, to be reconstituted.

Buffer (green strip): White or yellow paste, to be reconstituted.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate ( $^{99m}\text{Tc}$ ) solution and reconstitution, the solution of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine obtained, is indicated in adults for dynamic scintigraphy, in the following settings:

- Evaluation of nephropathies and uropathies especially for assessing relative kidney function, renal morphology, and renal perfusion

- Drainage of the upper urinary tract.

### 4.2 Posology and method of administration

This medicinal product is intended for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel.

#### Posology

##### Adults

The recommended activity for a patient of 70 kg average body weight is between 90 MBq and 120 MBq.

##### Elderly population

No adaptation is recommended

Renal impairment / hepatic impairment

There is no need to adapt the activity in these patients.

Paediatric population

The safety and efficacy of Edicis in children and adolescents have not yet been established.

Method of administration

Multidose use.

This medicinal product should be reconstituted before administration to the patient.

The radiolabelled solution should be administered intravenously as a single bolus into the brachial vein.

For instructions on extemporaneous preparation, of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition

The specific procedure (position of the patient during administration and acquisition, and the type of camera, sequence and number of images) depends on the indication of the exploration.

The scintigraphic examination begins immediately after injection of the product. The total duration of the examination is approximately 30 minutes.

When elimination of the product is slow, the number of images can be higher. Administering furosemide to the patient can increase elimination.

**4.3 Contraindications**

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

**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.

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.

Patient preparation

When a scintigraphy with other technetium ( $^{99m}\text{Tc}$ )-labelled agents was previously performed in the last 2 days before the examination, the physician should be informed and should estimate the indication.

In order to obtain valuable images for the evaluation of the drainage of the upper urinary tract and to reduce the radiation exposure of the bladder, patients should be encouraged to drink plenty of water from the time of arrival in the department to the actual injection of tracer (unless medically contraindicated) and empty their bladder prior to, and frequently for six hours after the imaging procedure.

After the procedure

Close contact with infants and pregnant women should be restricted during 24h.

Specific warnings

This medicinal product contains less than 1 mmol of sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

This medicinal product contains less than 1 mmol of potassium (39 mg) per vial, i.e. is essentially potassium free'.

Precautions with respect to environmental hazard see section 6.6.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Administered contrast media may impair tubular renal excretion and thereby influence the technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine clearance.

Probenecid inhibits the tubular secretion of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine.

Chronic administration of diuretics may lead to volume depletion resulting in a decrease in specificity. If possible they should be stopped several days before the study (unless medically contraindicated).

## 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. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), 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 dose 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 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 24 hours and the expressed feeds discarded.

Close contact with infants should be restricted during this period.

## 4.7 Effects on ability to drive and use machines

Edicis has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

No undesirable effect has been reported to date.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 1.19 mSv (unilateral renal obstruction) when the maximal recommended activity of 120 MBq is administered, these adverse reactions are expected to occur with a low probability.

### 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 online reporting option (preferred method) accessible from the IMB homepage ([www.imb.ie](http://www.imb.ie)). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.

**FREEPOST**

Pharmacovigilance Section  
Irish Medicines Board  
Kevin O'Malley House  
Earlsfort Centre  
Earlsfort Terrace  
Dublin 2  
Tel: +353 1 6764971  
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Website: [www.imb.ie](http://www.imb.ie)  
e-mail: [imbpharmacovigilance@imb.ie](mailto:imbpharmacovigilance@imb.ie)

## 4.9 Overdose

No case of overdose has been reported.

In the event of administration of a radiation overdose with technetium ( $^{99m}\text{Tc}$ ) ethylenedicycysteine, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

If the whole content of the vial containing the labelled substance is administered to one patient by mistake 2 mg of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine is introduced in the body. Preclinical toxicity studies have shown that clinical symptoms are not expected at this dose level (see section 5.3).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic Radiopharmaceuticals, ATC code: V09CA06

#### Mechanism of action

Technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine is a renal tubular agent with similar pharmacokinetic properties to ortho-iodohippurate and ( $^{99m}\text{Tc}$ )-MAG3. It is excreted from the kidneys by active transport mechanism and has a renal clearance which is closer to that of ortho-iodohippurate as compared to ( $^{99m}\text{Tc}$ )-MAG3.

Technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine has negligible hepatobiliary localisation and a high kidney-to-background ratio which improves the renal delineation and provides better image quality even in patients with severe renal failure.

#### Pharmacodynamic effects

At the chemical concentrations used for diagnostic examinations, technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine does not appear to have any pharmacodynamic activity.

### 5.2 Pharmacokinetic properties

#### Distribution

Following intravenous injection of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine, plasma protein-bound fraction is 30% and plasma clearance has been reported to be around 75% of ortho-iodohippurate (OIH) clearance both in normal individuals and patients. The distribution volume of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine is 20% of body-weight.

#### Organ uptake

Blood cell binding has been reported to be 5.7%. There is a negligible uptake in the liver and intestines.

#### Elimination

Technetium ( $^{99m}\text{Tc}$ ) - ethylenedicycysteine is excreted from the kidneys by active transport mechanism.

Within 1 hour, 70% of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine is excreted in urine.

### 5.3 Preclinical safety data

Toxicological studies with mice have demonstrated that with a single intravenous injection of the tested reconstituted kit containing ethylenedicysteine overloaded with 20% of impurities at 25 mg/kg, no deaths were observed.

This corresponds to 875 times the human dose of 0.028 mg/kg for adults (70 kg) resulting from the administration of a whole content of a reconstituted vial.

This medicinal product is not intended for regular or continuous administration.

Mutagenicity studies, long term carcinogenicity studies have not been carried out.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Edicis:

Disodium phosphate dihydrate (E339)

D-mannitol (E421)

Ascorbic acid (E300)

Disodium edetate dihydrate

Reducing agent:

Stannous chloride dihydrate (E512)

Tartaric acid (E334)

Ascorbic acid (E300)

Buffer:

Potassium dihydrogen phosphate (E340)

Ascorbic acid (E300)

### 6.2 Incompatibilities

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

### 6.3 Shelf life

1 year.

After radiolabelling: 8 hours. Do not store above 25°C after radiolabelling.

### 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep in the outer carton tightly closed in order to protect from light.

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

6 ml, type I, colourless glass vial, closed with chlorobutyl rubber stopper and crimped with an aluminium seal with lid. Vials are provided with a colour coded labels: red strip for Edicis (multidose vial), yellow strip for the reducing agent and green strip for the buffer.

Pack size:

Kit of 4 Edicis, 4 reducing agent and 4 buffer vials.

## 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 licences 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 vials are intended only for use in the preparation of technetium ( $^{99m}\text{Tc}$ ) -ethylenedicysteine and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on extemporaneous preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of the vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporaneous preparation is not radioactive. However, after sodium pertechnetate ( $^{99m}\text{Tc}$ ) Injection, Ph. Eur. 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, etc. 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

CIS bio international  
BP 32  
91192 GIF-sur-Yvette Cedex  
France

## 8 MARKETING AUTHORISATION NUMBER

PA0677/021/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15<sup>th</sup> November 2013

## 10 DATE OF REVISION OF THE TEXT

## 11 DOSIMETRY

Technetium ( $^{99m}\text{Tc}$ ) is produced by means of a ( $^{99}\text{Mo}/^{99m}\text{Tc}$ ) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium ( $^{99}\text{Tc}$ ) which, in view of its long half-life of  $2.13 \times 10^5$  years can be regarded as quasi stable.

The data listed below are from ICRP (International Commission of Radiological Protection, Publication 106) and are calculated according to the following assumptions: the effective dose has been calculated by using the absorbed doses determined for each individual organ, taking into account the weighting factors (radiation and tissue).

**Table 1: Absorbed dose after injection of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine: normal renal function**

Organ	Absorbed dose per unit activity administered (mGy/MBq)
	Adult
Adrenals	0.0005
Bladder	0.0950
Bone surfaces	0.0014
Brain	0.0002
Breasts	0.0002
Gall bladder	0.0007
Gastrointestinal tract:	
Stomach	0.0005
Small intestine	0.0022
Colon	0.0032
(Upper Large Intestine)	0.0017
(Lower Large Intestine)	0.0052
Heart	0.0003
Kidneys	0.0034
Liver	0.0005
Lungs	0.0003
Muscles	0.0014
Oesophagus	0.0003
Ovaries	0.0049
Pancreas	0.0006
Red marrow	0.0010
Skin	0.0005
Spleen	0.0005
Testes	0.0034
Thymus	0.0003
Thyroid	0.0003
Uterus	0.0110
Remaining organs	0.0014
<b>Effective dose (mSv/MBq)</b>	<b>0.0063</b>

Bladder wall contributes 76% of the effective dose.

The effective dose resulting from the administration of an activity of 120 MBq for an adult weighing 70 kg with a normal renal function is about 0.76 mSv.

For an administered activity of 120 MBq the typical radiation dose to the target organ (kidneys) is 0.41 mGy and the typical radiation dose to the critical organs are: bladder 11.40 mGy, uterus 1.32 mGy.

**Table 2: Absorbed dose after injection of technetium ( $^{99m}\text{Tc}$ ) - - ethylenedicysteine: abnormal renal function**

Organ	Absorbed dose per unit activity administered (mGy/MBq)
	Adult
Adrenals	0.0026
Bladder	0.0440
Bone surfaces	0.0036
Brain	0.0015
Breasts	0.0013
Gall bladder	0.0027
Gastrointestinal tract:	
Stomach	0.0022
Small intestine	0.0031
Colon	0.0034
(Upper Large Intestine)	0.0028
(Lower Large Intestine)	0.0043
Heart	0.0021
Kidneys	0.0110
Liver	0.0028
Lungs	0.0018
Muscles	0.0021
Oesophagus	0.0018
Ovaries	0.0043
Pancreas	0.0026
Red marrow	0.0021
Skin	0.0013
Spleen	0.0023
Testes	0.0029
Thymus	0.0018
Thyroid	0.0018
Uterus	0.0069
Remaining organs	0.0022
<b>Effective dose (mSv/MBq)</b>	<b>0.0046</b>

The effective dose resulting from the administration of an activity of 120 MBq for an adult weighing 70 kg-with renal impairment -is about 0.55 mSv.

For an administered activity of 120 MBq, the typical radiation dose to the target organ (kidneys) is 1.32 mGy and the typical radiation dose to the critical organs, bladder and uterus) are 5.3 mGy and 0.83 mGy, respectively.



**Table 3: Absorbed dose after injection of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine: acute unilateral renal blockage**

Organ	Absorbed dose per unit activity administered (mGy/MBq)
	Adult
Adrenals	0.0110
Bladder	0.0490
Bone surfaces	0.0031
Brain	0.0001
Breasts	0.0004
Gall bladder	0.0064
Gastrointestinal tract:	
Stomach	0.0040
Small intestine	0.0043
Colon	0.0038
(Upper Large Intestine)	0.0040
(Lower Large Intestine)	0.0035
Heart	0.0014
Kidneys	0.2000
Liver	0.0046
Lungs	0.0011
Muscles	0.0022
Oesophagus	0.0004
Ovaries	0.0036
Pancreas	0.0077
Red marrow	0.0030
Skin	0.0008
Spleen	0.0100
Testes	0.0018
Thymus	0.0004
Thyroid	0.0002
Uterus	0.0065
Remaining organs	0.0022
<b>Effective dose (mSv/MBq)</b>	<b>0.0099</b>

The effective dose resulting from the administration of an activity of 120 MBq for an adult weighing 70 kg-with an acute unilateral renal blockage- is 1.19 mSv.

For an administered activity of 120 MBq, the typical radiation dose to the target organ -kidneys- is 24 mGy and the typical radiation dose to the critical organs, bladder and uterus, are 5.9 mGy and 0.78 mGy, respectively.

## 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

This product contains no bacteriostatic preservative.

### Method of preparation

Before any step of solution withdrawal and transfer, the surface of the rubber stopper should be disinfected and allowed to air dry.

1. Put a vial **Edicis (redstrip)** into an appropriate lead shielded container. Using a syringe, introduce through the rubber stopper **2 ml** of sterile sodium pertechnetate ( $^{99m}\text{Tc}$ ) corresponding to a range of activity of **0.8-1.6 GBq**. Shake.

2. Take a **reducing agent vial (yellow strip)**. Using a syringe, introduce through the rubber stopper **2 ml** of sterile 9 mg/ml sodium chloride solution. Shake until complete dissolution.

Transfer **0.5 ml** of the solution of reducing agent with a syringe into a Edicis vial. Allow the Edicis vial to stand for 15 minutes while it is shaken once or twice.

3. Take a **buffer vial (green strip)**. Using a syringe, introduce through the rubber stopper **1 ml** of sterile 9 mg/ml sodium chloride solution. Shake until complete dissolution.

Transfer the whole solution of the buffer with a syringe into the Edicis vial. Shake.

4. Fill in the enclosed label and fix it to the radiolabelled solution vial.

The reconstituted product should not be further diluted.

After radiolabelling with sodium pertechnetate ( $^{99m}\text{Tc}$ ) injection and reconstitution with the reducing and buffering agents provided, the resulting solution for injection of technetium ( $^{99m}\text{Tc}$ ) - ethylenedicysteine should be clear and colourless, free from visible particles with a pH of 5 – 8, otherwise it should be discarded.

### Quality control

The radiochemical purity of the final radiolabelled preparation can be tested according to the following procedure:

#### **a) Method**

Paper chromatography (1<sup>st</sup> system) and thin layer chromatography (2<sup>nd</sup> system).

#### **b) Procedure**

##### **1<sup>st</sup> system: Determination of free pertechnetate**

Adsorbent: strips for paper chromatography (1 x 10 cm), type Whatman No. ET-31

Solvent: Acetone

1. Draw a starting line at 2 cm from the bottom of the strip and a front line at 1 cm of the top.

2. Apply 10 – 15  $\mu\text{l}$  of the labelled product onto the starting line of the paper strip.

3. **Let dry** and develop the chromatogram in acetone for 10 minutes. The labelled complex and reduced-hydrolyzed

technetium remain at the starting line ( $R_f \sim 0$ ) while free pertechnetate moves with the solvent front ( $R_f \sim 1$ ).

4. Remove the strip with the forceps.

Record the chromatograms using a gamma scanner **or** cut the strip at 5 cm from the bottom and measure the activity of the 2 parts in an appropriate dose calibrator.

5. Calculate the relative amount of free pertechnetate (FT, %) corresponding to the activity at the solvent front by the total activity (starting and front solvent line).

$$\text{Where, \% free technetium } (^{99m}\text{Tc}) = \frac{\text{Activity of strip at } R_f \sim 1}{\text{Total activity of strip}} \times 100$$

### 2<sup>nd</sup> system: Determination of reduced-hydrolyzed technetium

Adsorbent: strips for thin layer chromatography (1.0 x 10cm) coated with silica gel, type Kieselgel 60,

Solvent: Ethanol 96% (v/v) corresponding to 758 g/l

6. Draw a starting line at 2 cm from the bottom of the strip and a front line at 1 cm of the top.

7. Apply 5  $\mu$ l of the labelled solution onto the starting line of the paper strip

**8. Do not let dry** and start **immediately** to develop the chromatogram in ethanol for 30 minutes.

The reduced-hydrolysed technetium remains near to the starting line ( $R_f \sim 0.1$ ) while the labelled complex and free pertechnetate move up to  $R_f \sim 0.6$  (30 min is not long enough to separate the labelled complex from free pertechnetate).

9. Remove the strip with the forceps.

Record the chromatograms using a gamma scanner **or** cut the strip at 4 cm from the bottom and measure the activity of the 2 parts in an appropriate dose calibrator.

10. Calculate the relative amount of reduced-hydrolysed technetium (RHT, %) corresponding to the activity at start divided by the total activity (starting and front line).

$$\text{Where, \% reduced-hydrolysed technetium } (^{99m}\text{Tc}) = \frac{\text{Activity of strip at } R_f \sim 0.1}{\text{Total activity of strip}} \times 100$$

Calculate the radiochemical purity (RCP) of the labelled product as follows:

$$\text{RCP (\%)} = 100\% - \text{FT(\%)} - \text{RHT(\%)}$$

11. The radiochemical purity should be more than or equal to 95 %, otherwise the preparation should be discarded.

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

Detailed information on this medicinal product is available on the website of the Irish Medicines Board.