

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DTPA 9 mg powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of DTPA powder for injection

Quantity per vial

Function

Component

Active substance

Organ-specific chelating agent of ^{99m}Tc radioisotope

^{99m}Tc -DTPA radioactive injection

Quantity per vial

Function

Active substance

^{99m}Tc -DTPA

0.8-2.4 GBq

Organ-specific diagnostic information

The applied activity should ensure the appropriate patient dose (at the time of the administration) recommended for the type of examination. Recommended activities for examination of one patient:

- Examination of renal function: 111–185 MBq
- Examination of cerebral blood flow: 500–600 MBq
- Examination of gastrointestinal tract: 20–40 MBq
- II. For examination of the liquor circulation apply the following method. Introduce 600 – 1200 MBq sodium pertechnetate in a volume of 3 cm³ into the vial containing DTPA. Dilute the solution with 3 cm³ of water for injection. This solution (volume: 6 cm³) can be used for lumbar or cisternal administration in case of lumbar or cisternal puncture, respectively.

Recommended activities for examination of one patient in these cases:

- Examination of liquor circulation: 111–185 MBq

For paediatric examination use Webster's equation (given below) to determine the activity to be administered and see Chapter 4.3.

$$A_{child} = \frac{[(N + 1) A_{Adult}]}{N + 7}$$

where N: age of the child [year], A_{child}, A_{adult}: activity [MBq]

Timing of imaging by gamma scanner or camera depends on the type of the administration. For dynamic studies of renal function and in examination of cerebral blood flow administer the solution intravenously, as bolus to the patient sitting in front of, or lying under or above the camera. Start imaging and administration at the same time.

Time of data collection and scanning:

1. Dynamic studies of renal function: for 30 minutes from the time of administration, continuously
2. Examination of cerebral blood flow:
 - Instationary phase, first pass: 1 – 60 seconds, continuously
 - Equilibrium: from 30 seconds

3. Examination of gastrointestinal tract: Mix ^{99m}Tc -DTPA with drink or food, for example semolina, chicken liver or boiled egg and administer orally.

Time of data collection and scanning:

Motility of oesophagus: 1–120 seconds, continuously

Stomach reflux: 10–15 minutes

Emptying of the stomach: for 2 hours

4. Examination of liquor circulation: Use only the specified dilution of ^{99m}Tc -DTPA. Route of administration of the vial containing the labelled substance is administered to one patient by mistake 9.0 mg of ^{99m}Tc -DTPA is introduced in the body.

Acute toxicity studies on mice shows there are not any clinical symptom, if less than 1.6 mg/kg of bodyweight is administered. Besides, DTPA is applied as a treatment agent in cases of heavy metal poisoning. The recommended human dose in this case is 1790 mg (25.6 mg/kg of bodyweight) trisodium calcium DTPA daily. If the whole content of the vial containing the labelled substance is administered to one patient by mistake, not more than 0.5% of the recommended daily dose is introduced in the body. Thus, no toxic effects are expected in case of overdose.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Dynamic studies of kidney (function of kidney) by imaging technique

- Determination of kidney perfusion
- Camera renography, measurement of glomerular filtration rate (determination of GFR)
- Determination of total and partial kidney function
- Localisation of blockage/ obstruction of urinary passages
- Determination of vesicourethral reflux
- Determination of the volume of retained urine

Examination of the cerebral blood circulation

- Diagnosis of vascular and neoplastic brain injuries

Examination of the gastrointestinal tract by using ^{99m}Tc -DTPA labelled foodstuff or drink

- Localisation of blockade of the oesophagus
- Determination of blockage from the stomach to the oesophagus
- Examination of stomach emptying

Examination of liquor circulation

- Diagnosis of hydrocephalus of various origin
- Diagnosis of cysts, which communicate or do not communicate with the liquor circulation
- Diagnosis of nasal, nasopharyngeal and spinal liquorhea to indicate neurosurgical interventions

4.2 Posology and method of administration

Posology and method of administration depends on the type of examination.

Labelling of ^{99m}Tc -DTPA can be performed in two different ways

1. Label the content of one vial of DTPA kit by using 0.8 - 2.4 GBq activity.

^{51}Cr is too low to take images; only the activity of the blood samples can be measured.

Alternative solution is the use of EDTA and DTPA complexes of ^{99m}Tc radioisotope. However, there is no binding between ^{51}Cr -EDTA and the plasma proteins, both in case of ^{99m}Tc -EDTA and ^{99m}Tc -DTPA a certain binding is observed (3–10 %), varying individually.

The different plasma-binding properties bring about that the GFR (glomerular filtration rate) values determined by using ^{51}Cr -EDTA and ^{99m}Tc -DTPA are different. To correct the deviations the plasma-binding ratio should be determined for each patient.

More than 90% of ^{99m}Tc -DTPA leaves the bloodstream quickly after intravenous administration and goes to the kidneys where it is excreted glomerularly. No binding in the kidneys has been observed and 90% of the introduced activity leaves the body within 24 hours with the urine. The normal way of excretion is: kidneys-ureter-urinary bladder. It is a general principle that in the course of isotope diagnostic imaging the radioactive tracer should not influence the examined system, i.e. the physiological processes taking place in the human body. For the present case the requirement is that the tracer should not has or has only a negligible effect upon the glomerular filtration of the kidneys. This pharmaceutical product complies with the requirement since not more than 1.5 mg and no more than 3.0 mg is administered to a patient. Pharmaceutical and pharmacodynamic effects of these small amounts of substance cannot be observed.

5.2 Pharmacokinetic properties

Intravenously administered ^{99m}Tc -DTPA eliminates from the bloodstream in four parallel processes, which can be described with exponential curves:

- (i) 58 % of the activity has a $T_{1/2}$ of 3.8 minutes.
 - (ii) 24 % of the activity has a $T_{1/2}$ of 15.6 minutes.
 - (iii) 16 % of the activity has a $T_{1/2}$ of 11.8 minutes.
 - (iv) 2 % of the activity has a $T_{1/2}$ of 13.6 hours.
- where $T_{1/2}$ is the biological half-life.

(i) can be explained by the rapid diffusion of ^{99m}Tc -DTPA in the capillaries leading to the extravascular, extracellular space. The highest activity of ^{99m}Tc -DTPA in the kidneys can be observed 3.8 min after administration. At this time 4.4% of the total administered activity is present in the kidneys. The glomerular filtration in the kidneys is significantly faster in dogs than in humans, but the cumulative excretion after 12 hours is similar: approximately 90%.

The excretion from the kidneys can be described with a two-compartment model:

- (i) 69 % of the activity has a $T_{1/2}$ of 1.73 hours.
 - (ii) 27 % of the activity has a $T_{1/2}$ of 9.2 hours.
- where $T_{1/2}$ is the biological half-life.
- The steps of excretion are of different speeds. As a result of the slower metabolic processes there is enough activity in the blood to perform examination of the circulation, which takes 1 – 10 minutes. These pharmacokinetic properties of the elimination via the kidneys enables that ^{99m}Tc -DTPA can be used for examinations of the blood circulation. Moreover, excretion via the kidneys eliminates the need for blocking the thyroid, which is normally necessary when $[^{99m}\text{Tc}]$ -pertechnetate is used. This applies to gastrointestinal studies as well. After administration to the liquor circulation, selective pharmacokinetic effect cannot be observed. In this case, blending of ^{99m}Tc -DTPA in the liquor and its flow are traced (physical tracing of a streaming system).

5.3 Preclinical safety data

Acute toxicity studies on mice shows there are not any clinical symptom, if less than 1.6 mg/kg of bodyweight is administered. According to the recommendations quantity of ^{99m}Tc -DTPA introduced to one patient is not less than 1.5 mg and not more than 3.0 mg. Besides, DTPA is applied as a treatment agent in cases of heavy metal poisoning. The recommended human dose in this case is 1790 mg (25.6 mg/kg of bodyweight) trisodium calcium DTPA daily. If the whole content of the vial containing the labelled substance is introduced in the body. Thus, no toxic effects are expected in the body. Further advantage of the product is that radiochemical purity of the preparation is not affected by the applied activity of $[^{99m}\text{Tc}]$ -pertechnetate case of overdose. Further advantage of the product is that radiochemical purity of the preparation is not affected by the applied activity of $[^{99m}\text{Tc}]$ -pertechnetate

4.6 Pregnancy and lactation

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 pregnant until proven otherwise. Alternative techniques which do not involve ionising radiation should be considered.

Treatment of women of child bearing potential is recommended in the first 10 days after menstruation.

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.

In occurrence of unexpected adverse reactions driving and/or working with machines should be reconsidered.

4.8 Undesirable effects

Exposure to ionising radiation is linked with cancer induction and a potential risk for development of hereditary defects. However these effects are hardly expected regarding the applied amount of activity.

Adverse event and reactions have not been reported ever since the authorization of the product (1988) nor registered in the literature. Considering the number of the examinations carried out since, no adverse reactions are expected (frequency less than 1/10000).

4.9 Overdose

No case of overdose has been reported. In the unlikely event of overdose the vital functions of the patient should be supported. Administration of higher activities than prescribed is unnecessary and must be avoided in order to avoid the excess absorbed radiation dose of the patient and his/her environment.

In case of incidental overdose, the effectively administered activity of ^{99m}Tc must be determined (in MBq) and the actual absorbed radiation dose must be calculated by using the data of the dosimetric table of Chapter 11. Necessity and method of further treatment should be concluded based on these results. The table of Chapter 11 contains absorbed radiation dose data in μGy in case of intravenous administration of 1 MBq of ^{99m}Tc -DTPA. Multiply these specific absorbed radiation dose data by the effectively administered activity (in MBq) to obtain the required absorbed radiation dose data in μGy .

According to the recommendations quantity of ^{99m}Tc -DTPA introduced to one patient is not less than 1.5 mg and not more than 3.0 mg. If the whole content of the vial containing the labelled substance is administered to one patient by mistake 9.0 mg of ^{99m}Tc -DTPA is introduced in the body.

Acute toxicity studies on mice shows there are not any clinical symptom, if less than 1.6 mg/kg of bodyweight is administered.

Besides, DTPA is applied as a treatment agent in cases of heavy metal poisoning. The recommended human dose in this case is 1790 mg (25.6 mg/kg of bodyweight) trisodium calcium DTPA daily. If the whole content of the vial containing the labelled substance is administered to one patient by mistake, not more than 0.5% of the recommended daily dose is introduced in the body. Thus, no toxic effects are expected in case of overdose.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical, ATC code: V09CA01

It is well-known that the hydrophilic, polar molecules, which not or only slightly bound to the blood plasma, are filtrated by the glomerules of the kidneys and eliminated from the body with the primary urine. The most specific glomerularly filtrated compounds are inulin and creatinine, which do not bind to the blood plasma. However, no radionuclide as heteroatom can be introduced to these molecules without dramatically changing their physiological properties.

Consequently for labelling these molecules only the following radioisotopes can be used: ^{113}In , ^{14}C , ^{35}Cl , ^{15}O for both molecules, furthermore ^{13}N for creatinine. However, except ^{14}C they are positron emitters with a very short (2–20 min) physical half life, therefore extremely quick synthesis and a PET machine would be necessary to use them in imaging kidney studies. Beta emission of ^{14}C is not suitable for imaging.

^{99m}Tc -EDTA, which does not bind to the blood plasma, is a fully glomerularly excreted radioactive complex whose physiological properties are almost identical to those of inulin. From physiological point of view it is suitable to carry out dynamic kidney examinations. Unfortunately, the photon yield of

4.10 Special warnings and precautions for use

Radioactive medicinal products should be received, used and administered only by authorised person in designated clinical settings. Receipt, storage, use, transfer and disposal of the radioactive medicinal products are subject to the regulations and appropriate licences of the competent authorities.

Use of the product is contraindicated for patients under 18 years of age. See section 4.4) except if the necessity and importance of obtaining the diagnostic information outweighs the risk associated with the radiation exposure.

Under 18 years of age (See section 4.4) except if the necessity and importance of obtaining the diagnostic information outweighs the risk associated with the radiation exposure

4.11 Special warnings and precautions for use
Radioactive medicinal products should be received, used and administered only by authorised person in designated clinical settings. Receipt, storage, use, transfer and disposal of the radioactive medicinal products are subject to the regulations and appropriate licences of the competent authorities.

Use of the product is contraindicated for patients under 18 years of age. See section 4.4) except if the necessity and importance of obtaining the diagnostic information outweighs the risk associated with the radiation exposure.

4.12 Interaction with other medicinal products and other forms of interaction
No interactions are known.

(0.8–2.4 GBq. Quantity of radiochemical impurities are always less than 10 %, therefore the kit is safe from the point of view of labelling.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients	Quantity per vial	Function
Excipients		
Stannous chloride dihydrate	0.6 mg	Reducing agent of ^{99m}Tc -pertechnetate
Ascorbic acid	0.5 mg	Stabiliser
Sodium chloride	20.0 mg	Filter

6.2 Incompatibilities

When preparing ^{99m}Tc -DTPA injection by using DTPA in vivo kit, only physiological saline and ^{99m}Tc -pertechnetate can be used (see section 12).

Stannous chloride component of DTPA kit is a reducing agent. It reduces free pertechnetate from +7 oxidation state to +4 oxidation state, in which technetium readily forms complex with DTPA. It is important to keep away the content of the vials from moisture and oxidising agents, for example chemical oxidation agents or oxygen of the air. Alkaline media facilitate the oxidation of Sn(II) before the labelling reaction this is why the product is incompatible with bases. As a result of these incompatibilities it is recommended to remove the closure of the closed injection vials just before the labelling reaction. Perform the labelling by observing the instructions detailed in Chapter 12.

6.3 Shelf life

Shelf life of DTPA kit (lyophilised, non-radioactive components in injection vials closed with rubber stopper and aluminium cap) is 12 month from the date of the manufacture. One paper box contains 6 of injection vials, which can be labelled at different times within the expiry time.

6.4 Special precautions for storage

DTPA powder for injection: Do not store above 25°C. ^{99m}Tc -DTPA is to be stored also below 25°C, considering the regulations for radiation safety.

6.5 Nature and contents of container

The injection vials containing the freeze-dried product are closed with rubber stopper and tear-off kombicap (aluminium and plastic). Six vials of DTPA kit are packed into one paper box, with Summary of Product Characteristic (SPC) and Patient Information Leaflet (PIL) in English and in Hungarian and six label with radioactive symbol.

6.6 Special precautions for disposal &and other handling>

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

7. MARKETING AUTHORISATION HOLDER

Institute Of Isotopes Co. Ltd.
Adresse: 1121 Budapest, Konkoly Thege Miklós str. 29-33.
 1535 Budapest, P.O.B. 851.
Tel.: 36 1 392 2577, 395 9081, Fax: 36 1 395 9247; 392 2575
E-mail: commerce@izotop.hu

8. MARKETING AUTHORISATION NUMBER(S)

OGY-T-9244/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 January 1988 / 21 December 2009

10. DATE OF REVISION OF THE TEXT

21 December 2009

This SPC was translated by the manufacturer based on the original Hungarian document, authorized by the Hungarian National Institute of Pharmacy on 21.12.2009.

11. DOSIMETRY

Individual patient dose is 20 – 600 MBq. Estimated absorbed dose values of 1 MBq of the injection for an average body weight of 70 kg are given in the table below.

PACKAGE LEAFLET: INFORMATION FOR THE USER

DTPA 9 mg powder for injection

Diethylene-triamino-pentaacetic acid

Absorbed dose

[$\mu\text{Gy} / \text{MBq}]$

13.5

150.0

5.13

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32

4.32