12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Any unused product, containers and other material which contained the radioactive substance must be disposed of as radioactive waste in accordance with local requirements.

The kit for preparation of radiopharmaceutical Techimmuna should be labelled with technetium-99m in the form of sodium pertechnetate ($^{99m}$Tc) solution for injection, in order to prepare radiopharmaceuticals.

Method of preparation of radiopharmaceutical product intended for direct intravenous administration to the patient:

Use aseptic technique throughout the preparation and mixing of the components. The user should wear rubber gloves, the shielding must be used at all times when handling vials or syringes containing the radioactive agent.

The radioactivity of the preparation Techimmuna should be measured just before administration.

Techimmuna is administered intravenously in a single dose after labelling of the kit using a sterile, oxidant-free sodium pertechnetate ($^{99m}$Tc) solution for injection in accordance with the labelling instruction described below:

1. Take Vial II. Using a syringe, introduce through the rubber seal 10 mL of water for injection and gently stir to dissolve completely all components.
2. From such prepared solution, draw 0.5 mL of the solution and using a syringe introduce it into Vial I, containing human immunoglobulin G (modified).
3. After proper stirring, using a syringe, introduce through the rubber seal not more than 1 mL of sodium pertechnetate ($^{99m}$Tc) with the activity not more than 525 MBq (25 mCi). Do not take off the needle, use the same syringe to withdraw an equivalent volume of air in order to avoid excess pressure in the vial.
4. Stir gently the content of the vial. Than incubate in temperature of 37°C within 30 minutes.
5. When the incubation is finished allow the vial to cool to the room temperature.
6. The solution is ready to use radiopharmaceutical for injection. Techimmuna may be used within 3 hours after completion of the labelling procedure.

Equipment:
1. Minicolumn filled with Sephadex G-25 gel Glass Vials
2. The radioactivity counter suitable for measuring the radioactivity of glass vials and chromatographic column

Reagents:
1. 0.9% NaCl
2. Human Albumin

Method description:
Prepare the chromatographic column by prewashing it with 15 mL of 1% human albumin solution in 0.9% NaCl. Apply to the column 100 μL of radiolabelled Techimmuna. Elute the column with 11 mL of 0.9% NaCl collecting 1 mL fractions. Measure the radioactivity of each fraction and radioactivity retained on the column.

$^{99m}$Tc-Techimmuna complex is eluted in fractions 3-7 mL, unbound pertechnetate ($^{99m}$Tc) in fractions 9-11 mL, and technetium ($^{99m}$Tc) in colloidal form is retained on the column.

Calculate the content of $^{99m}$Tc-Techimmuna complex, as a percentage of radioactivity of fractions containing the $^{99m}$Tc-Techimmuna (3-7) relative to the total radioactivity of collected fractions and radioactivity retained on the column.

Radiochemical purity of $^{99m}$Tc-Techimmuna in the final formulation ready for patient use should be not less than 92%.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Techimmuna, 2 mg, kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human immunoglobulin G (modified). 2 mg

For a full list of excipients, see section 6.1.

Human immunoglobulin G is a polyclonal antibody, obtained by the fractionation of plasma proteins using Cohn’s alcohol fractionation method.

To allow binding with radiouclide technetium-99m, human immunoglobulin G is derivatized in reaction with hydrazinonicotinic acid (HYNID).

The radionuclide is not part of the kit.

3. PHARMACEUTICAL FORM

Kit (two vials) for radiopharmaceutical preparation. White or almost white lyophilisates.

For radiolabelling with sodium pertechnetate ($^{99m}$Tc) solution of Ph. Eur. quality.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
This medicinal product is for diagnostic use only.

Human immunoglobulin G labelled with radiouclide technetium-99m, is used for detection and localization of inflammatory activity, in particular in rheumatoid arthritis.

4.2 Posology and method of administration
The medicinal product is for hospital use or in designated nuclear medicine facilities only, by persons experienced in the radiopharmaceuticals application.

Techimmuna is administered intravenously in a single dose after labelling of the kit using a sterile, oxidant-free sodium pertechnetate ($^{99m}$Tc) solution for injection (eluate of $^{99m}$Tc-radiouclide generator) in accordance with the instructions for preparation use and disposal of radiopharmaceutical – see section 12.

The recommended activity range is from 555 to 740 MBq (15-20 mCi). Radioactivity of administered dose should be always adjusted with respect to its diagnostic usefulness.

Preparation of the patient
Patient does not require special preparation, though an adequate hydration of a patient (within 4-6 hours after administration of product) and frequent voiding are necessary to minimize radiation dose to the bladder.

Posology
Dose (activity) of Techimmuna used in adults
The recommended radioactivity dosage for single examination of adult is approximately from 555 MBq to 740 MBq (15-20 mCi).

Children and adolescents
Safety and efficacy of the radiopharmaceutical product Techimmuna has not been established in children, yet. The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk and benefit ratio in this patient group. The activity to be administered to children is lower and follows methods of calculation activities.

Elderly patients (more than 65 years)
Based on literature data there is no special dosage requirements for the elderly patient.

Repeated administration
Techimmuna is intended for a single intravenous use only. if there is a need for repeated administration, clinical indication and potential adverse events should be considered.

Method of administration
Techimmuna is administered slowly by intravenous injection to the respective forearm vein.

Images acquisition should start about 4 hours after administration. Imaging after 24 hours does not provide information about other lesions and for a given indication is not required.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Product Techimmuna is not recommended for use in patients with antibodies of class IgA deficiency or who are hypersensitive to given blood and blood medicinal products.

4.4 Special warnings and precautions for use
The content of the kit vials is intended for preparation of radiopharmaceutical Techimmuna and may be administered to a patient only after completion of labelling procedure – see section 12. The preparation should not be administered before labelling. 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.

Pregnancy, see section 4.6.

Use in children, see section 4.2.

Renal and (or) hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. In such situations the radioactivity of the preparation should be decreased.
Patient with renal impairment should be under a special care - exception by the kidney is longer, and the patient is exposed to higher radiation. Special care should also be considered in patients with hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction
No studies has been conducted considering interactions.

4.6 Fertility, pregnancy and lactation

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

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Therefore in pregnant women only necessary radioisotope examinations are conducted and only when the radiation exposure is justifiable by the likely benefit.

Breast-feeding
Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given as to whether the investigation could reasonably be delayed until the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made.

If the administration of radioactive medicinal product is considered to be necessary, the breast-feeding should be interrupted for at least 12 hours.

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.

4.8 Undesirable effects
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.

Exposure to ionising radiation is associated with a risk of developing cancer and hereditary defects. Current evidence indicates little likelihood of such adverse reactions in the case of diagnostic tests in nuclear medicine.

Most diagnostic examinations used in nuclear medicine delver radiation dose (effective dose) lower than 20 mSv. In some particular cases higher activities can be justifiable.

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. Health-care professionals are asked to report any suspected adverse reactions via Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products:
Al. Jeruzalemskie 181C
02-222 Warsaw, Poland
Phone: +48 22 4921 301
Fax: +48 22 4921 309
e-mail: ndl@urtipi.gov.pl

4.9 Overdose
In case of overdose, the dose absorbed by the patient may be reduced by increasing the elimination of the radionuclide from the body by forced diuresis and frequent urinary voiding.

5. PHARMACOLOGICAL PROPERTIES

In the inflammatory processes IgG labelled with technetium (Tc-99m) is sufficiently taken up, to reduce background radioactivity and allow scintigraphic localization of the inflammatory process.

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Diagnostic Radiopharmaceuticals, inflammation and infection detection, technetium (Tc-99m) compounds, technetium (Tc-99m) human immunoglobulin. ATC code: V09DA01

5.2 Pharmacokinetic properties
After intravenous administration, Tc-99m-IgG for a longer time is present in the bloodstream. Main blood pool is clearly visible after 4 hours. Radioactivity in liver is slightly higher than it could be estimated based on the presence of radiopharmaceutical product in the blood. Uptake doesn’t increase adequately to the time. There is no secretion into bile. Shortly after administration the kidneys and bladder are visible. Approximately 50% of the administered radioactivity is secreted by the kidneys within 24 hours. The spleen is visible, but the accumulation of radioactivity is significantly lower than in the liver or kidney. There is no specific uptake in other organs. There is no non-specific uptake in the joints.

5.3 Preclinical safety data
Polyclonal human immunoglobulin G (IgG) is obtained by ethaonal fractionation of plasma collected from venous blood. Plasma honour donors is always tested after downloading.

It is necessary to meet the following requirements:
- Negative test HbsAg (surface antigen, hepatitis B)
- Negative test HCV and HBV-2
- Negative test for antibodies to HCV.
Fractionation of ethanol and an integrated system Theraflex MB Plasma eliminates the risk of transmission of viral diseases. In studies in mice, the product does not exhibit excessive toxicity. There was no mutagenic activity and acute toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Vial I:
- Sodium citrate dihydrate
- Citric acid monohydrate
Vial II:
- Stannous chloride dihydrate
- Tricine
- PBS: Sodium chloride
- Potassium chloride
- Disodium hydrogen phosphate
- Potassium dihydrogen phosphate

6.2 Incompatibilities
Not known.

6.3 Shelf life
Kit for radiopharmacopeia preparation
Kit shelf life: 9 months.
Store in the fridge (2°C – 8°C).

Kit for technetium (Tc-99m) labelling
Shelf life: up to 3 hours after labelling.

6.4 Special precautions for storage
After labelling the product should be stored not longer than 3 hours at the temperature up to 25°C and in radiation shielding container.
During transportation (not longer than 2 days) up to 35°C. This product should be stored in accordance with national regulations concerning radioactive products.

6.5 Nature and contents of container

The kit package contains two glass vials (Vial I and Vial II) of 10 mL volume, closed with a rubber stopper and an aluminium crim cap. The vials are supplied in cardboard boxes. Vials I and II contain components for preparation of Techimmun.

6.6 Special precautions for disposal and other handling
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.

Content of the vial from the kit intended for use only after adequate preparation. The content is not intended for direct use to the patient without proper preparation.

The content of the kit, before preparation, is not radioactive. But when combined with sodium pertechnetate (Tc-99m) solution, the product should be stored in the shielding container.
If at any time in the preparation process of this product the integrity of this vial is compromised, it should not be used.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.
The residual activity of the generator must be estimated before disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instruction for product preparation is described in section 12.