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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC and package leaflet for (^{99}Mo/^{99m}Tc) generator

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Executive summary

This guideline describes the information to be included in the Summary of Products Characteristics (SmPC) and Package Leaflet for (^{99}Mo/^{99m}Tc) generator.

1. Introduction (background)

The purpose of this core SmPC and Package Leaflet is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC) for (^{99}Mo/^{99m}Tc) generator [1]. This guideline should be read in conjunction with the core SmPC and Package Leaflet for Radiopharmaceuticals, the QRD product information templates and the guideline on Summary of Product Characteristics.

This Core SmPC has been prepared on the basis of national SmPCs taking into account the approved Core Safety Profile (CSP) from the recently finished PSUR worksharing procedure and recently finalised European procedures. However, any new application for a (^{99}Mo/^{99m}Tc) generator should be submitted with all the needed and adequate data in order to be valid.

The indications concerning labelling of red blood cells are not part of this generator's Core SmPC as they are authorised with the respective kit for pre-treatment with a reducing agent. The indication brain scintigraphy which was included in the previous core SmPC is considered no more clinically relevant and was therefore deleted.

The activities to be administered to children and to adolescents may be calculated according to the EANM Dosage Card [Lassmann M et al. Eur J Nucl Med Mol Imaging (2008) 35:1667].

Note: Section 4.8 Undesirable effects was completely revised to meet the current medical knowledge. The content of the CSP resulting from the PSUR worksharing was included completely. Section 4.8. of the CSP is probably based on the original SmPC version from 1992 and has not been updated since. Therefore, a comprehensive search of the marketing authorisation holder's (MAH) adverse reactions database was performed covering the complete lifetime of the medicinal product, and all reported side effects were medically assessed for inclusion into the SmPC. The frequency was set to unknown for all symptoms, since all information was solely derived from the spontaneous reporting system. Compared to the CSP a table was introduced and includes a MedDRA tabulation of adverse reactions to adapt the structure to the current requirements for SmPCs. The symptom "coma" as listed in the CSP was included into the SmPC even though no spontaneous reports of coma have been received by the MAH to date.

2. Scope

This core SmPC and Package Leaflet covers (^{99}Mo/^{99m}Tc) generator.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

[1] Concept paper on the harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products (EMEA/CHMP/EWP/12052/2008)

4. Core SmPC and package leaflet for (^{99}Mo/^{99m}Tc) generator

Core SmPC and package leaflet for (^{99}Mo/^{99m}Tc) generator

Annex I

Summary of product characteristics

< ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.>

1. Name of the medicinal product

{(Invented) name strength} GBq radionuclide generator

2. Qualitative and quantitative composition

Sodium pertechnetate (^{99m}Tc) injection is produced by means of a (^{99}Mo/^{99m}Tc) generator. Technetium (^{99m}Tc) decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.01 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13 x 10^5 years, can be regarded as quasi stable.

The radionuclide generator containing the parent isotope ^{99}Mo, adsorbed on a chromatographic column delivers sodium pertechnetate (^{99m}Tc) injection in sterile solution.

The ^{99}Mo on the column is in equilibrium with the formed daughter isotope ^{99m}Tc. The generators are supplied with the following ^{99}Mo activity amounts at activity reference time which deliver the following technetium (^{99m}Tc) amounts, assuming a 100% theoretical elution yield and 24 hours time from previous elution and taking into account that branching ratio of ^{99}Mo is about 87%: *[Product specific]*

^{99m}Tc activity (Maximal theoretical eluable activity at calibration date, {XX} CET)	*i.e.* 2.0										GBq
^{99}Mo activity (at calibration date, {XX} CET)	*i.e.* 2.5										GBq

The technetium (^{99m}Tc) amounts available by a single elution depend on the real yields of the kind of generator used itself declared by manufacturer and approved by NCA.

Excipient(s) with known effect

Each mL of sodium pertechnetate (^{99m}Tc) solution contains {XX} mg of sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Radionuclide generator.

[Appearance product specific]

4. Clinical particulars

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

The eluate from the radionuclide generator (sodium pertechnetate (^{99m}Tc) injection) is indicated for:

labelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such solution

Thyroid scintigraphy: direct imaging and measurement of thyroid uptake to give information on the size, position, nodularity and function of the gland in case of thyroid disease.

Salivary gland scintigraphy: diagnosis of chronic sialadenitis (e.g. (Sjögren's Syndrom) as well as assessment of salivary gland function and duct patency in salivary glands disorders and monitoring of the response to therapeutic interventions (in particular radio iodine therapy).

Location of ectopic gastric mucosa (Meckel's diverticulum).

Lacrimal duct scintigraphy: to assess functional disorders of lacrimation and monitoring of the response to therapeutic interventions

4.2 Posology and method of administration

Posology

If sodium pertechnetate (^{99m}Tc) is administered intravenously, activities may vary widely according to the clinical information required and the equipment employed. The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified. for certain indications. Recommended activities are as follows:

Adults (70kg) and elderly population

- Thyroid scintigraphy: 20-80 MBq
- Salivary gland scintigraphy: 30 to 150 MBq for static images up to 370 MBq for dynamic images
- Meckel's diverticulum scintigraphy: 300-400 MBq
- Lacrimal duct scintigraphy: 2-4 MBq per drop per eye

Renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group.

The activity to be administered to children and adolescents must be adapted <and may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card>; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent correction factor given in the table below (see Table 1).

$$A[MBq]_{Administered} = \text{Baseline Activity} \times \text{Multiple}$$

Thyroid scintigraphy: Activity administered [MBq] = 5.6 MBq x correction factor (Table 1). A minimal activity of 10 MBq is necessary for obtaining images of sufficient quality.

Identification/location of ectopic gastric mucosa: Activity administered [MBq] = 10.5 MBq x correction factor (Table 1). A minimal activity of 20 MBq is necessary in order to obtain images of sufficient quality.

Table 1: Weight-dependent correction factors in the paediatric population (for thyroid scintigraphy and identification/location of ectopic gastric mucosa) according to the EANM-May 2008 guidelines

Weight [kg]	Multiple	**Weight [kg]**	Multiple	**Weight [kg]**	Multiple
3	1	**22**	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57
6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

Salivary gland scintigraphy: The Paediatric Task Group of EANM (1990) recommends that the activity to be administered to a child should be calculated from the body weight according to the table below (see Table 2) with a minimum dose of 10 MBq in order to obtain images of sufficient quality.

Table 2: Weight-dependent correction factor in the paediatric population (for salivary gland scintigraphy) according toEANM 1990 recommendations

Weight [kg]	Factor	**Weight [kg]**	Factor	**Weight [kg]**	Factor
3	0.1	**22**	0.50	**42**	0.78
4	0.14	**24**	0.53	**44**	0.80
6	0.19	**26**	0.56	**46**	0.82
8	0.23	**28**	0.58	**48**	0.85
10	0.27	**30**	0.62	**50**	0.88
12	0.32	**32**	0.65	**52-54**	0.90
14	0.36	**34**	0.68	**56-58**	0.92
16	0.40	**36**	0.71	**60-62**	0.96
18	0.44	**38**	0.73	**64-66**	0.98
20	0.46	**40**	0.76	**68**	0.99

Lacrimal duct scintigraphy: Recommended activities apply as well for adults as for children.

Method of administration

For intravenous or ocular use.

For multidose use.

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

For patient preparation, see section 4.4.

In thyroid scintigraphy, salivary gland scintigraphy and identification/location of ectopic gastric mucosa, the sodium pertechnetate (^{99m}Tc) solution is administered by intravenous injection.

In lacrimal duct scintigraphy, drops are instilled in each eye (ocular use).

Image acquisition

Thyroid scintigraphy: 20 minutes after intravenous injection.

Salivary gland scintigraphy: immediately after intravenous injection and at regular intervals for 15 minutes.

Identification/location of ectopic gastric mucosa (Meckel Diverticulum): immediately after intravenous injection and at regular intervals for 30 minutes.

Lacrimal duct scintigraphy: dynamic acquisition within 2 minutes after instillation, followed by static images acquired at regular intervals within 20 minutes.

4.3 Contraindications

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

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 <and therapeutic effect>.

Renal impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population

For information on the use in paediatric population, see section 4.2 <or 5.1>.

Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Thyroid blocking is of special importance in the paediatric patient population except for thyroid scintigraphy.

Patient preparation

Pre-treatment of patients with thyroid-blocking medicinal products may be necessary for certain indications.

The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

To avoid false positives or to minimise irradiation by reduction of pertechnetate accumulation in the thyroid and salivary glands, a thryroid blocking agent should be given prior to lacrimal duct scintigraphy or Meckel's diverticulum scintigraphy. Conversely a thyroid blocking agent must NOT be used before thyroid, parathyroid or salivary glands scintigraphy.

Before the application of sodium (^{99m}Tc)pertechnetate solution for scintigraphy of Meckel's diverticulum the patient must keep an empty stomach for 3 to 4 hours to reduce intestinal peristalsis.

After in vivo labelling of erythrocytes using stannous ions for reduction sodium pertechnetate (^{99m}Tc) is primarily built into erythrocytes, therefore Meckel's scintigraphy should be performed before or some days after in vivo labelling of erythrocytes.

After the procedure

Close contact with infants and pregnant women should be restricted during 12 hours.

Specific warnings

<Sodium pertechnetate (^{99m}Tc) solution for injection contains {XX} mg/mL of sodium.

Depending on the time when the injection is administered, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg). This should be taken into account in patient on low sodium diet.>

When sodium pertechnetate (^{99m}Tc) solution is used for labelling of a kit, the determination of the overall sodium content must take into account the sodium derived from the eluate and the kit. Please refer to the package leaflet of the kit.

In salivary gland scintigraphy a lower specificity of the method should be expected compared to magnetic resonance sialography.

For precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Atropine, isoprenaline and analgesics may cause a delay of gastric emptying and thereby cause a redistribution of (^{99m}Tc) pertechnetate in abdominal imaging.

Administration of laxatives should be withheld since they irritate the gastrointestinal tract. Contrast-enhanced studies (e.g. barium) and upper gastro-intestinal examination should be avoided within 48h prior to administration of pertechnetate (^{99m}Tc) for Meckel's diverticulum scintigraphy.

Many pharmacological medicinal products are known to modify the thyroid uptake.

- antithyroid medicinal products (e.g. carbimazole or other imidazole derivatives such as propylthiouracil), salicylates, steroids, sodium nitroprusside, sodium sulfobromophtalein, perchlorate should be withheld for 1 week prior thyroid scintigraphy ;
- phenylbutazone and expectorants should be withheld for 2 weeks ;
- natural or synthetic thyroid preparations (e.g. sodium thyroxine, sodium liothyronine, thyroid extract) should be withheld for 2-3 weeks
- amiodarone, benzodiazepines, lithium should be withheld for 4 weeks
- intravenous contrast agents should not have been administered within 1-2 months.

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

Administration of pertechnetate (^{99m}Tc) to a woman who is known to be pregnant should be justified by medical need and a positive individual benefit risk assessment for the mother and the foetus. Alternative non-irradiating diagnostic modalities should be taken into account.

^{99m}Tc (as free pertechnetate) has been shown to cross the placental barrier.

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding 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, breast-feeding should be interrupted for 12 hours post administration 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

Sodium pertechnetate (^{99m}Tc) solution has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Information on adverse reactions is available from spontaneous reporting. The reported reaction types are anaphylactoid reactions, vegetative reactions, as well as different kinds of injection site reactions. Sodium pertechnetate (^{99m}Tc) from the {(Invented) name} radionuclide generator is used for radioactive labelling of a variety of compounds. These medicinal products generally have a higher potential for adverse reactions than ^{99m}Tc, and therefore the reported adverse reactions are rather related to the labelled compounds than to ^{99m}Tc. The possible types of adverse reactions following intravenous administration of a ^{99m}Tc-labelled pharmaceutical preparation will be dependent on the specific compound being used. Such information can be found in the SmPC of the kit used for radiopharmaceutical preparation.

Tabulated list of adverse reactions

The frequency of undesirable effects is defined as follows:

Not known (cannot be estimated from the available data).

Immune system disorders

Frequency unknown*: Anaphylactoid reactions (e.g. dyspnoea, coma, urticaria, erythema, rash, pruritus, oedema at various location e.g. face oedema)

Nervous system disorders

Frequency unknown*: Vasovagal reactions (e.g. syncope, tachycardia, bradycardia, dizziness, headache, vision blurred, flushing)

Gastrointestinal disorders

Frequency unknown*: Vomiting, nausea, diarrhoea

General disorders and administration site conditions

Frequency unknown*: Injection site reactions due to extravasation (e.g. cellulitis, pain, erythema, swelling)

* Adverse reactions derived from spontaneous reporting

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 5.2 mSv when the maximal recommended activity of 400 MBq is administered these adverse reactions are expected to occur with a low probability.

Description of selected adverse reactions

Anaphylactic reactions (e.g. dyspnoea, coma, urticaria, erythema, rash, pruritus, oedema at various locations [e.g. face oedema])

Anaphylactic reactions have been reported following intravenous injection of sodium perchtechnetate (^{99m}Tc) and include various skin or respiratory symptoms like skin irritations, oedema, or dyspnoea.

Vegetative reactions (nervous system and gastrointestinal disorders)

Single cases of severe vegetative reactions have been reported, however, most of the reported vegetative reactions include gastrointestinal reactions like nausea or vomiting. Other reports include vasovagal reactions like headache or dizziness. Vegetative reactions are rather considered to be related to the examinational setting than to technetium (^{99m}Tc), especially in anxious patients.

General disorders and administration site conditions

Other reports describe local injection site reactions. Such reactions are related to extravasation of the radioactive material during the injection, and the reported reactions rank from local swelling up to cellulitis. Depending on the administered radioactivity and the labeled compound, extended extravasation may necessitate surgical treatment.

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 national reporting system listed in Appendix V*.

[**For the printed material, please refer to the guidance of the annotated QRD template.*]

4.9 Overdose

In the event of administration of a radiation overdose with sodium pertechnetate (^{99m}Tc), the absorbed dose should be reduced where possible by increasing the elimination of the radionuclide from the body by defaecation, forced diuresis and frequent bladder voiding.

The uptake in the thyroid, salivary glands and the gastric mucosa can be significantly reduced when sodium or potassium perchlorate is given immediately after an accidentally high dose of sodium pertechnetate (^{99m}Tc) was administered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, various thyroid diagnostic radiopharmaceuticals, ATC code: V09FX01.

No pharmacological activity has been observed in the range of doses administered for diagnostic purposes.

<Paediatric population>

<The European Medicines Agency has waived the obligation to submit the results of studies with <{(Invented) Name}> [or for generics: <the reference medicinal product containing {name of the active substance(s)}>] in all subsets of the paediatric population in {condition as per Paediatric Investigation Plan (PIP) decision, for the granted indication} (see section 4.2 for information on paediatric use).>

<The European Medicines Agency has deferred the obligation to submit the results of studies with <{(Invented) Name}> [or for generics: <the reference medicinal product containing {name of the active substance(s)}>] in one or more subsets of the paediatric population in {condition, as per Paediatric Investigation Plan (PIP) decision for the granted indication} (see section 4.2 for information on paediatric use).>

<This medicinal product has been authorised under a so-called 'conditional approval' scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on the product every year and this SmPC will be updated as necessary.>

<This medicinal product has been authorised under 'exceptional circumstances'.

This means that due to <the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.>

5.2 Pharmacokinetic properties

Distribution

The pertechnetate ion has similar biological distribution to iodide and perchlorate ions, concentrating temporarily in salivary glands, choroid plexus, stomach (gastric mucosa) and in the thyroid gland, from which it is eliminated, unchanged. The pertechnetate ion also tends to concentrate in areas with increased vascularisation or with abnormal vascular permeability, particularly when pre-treatment with blocking agents inhibits uptake in glandular structures. With intact blood brain barrier, sodium pertechnetate (^{99m}Tc) does not penetrate into the brain tissue.

Organ uptake

In the blood 70-80% of the intravenously injected sodium pertechnetate (^{99m}Tc) is bound to proteins, primarily in an unspecific way to albumin. The unbound fraction (20-30%) accumulates temporarily in thyroid and salivary glands, stomach and nasal mucous membranes as well as in the plexus chorioideus.

Sodium pertechnetate (^{99m}Tc) in contrast to iodine, nevertheless, is neither used for the thyroid hormone synthesis (organification), nor absorbed in the small intestine. In the thyroid the maximum accumulation, depending on functional status and iodine saturation (in euthyroidism approx. 0.3-3%, in hyperthyroidism and iodine depletion up to 25%) is reached about 20 min after injection and then decreases quickly. This also applies for the stomach mucous membrane parietal cells and the salivary glands acinar cells.

In contrast to the thyroid which releases sodium pertechnetate (^{99m}Tc) in the bloodstream the salivary glands and the stomach secrete sodium pertechnetate (^{99m}Tc) in the saliva and gastric juice, respectively. The accumulation by the salivary gland lies in the magnitude of 0.5% of the applied activity with the maximum reached after about 20 minutes. One hour after injection, the concentration in the saliva is about 10-30 fold higher than in the plasma. The excretion can be accelerated by lemon juice or by stimulation of the parasympathetic nerve system, the absorption is reduced by perchlorate.

Elimination

Half life in plasma is approximately 3 hours. Sodium pertechnetate (^{99m}Tc) is not metabolised in the organism. One fraction is eliminated very quickly renally, the rest more slowly via faeces, salivary and tear liquid. Excretion during the first 24 hours following administration is mainly urinary (approximately 25%) with faecal excretion occurring over the next 48 hours. Approximately 50% of the administered activity is excreted within the first 50 hours. When selective uptake of pertechnetate (^{99m}Tc) in glandular structures is inhibited by the preadministration of blocking agents, excretion follows the same pathways but there is a higher renal clearance.

The above data are not valid when sodium pertechnetate (^{99m}Tc) is used for labelling of another radiopharmaceutical.

5.3 Preclinical safety data

There is no information on acute, subacute and chronic toxicity from single or repeated dose administration. The quantity of sodium pertechnetate (^{99m}Tc) administered during clinical diagnostic procedures is very small and, apart from allergic reactions, no other adverse reactions have been reported.

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

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

Reproductive toxicity

Placental transfer of ^{99m}Tc from intravenously administered sodium pertechnetate (^{99m}Tc) has been studied in mice. The pregnant uterus was found to contain as much as 60% of the injected ^{99m}Tc when administered without perchlorate pre-administration. Studies performed on pregnant mice during gestation, gestation and lactation, and lactation alone showed changes in progeny which included weight reduction, hairlessness and sterility.

6. Pharmaceutical particulars

6.1 List of excipients

[Product specific, including accessories which belong to the radionuclide generator as the solution for elution]

6.2 Incompatibilities

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

6.3 Shelf life

[Product specific]

Generator: {XX} days from manufacturing date.

The calibration date and the expiry date are stated on the label.

Sodium pertechnetate (^{99m}Tc) eluate: After elution, use within {XX} hours. This medicinal product does not require any special storage conditions.

Elution vials: {XX} months.

Solution for elution: {XX} months

6.4 Special precautions for storage

[Product specific]

Eluate: For storage conditions after elution 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

[Product specific, including containers of the accessories, package sizes]

6.6 Special precautions for disposal and other handling

General warnings

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.

If at any time the integrity of the generator or the vial with the eluted solution 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 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.

7. Marketing Authorisation Holder

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. Marketing Authorisation number

9. Date of first authorisation/renewal of the authorisation

<Date of first authorisation: {DD month YYYY}>

<Date of latest renewal: {DD month YYYY}>

10. Date of revision of the text

<{MM/YYYY}>

<{DD/MM/YYYY}>

<{DD month YYYY}>

11. Dosimetry

The data listed below are from ICRP 80 and are calculated according to the following assumptions:

(I) Without pre-treatment with a blocking agent:

Organ	**Absorbed dose per administered unit of activity (mGy/MBq)**				
	Adults	**15 years**	**10 years**	**5 years**	**1 year**
Adrenal glands	0.0037	0.0047	0.0072	0.011	0.019
Bladder wall	0.018	0.023	0.030	0.033	0.060
Bone surfaces	0.0054	0.0066	0.0097	0.014	0.026
Brain	0.0020	0.0025	0.0041	0.0066	0.012
Breasts	0.0018	0.0023	0.0034	0.0056	0.011
Gallbladder	0.0074	0.0099	0.016	0.023	0.035
Gastrointestinal tract					
- Stomach wall	0.026	0.034	0.048	0.078	0.16
- Small intestine	0.016	0.020	0.031	0.047	0.082
- Colon	0.042	0.054	0.088	0.14	0.27
- Ascending colon wall	0.057	0.073	0.12	0.20	0.38

- Descending colon wall	0.021	0.028	0.045	0.072	0.13
Heart	0.0031	0.0040	0.0061	0.0092	0.017
Kidneys	0.0050	0.0060	0.0087	0.013	0.021
Liver	0.0038	0.0048	0.0081	0.013	0.022
Lungs	0.0026	0.0034	0.0051	0.0079	0.014
Muscles	0.0032	0.0040	0.0060	0.0090	0.016
Oesophagus	0.0024	0.0032	0.0047	0.0075	0.014
Ovaries	0.010	0.013	0.018	0.026	0.045
Pancreas	0.0056	0.0073	0.011	0.016	0.027
Red bone marrow	0.0036	0.0045	0.0066	0.0090	0.015
Salivary glands	0.0093	0.012	0.017	0.024	0.039
Skin	0.0018	0.0022	0.0035	0.0056	0.010
Spleen	0.0043	0.0054	0.0081	0.012	0.021
Testes	0.0028	0.0037	0.0058	0.0087	0.016
Thymus	0.0024	0.0032	0.0047	0.0075	0.014
Thyroid	0.022	0.036	0.055	0.12	0.22
Uterus	0.0081	0.010	0.015	0.022	0.037
Other tissue	0.0035	0.0043	0.0064	0.0096	0.017
Effective dose (mSv/MBq)	**0.013**	**0.017**	**0.026**	**0.042**	**0.079**

(II) With pre-treatment with a blocking agent:

Organ	**Absorbed dose per administered unit of activity (mGy/MBq) when blocking agents are administered**				
	Adults	**15 years**	**10 years**	**5 years**	**1 year**
Adrenal glands	0.0029	0.0037	0.0056	0.0086	0.016
Bladder wall	0.030	0.038	0.048	0.050	0.091
Bone surfaces	0.0044	0.0054	0.0081	0.012	0.022
Brain	0.0020	0.0026	0.0042	0.0071	0.012
Breasts	0.0017	0.0022	0.0032	0.0052	0.010
Gallbladder	0.0030	0.0042	0.0070	0.010	0.013
Gastrointestinal tract					
- Stomach wall	0.0027	0.0036	0.0059	0.0086	0.015
- Small intestine	0.0035	0.0044	0.0067	0.010	0.018
- Colon	0.0036	0.0048	0.0071	0.010	0.018
- Ascending colon wall	0.0032	0.0043	0.0064	0.010	0.017
- Descending colon wall	0.0042	0.0054	0.0081	0.011	0.019
Heart	0.0027	0.0034	0.0052	0.0081	0.014
Kidneys	0.0044	0.0054	0.0077	0.011	0.019
Liver	0.0026	0.0034	0.0053	0.0082	0.015
Lungs	00023	0.0031	0.0046	0.0074	0.013
Muscles	0.0025	0.0031	0.0047	0.0072	0.013
Oesophagus	0.0024	0.0031	0.0046	0.0075	0.014
Ovaries	0.0043	0.0054	0.0078	0.011	0.019
Pancreas	0.0030	0.0039	0.0059	0.0093	0.016
Red bone marrow	0.0025	0.0032	0.0049	0.0072	0.013

Organ	Absorbed dose per administered unit of activity (mGy/MBq) when blocking agents are administered				
Skin	0.0016	0.0020	0.0032	0.0052	0.0097
Spleen	0.0026	0.0034	0.0054	0.0083	0.015
Testes	0.0030	0.0040	0.0060	0.0087	0.016
Thymus	0.0024	0.0031	0.0046	0.0075	0.014
Thyroid	0.0024	0.0031	0.0050	0.0084	0.015
Uterus	0.0060	0.0073	0.011	0.014	0.023
Other tissue	0.0025	0.0031	0.0048	0.0073	0.013
Effective dose (mSv/MBq)	**0.0042**	**0.0054**	**0.0077**	**0.011**	**0.019**

The effective dose resulting from the intravenous administration of 400 MBq of sodium pertechnetate (^{99m}Tc) to an adult weighing 70 kg is about 5.2 mSv.

After pretreatment of patients with a blocking agent and administration of 400 MBq of sodium pertechnetate (^{99m}Tc) to an adult weighing 70 kg the effective dose is 1.7 mSv.

The radiation dose absorbed by the lens of the eye following administration of sodium pertechnetate (^{99m}Tc) for lacrimal duct scintigraphy is estimated to be 0.038 mGy/MBq. This results in an effective dose equivalent of less than 0.01 mSv for an administered activity of 4 MBq.

The specified radiation exposure is only applicable if all organs accumulating sodium pertechnetate (^{99m}Tc) will function normally. Hyper/hypofunction (e.g. of the thyroid, gastric mucosa or kidney) and extended processes with impairment to the blood-brain-barrier or renal elimination disorders, may result in changes to the radiation exposure, locally even in strong increases of it.

The surface dose rates and the accumulated dose depends on many factors. Overall, radiation measurement on the environment and during work are critical and should be practised.

12. Instructions for preparation of radiopharmaceuticals

[Product specific: e. g. handling of the radionuclide generator, elution frequency, configuration of the radionuclide generator, use and specifics of the accessories, description of the correlation technetium (^{99m}Tc) elution yield, mandatory quality testing by the user, e. g. tests on molybdenum (^{99}Mo) break through.]

Elution of the generator must be performed in premises complying with the national regulations concerning the safety of use of radioactive products.

The solution eluted is a clear and colourless sodium pertechnetate (^{99m}Tc) solution, with a pH between {XX} and {XX} and a radiochemical purity equal to or greater than {XX}.

When sodium pertechnetate (^{99m}Tc) solution is used for kit labelling, please refer to the package leaflet of the concerned kit.

Quality control

Radioactivity and the molybdenum (^{99}Mo) break-through must be checked before administration.

The test for molybdenum (^{99}Mo) break-through can be performed either according to Ph. Eur. or to any other validated methods able to determine a molybdenum (^{99}Mo) content below 0.1 per cent of total radioactivity at the date and hour of administration.

<The first eluate obtained from this generator can be normally used, unless otherwise specified. Eluates even eluted later than 24 hours from the last elution can be used for kit labelling, unless it is excluded by the specifications of the relevant kit SmPC.>

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.

B. Package leaflet

Package leaflet: Information for the patient

{(Invented) name strength} GBq radionuclide generator

Sodium pertechnetate (^{99m}Tc) solution

< ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.>

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What X is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only.

X is a technetium (^{99m}Tc) generator, which means it is a device used to obtain a solution for injection of sodium pertechnetate (^{99m}Tc). When this radioactive solution is injected, it temporarily collects in certain areas of the body. The low quantity of radioactivity injected can be detected outside of the body by special cameras. The nuclear medicine doctor will then take an image (scan) of the concerned organ which can give him valuable information about the structure and the function of this organ.

After injection the sodium pertechnetate (^{99m}Tc) solution is used to obtain images of various body parts such as the:

- thyroid gland
- salivary glands
- appearance of stomach tissue in an abnormal location (Meckel diverticulum)
- tear ducts of the eyes

The sodium pertechnetate (^{99m}Tc) solution can also be used in combination with another product to prepare another radiopharmaceutical medicine. In this case, please refer to the corresponding package leaflet.

The nuclear medicine doctor will explain to you what type of examination will be performed with this product.

The use of sodium pertechnetate (^{99m}Tc) solution does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. What you need to know before the sodium pertechnetate (^{99m}Tc) solution obtained with X is used

The sodium pertechnetate (^{99m}Tc) solution obtained with X must not be used

- if you are allergic to sodium pertechnetate (^{99m}Tc) or any of the other ingredients of this medicine (listed in section 6).

Warning and precautions

Inform your nuclear medicine doctor in the following cases:

- if you suffer from allergies, as a few cases of allergic reactions have been observed after administration of sodium pertechnetate (^{99m}Tc) solution
- if you suffer from kidney disease
- if you are pregnant or believe you may be pregnant
- if you are breast-feeding

Your nuclear medicine doctor will inform you if you need to take any special precautions after using this medicine. Talk to your nuclear medicine doctor if you have any questions.

Before administration of sodium pertechnetate (^{99m}Tc) solution you should:

- drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the study.
- you should be fasting for 3 to 4 hours before Meckel's diverticulum scintigraphy to keep the small bowel peristalsis low.

Children and adolescents

Please talk to your nuclear medicine doctor if you or your child are under 18 year old.

Other medicines and sodium pertechnetate (^{99m}Tc) solution

Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines since they may interfere with the interpretation of the images; and especially the following medicines:

- **atropine**, used for example:
  - to reduce stomach, bowel or gall bladder spasms
  - to reduce pancreas secretions
  - in ophthalmology

  - before administering an anaesthesia
  - to treat reduced heart beat or
  - as an antidote
- **isoprenaline**, a medicine to treat reduced heart beat
- **pain killers**
- **laxatives** (they should not be taken during this procedure since they irritate the gastrointestinal tract)
- if you had **contrast-enhanced studies** (e.g. with the contrast agent barium) or upper gastro-intestinal examination (as these should be avoided within 48h prior to Meckel's diverticulum scintigraphy)
- **antithyroid medicines** (e.g. carbimazole or other imidazole derivatives such as propylthiouracil), **salicylates**, **steroids**, **sodium nitroprusside**, **sodium sulfobromophtalein**, **perchlorate**) (as they should not be taken for 1 week prior to scintigraphy)
- **phenylbutazone** to treat fever, pain and inflammation in the body (as it should not be taken for 2 weeks prior to scintigraphy)
- **expectorants** (as they should not be taken for 2 weeks prior to scintigraphy)
- **natural or synthetic thyroid preparations** (e.g. sodium thyroxine, sodium liothyronine, thyroid extract) (as they should not be taken for 2-3 weeks prior to scintigraphy)
- **amiodarone** an antiarrhythmic agent (as it should not be taken for 4 weeks prior to scintigraphy)
- **benzodiazepines** used for example for sedation, or as anti-anxiety or anti-convulsion or muscle relaxant medication or **lithium** used as a a mood stabiliser in manic-depressive illness (as both should not be taken for 4 weeks prior to scintigraphy)
- **intravenous contrast agents** for radiologic examinations of the body (as they should not have been administered for 1-2 months prior to scintigraphy)

Please ask your nuclear medicine specialist before taking any medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.

You must inform the nuclear medicine doctor before the administration of sodium pertechnetate (^{99m}Tc) solution if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding. When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

If you are pregnant, your nuclear medicine doctor will only administer this medicine during pregnancy if a benefit is expected which would far outweigh the risks.

If you are breast-feeding, please tell your nuclear medicine doctor, as he/she will advise you to stop doing so until the radioactivity has left your body. This takes about 12 hours. The expressed milk should be discarded. Resuming breast-feeding should be in agreement with the specialist in Nuclear Medicine who will supervise the procedure.

Driving and using machines

Sodium pertechnetate (^{99m}Tc) solution has no influence on the ability to drive and use machines.

Sodium pertechnetate solution contains sodium

Sodium pertechnetate solution contains {XX} mg/mL of sodium. Depending on the volume injected, the limit of 1 mmol (23 mg) of sodium per dose administered may be exceeded. This must be taken into account if you are on a low-salt diet.

3. How the sodium pertechnetate (^{99m}Tc) solution obtained with X is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. X will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of sodium pertechnetate (^{99m}Tc) solution to be used in your case. It will be the smallest quantity necessary to get the desired information.

The quantity usually recommended to be administered for an adult ranges depending on the test to be performed, and ranges between 2 and 400 MBq (megabecquerel, the unit used to express radioactivity).

Use in children and adolescents

In children and adolescents, the quantity to be administered will be adapted to the child's weight.

Administration of sodium pertechnetate (^{99m}Tc) solution and conduct of the procedure

Depending on the purpose of the examination, the product will be administered by injection into an arm vein or may be instilled into the eyes in the form of drops.

One administration is sufficient to conduct the test that your doctor needs.

Duration of the procedure

Your nuclear medicine doctor will inform you about the usual duration of the procedure.

Scans can be performed at any time, between the time of injection and for up to 24 hours after the administration, depending on the type of examination.

After administration of sodium pertechnetate (^{99m}Tc) solution has been performed, you should:

- avoid any close contact with young children and pregnant women for the 12 hours following the injection
- urinate frequently in order to eliminate the product from your body
- after administration, you will be offered a drink and asked to urinate immediately preceding the test.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more sodium pertechnetate (^{99m}Tc) solution obtained with X than you should

An overdose is almost impossible because you will only receive a single dose of sodium pertechnetate (^{99m}Tc) solution precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. In particular, the nuclear medicine doctor in charge of the procedure may recommend that you drink plenty of fluids to remove the traces of radioactivity from your body.

Should you have any further questions on the use of this product, please ask your nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effect with frequency not known (cannot be estimated from the available data):

- allergic reactions, with symptoms such as
    - skin rash, itching
    - hives
    - swelling at various locations, e.g. of the face
    - shortage of breath
    - redness of the skin
    - coma
- circulatory reactions, with symptoms such as
    - rapid heart beat, slow heart beat
    - fainting
    - blurred vision
    - dizziness
    - headache
    - flushing
- gastrointestinal disorders, with symptoms such as
    - being sick (vomiting)
    - feeling sick (nausea)
    - diarrhoea
- injection site reactions, with symptoms such as
    - skin inflammation
    - pain
    - swelling
    - redness

This radiopharmaceutical product will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities.

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

[**For the printed material, please refer to the guidance of the annotated QRD template.*]

5. How X is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The information is intended for the specialist only.

This medicine must not be used after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>

<This medicine will not be used if it is noticed {description of the visible signs of deterioration}.>

6. Contents of the pack and other information

What X contains

The active substance is sodium pertechnetate (^{99m}Tc) solution.

The other ingredients are: [*Product specific*].

What X looks like and contents of the pack

The product is sodium pertechnetate (^{99m}Tc) solution provided by a radionuclide generator.

X has to be eluted and the obtained solution may be used itself or to radiolabelled some particular kits for radiopharmaceutical preparation.

Pack size

[Product specific]

Marketing Authorisation Holder and Manufacturer

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

This leaflet was last revised in {MM/YYYY} {month YYYY}

<This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on the medicine every year and this leaflet will be updated as necessary.>

<This medicine has been authorised under 'exceptional circumstances'. This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.>

<Other sources of information>

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.

<This leaflet is available in all EU/EEA languages on the European Medicines Agency website.>

The following information is intended for healthcare professionals only:

The complete SmPC of {(Invented) name} is provided <as a separate document> <as a tear-off section at the end of the printed leaflet> in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC [SmPC should be included in the box].