



ELUMATIC III®

TECHNETIUM [^{99m}Tc] GENERATOR

TECHNICAL LEAFLET:
SUMMARY OF PRODUCT CHARACTERISTICS

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1. TRADE NAME OF THE MEDICINAL PRODUCT

ELUMATIC III®
TECHNETIUM [^{99m}Tc] GENERATOR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The generator ELUMATIC III® is a system allowing elution of sodium pertechnetate [^{99m}Tc] injection (fission). The obtained technetium-99m solution is sterile and pyrogen-free, and complies with the requirements of the European Pharmacopoeia and of the U.S. Pharmacopoeia, including those for radiochemical purity (more than or equal to 95 %, average analysis : 99 %), and radionuclidic purity (at expiry date : ⁹⁹Mo ≤ 0.1 %, ¹³¹I ≤ 5.10⁻³ %, ¹⁰³Ru ≤ 5.10⁻³ %, ⁸⁹Sr ≤ 6.10⁻⁵ %, ⁹⁰Sr ≤ 6.10⁻⁶ %, alpha-emitting impurities ≤ 1.10⁻⁷ %, other gamma-emitting impurities ≤ 0.01 %). The solution is clear and colourless, with a pH ranging between 5.0 and 7.0, and contains no antimicrobial preservative. It is eluted from alumina chromatographic column on which fission produced molybdenum-99 (T_{1/2} = 66 h) parent of technetium-99m (T_{1/2} = 6.02 h) is fixed. The system is automatic and highly shielded.

Description

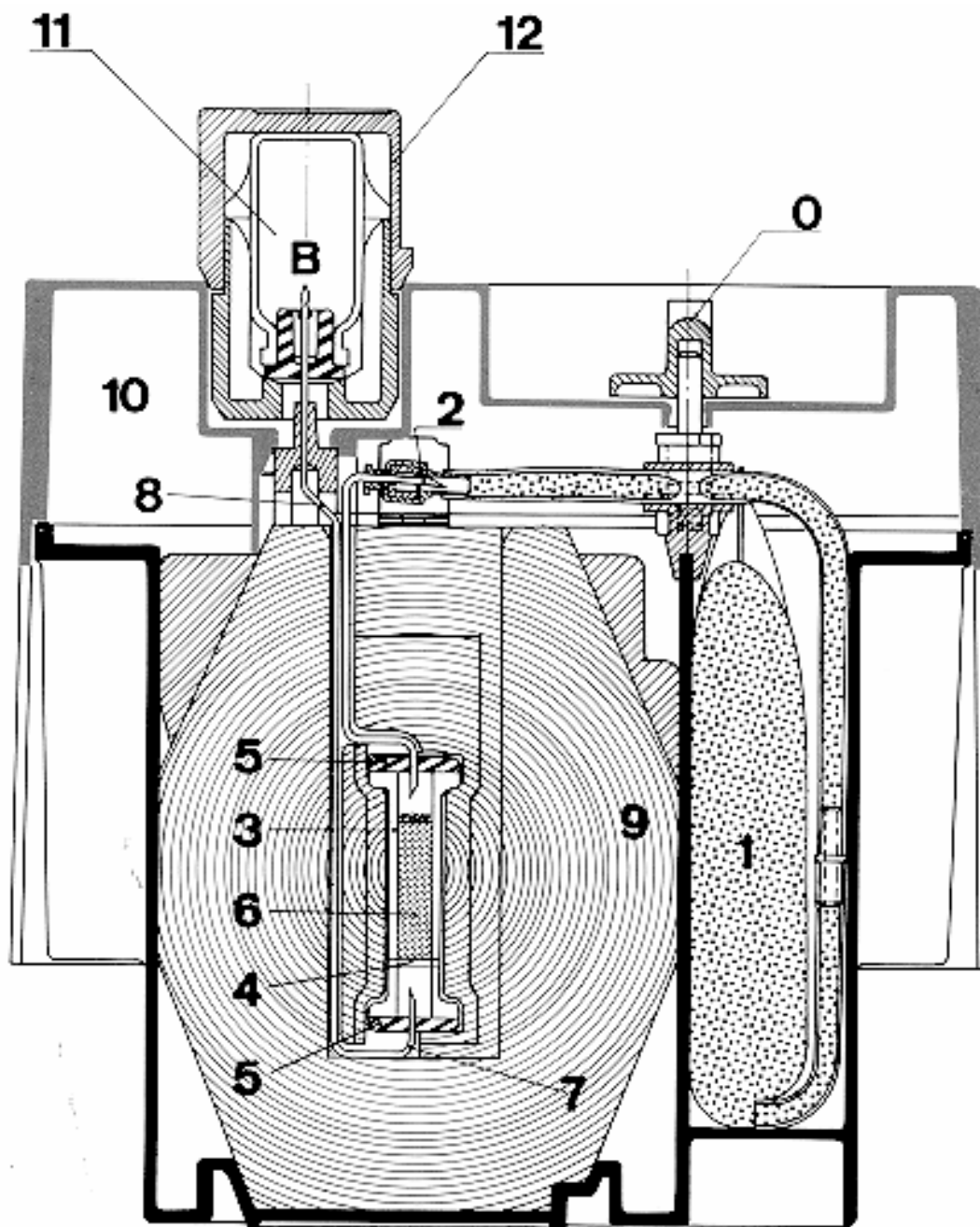
The system includes :

- A supple plastic bag (1) containing the eluent (0.9 % sodium chloride and 0.005 % sodium nitrate aqueous solution). The bag is connected by a stainless steel needle (2) to the top of the chromatographic column.
- A glass chromatographic column (3) with a filter at the bottom (4) to prevent any leakage of alumina. The column is obturated at both ends by caps maintained by metallic capsules (5). This column contains the alumina (6) which adsorbs the molybdate ions and is inert towards the pertechnetate ions.
- A needle (7) with one end connected to the bottom of the column. The other end (8) is to receive either a vacuum vial to elute the column, or a vial with a bacteriostatic solution so as to preserve sterility between two elutions.

The column and the needles are protected by a cylindro-conical lead shielding (9) with a minimal thickness of 52 mm. The whole system is placed in a parallelepipedic cover (23 x 21 x 14 cm) made of moulded nylon (10).

At the top part of the cover is the elution station protected by a (12) cylindrical container (B) in which a vial with a bacteriostatic solution (11) is placed. The end of the needle plunges in the solution. This vial contains an aqueous solution of lauryl bromide dimethylbenzylammonium (0.02 %).

Near the elution station is a cavity with a safety valve (O) turned off during the transport (O).



The sodium pertechnetate [^{99m}Tc] injection obtained meets the requirements of the European Pharmacopœia and of the U.S. Pharmacopœia.

The ELUMATIC III® is delivered in a tight metal drum.

Quantitative composition

Sodium pertechnetate [^{99m}Tc] (technetium-99m produced by radioactive decay of the parent radionuclide fission molybdenum-99 adsorbed on alumina) : Activity of the generator at the calibration date

Alumina : As required

Elution solution containing 0.9 % sodium chloride and 0.005 % sodium nitrate in a PVC bag : 200 ml

Bacteriostatic solution (lauryl-dimethylbenzylammonium bromide) : 0.25 ml per vial of bacteriostatic solution

Available activities

2	4	6	8	10	12	16	20	GBq
54	108	162	216	270	324	432	540	mCi

They are expressed in available technetium-99m, not in molybdenum-99.

Physical characteristics

Technetium-99m is produced by means of radioactive decay of molybdenum-99. Technetium-99m 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 which, in view of its long half-life of 2.13×10^5 years can be regarded as quasi stable.

Decay table for ⁹⁹Mo (half-life : 66 hours)

Days	Hours	%	Days	Hours	%	Days	Hours	%	Days	Hours	%	Days	Hours	%	Days	Hours	%
-8 d	-192	750.82	-4 d	-96	274.01	Calibration date	0	100.00	4 d	96	36.49	8 d	192	13.31	12 d	288	4.86
	-190	735.22		-94	268.32		2	97.92		98	35.73		194	13.04		290	4.76
	-188	719.94		-92	262.74		4	95.89		100	34.99		196	12.77		292	4.66
	-186	704.96		-90	257.28		6	93.89		102	34.26		198	12.50		294	4.56
	-184	690.33		-88	251.93		8	91.94		104	33.55		200	12.24		296	4.47
	-182	675.98		-86	246.70		10	90.03		106	32.85		202	11.99		298	4.38
	-180	661.94		-84	241.57		12	88.16		108	32.17		204	11.74		300	4.29
	-178	648.18		-82	236.55		14	86.33		110	31.50		206	11.49		302	4.20
	-176	634.71		-80	231.64		16	84.53		112	30.84		208	11.25		304	4.11
	-174	621.52		-78	226.82		18	82.78		114	30.20		210	11.02		306	4.02
	-172	608.61		-76	222.11		20	81.06		116	29.57		212	10.79		308	3.94
	-170	595.96		-74	217.49		22	79.37		118	28.96		214	10.57		310	3.86
-7 d	-168	583.57	-3 d	-72	213.01	1 d	24	77.72	5 d	120	28.36	9 d	216	10.35	13 d	312	3.78
	-166	571.45		-70	208.58		26	76.10		122	27.77		218	10.13		314	3.70
	-164	559.57		-68	204.25		28	74.52		124	27.19		220	9.92		316	3.62
	-162	547.94		-66	200.00		30	72.97		126	26.63		222	9.72		318	3.55
	-160	536.56		-64	195.84		32	71.46		128	26.07		224	9.51		320	3.47
	-158	525.41		-62	191.77		34	69.97		130	25.53		226	9.32		322	3.40
	-156	514.49		-60	187.79		36	68.52		132	25.00		228	9.12		324	3.33
	-154	503.80		-58	183.88		38	67.09		134	24.48		230	8.93		326	3.26
	-152	493.33		-56	180.06		40	65.70		136	23.97		232	8.75		328	3.19
	-150	483.07		-54	176.32		42	64.33		138	23.47		234	8.56		330	3.13
	-148	473.04		-52	172.65		44	63.00		140	22.99		236	8.39		332	3.06
	-146	463.21		-50	169.06		46	61.69		142	22.51		238	8.21		334	3.00
-6 d	-144	453.58	-2 d	-48	165.55	2 d	48	60.40	6 d	144	22.04	10 d	240	8.04	14 d	336	2.94
	-142	444.15		-46	162.11		50	59.15		146	21.58		242	7.87			
	-140	434.92		-44	158.74		52	57.92		148	21.13		244	7.71			
	-138	425.89		-42	155.44		54	56.872		150	20.69		246	7.55			
	-136	417.04		-40	152.21		56	55.54		152	20.26		248	7.39			
	-134	408.37		-38	149.05		58	54.38		154	19.84		250	7.24			
	-132	399.88		-36	145.95		60	53.25		156	19.43		252	7.09			
	-130	391.57		-34	142.91		62	52.15		158	19.03		254	6.94			
	-128	383.44		-32	139.94		64	51.06		160	18.63		256	6.80			
	-126	375.47		-30	137.04		66	50.00		162	18.24		258	6.66			
	-124	367.66		-28	134.19		68	48.96		164	17.86		260	6.52			
	-122	360.02		-26	131.40		70	47.94		166	17.49		262	6.38			
-5 d	-120	352.54	-1 d	-24	128.67	3 d	72	46.95	7 d	168	17.13	11 d	264	6.25			
	-118	345.22		-22	125.99		74	45.97		170	16.77		266	6.12			
	-116	338.04		-20	123.37		76	45.02		172	16.42		268	5.99			
	-114	331.02		-18	120.81		78	44.08		174	16.08		270	5.87			
	-112	324.14		-16	118.30		80	43.16		176	15.75		272	5.75			
	-110	317.40		-14	115.84		82	42.27		178	15.42		274	5.63			
	-108	310.81		-12	113.43		84	41.39		180	15.10		276	5.51			
	-106	304.35		-10	111.07		86	40.53		182	14.79		278	5.40			
	-104	298.02		-8	108.76		88	39.69		184	14.48		280	5.28			
	-102	291.83		-6	106.50		90	38.86		186	14.18		282	5.17			
	-100	285.77		-4	104.29		92	38.05		188	13.88		284	5.07			
	-98	279.83		-2	102.12		94	37.26		190	13.60		286	4.96			

TABLE 1

Decay table for ^{99m}Tc (half-life : 6.02 hours) :

H.Min	%	H.Min	%	H.Min	%	H.Min	%	H.Min	%	H.Min	%
0.05	99.05	2.05	78.67	4.05	62.49	6.05	49.64	8.05	39.43	10.05	31.32
0.10	98.10	2.10	77.92	4.10	61.89	6.10	49.16	8.10	39.05	10.10	31.02
0.15	97.16	2.15	77.18	4.15	61.30	6.15	48.69	8.15	38.68	10.15	30.72
0.20	96.23	2.20	76.44	4.20	60.72	6.20	48.23	8.20	38.31	10.20	30.43
0.25	95.32	2.25	75.71	4.25	60.14	6.25	47.77	8.25	37.94	10.25	30.14
0.30	94.41	2.30	74.99	4.30	59.56	6.30	47.31	8.30	37.58	10.30	29.85
0.35	93.50	2.35	74.27	4.35	58.99	6.35	46.86	8.35	37.22	10.35	29.57
0.40	92.61	2.40	73.56	4.40	58.43	6.40	46.41	8.40	36.87	10.40	29.28
0.45	91.73	2.45	72.86	4.45	57.87	6.45	45.97	8.45	36.51	10.45	29.00
0.50	90.85	2.50	72.16	4.50	57.32	6.50	45.53	8.50	36.17	10.50	28.73
0.55	89.98	2.55	71.47	4.55	56.77	6.55	45.10	8.55	35.82	10.55	28.45
1.00	89.12	3.00	70.79	5.00	56.23	7.00	44.66	9.00	35.48	11.00	28.18
1.05	88.27	3.05	70.12	5.05	55.69	7.05	44.24	9.05	35.14	11.05	27.91
1.10	87.43	3.10	69.45	5.10	55.16	7.10	43.82	9.10	34.80	11.10	27.64
1.15	86.60	3.15	68.78	5.15	54.64	7.15	43.40	9.15	34.47	11.15	27.38
1.20	85.77	3.20	68.13	5.20	54.11	7.20	42.98	9.20	34.14	11.20	27.12
1.25	84.95	3.25	67.48	5.25	53.60	7.25	42.57	9.25	33.82	11.25	26.86
1.30	84.14	3.30	66.83	5.30	53.09	7.30	42.17	9.30	33.49	11.30	26.60
1.35	83.33	3.35	66.19	5.35	52.58	7.35	41.76	9.35	33.17	11.35	26.35
1.40	82.54	3.40	66.56	5.40	52.08	7.40	41.36	9.40	32.86	11.40	26.10
1.45	81.75	3.45	64.94	5.45	51.58	7.45	40.97	9.45	32.54	11.45	25.85
1.50	80.97	3.50	64.32	5.50	51.09	7.50	40.58	9.50	32.23	11.50	25.60
1.55	80.20	3.55	63.70	5.55	50.60	7.55	40.19	9.55	31.92	11.55	25.36
2.00	79.43	4.00	63.09	6.00	50.12	8.00	39.81	10.00	31.62	12.00	25.12

TABLE 2

The maximal radioactivity of elutable sodium pertechnetate [^{99m}Tc] for each content of generator can be determined by reference to the following table :

		-8	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	
GBq	2	15.02	11.67	9.07	7.05	5.48	4.26	3.31	2.57	2	1.55	1.21	0.94	0.73	0.57	0.44	0.34	0.27	0.21	0.16	0.13	0.10	0.08	0.06	2
mCi	54	405	315	245	190	148	115	89	69	54	42	33	25	20	15	12	9	7	6	4	3	3	2	2	54
GBq	4	30.03	23.34	18.14	14.10	10.96	8.52	6.62	5.15	4	3.11	2.42	1.88	1.46	1.13	0.88	0.69	0.53	0.41	0.32	0.25	0.19	0.15	0.12	4
mCi	108	811	630	490	381	296	230	179	139	108	84	65	51	39	31	24	19	14	11	9	7	5	4	3	108
GBq	6	45.05	35.01	27.21	21.15	16.44	12.78	9.93	7.72	6	4.66	3.62	2.82	2.19	1.70	1.32	1.03	0.80	0.62	0.48	0.38	0.29	0.23	0.18	6
mCi	162	1216	945	735	571	444	345	268	208	162	126	98	76	59	46	36	28	22	17	13	10	8	6	5	162
GBq	8	60.07	46.69	36.29	28.20	21.92	17.04	13.24	10.29	8	6.22	4.83	3.76	2.92	2.27	1.76	1.37	1.07	0.83	0.64	0.50	0.39	0.30	0.24	8
mCi	216	1622	1261	980	761	592	460	358	278	216	168	130	101	79	61	48	37	29	22	17	14	10	8	6	216
GBq	10	75.08	58.36	45.36	35.25	27.40	21.30	16.55	12.87	10	7.77	6.04	4.70	3.65	2.84	2.20	1.71	1.33	1.04	0.80	0.63	0.49	0.38	0.29	10
mCi	270	2027	1576	1225	952	740	575	447	347	270	210	163	127	99	77	60	46	36	28	22	17	13	10	8	270
GBq	12	90.10	70.03	54.43	42.31	32.88	25.56	19.86	15.44	12	9.33	7.25	5.63	4.38	3.40	2.65	2.06	1.60	1.24	0.96	0.75	0.58	0.45	0.35	12
mCi	324	2433	1891	1470	1142	888	690	536	417	324	252	196	152	118	91	71	56	43	34	26	20	16	12	10	324
GBq	16	120.13	93.37	72.57	56.41	43.84	34.08	26.49	20.59	16	12.44	9.67	7.51	5.84	4.54	3.53	2.74	2.13	1.66	1.29	1.00	0.78	0.60	0.47	16
mCi	432	3244	2521	1959	1523	1184	920	715	556	432	336	261	203	158	123	95	74	58	45	35	27	21	16	13	432
GBq	20	150.16	116.71	90.72	70.51	54.80	42.59	33.11	25.73	20	15.54	12.08	9.39	7.30	5.67	4.41	3.43	2.66	2.07	1.61	1.25	0.97	0.76	0.60	20
mCi	540	4054	3151	2449	1904	1480	1150	894	695	540	420	326	254	197	153	119	93	72	56	43	34	26	20	16	540

TABLE 3

Note : The days with a minus sign are the days preceding the date shown on the label (calibration date) and the date with plus sign are the days after this date.

3. PHARMACEUTICAL FORM

Radionuclide generator

4. CLINICAL PARTICULARS

4.1. Indications

The eluate from the generator (sodium pertechnetate [^{99m}Tc] injection (fission), European Pharmacopoeia), may be used as a reagent for labelling of various carrier compounds supplied as kits or administered directly in vivo.

When administered intravenously, the sterile sodium pertechnetate [^{99m}Tc] solution is used as a diagnostic aid in the following :

- a) **Thyroid scintigraphy** : direct imaging and measurement of thyroid uptake to give information on the size, position, nodularity and function of the gland in thyroid disease.
- b) **Salivary gland scintigraphy** : to assess salivary gland function and duct patency.
- c) **Location of ectopic gastric mucosa** : Meckel's diverticulum.
- d) **Cerebral scintigraphy** : to identify breaches in the blood-brain barrier caused by tumour, infarction, haemorrhage and oedema, when no other methods are available.

When used in conjunction with pre-treatment with a reducing agent to effect technetium-99m labelling of red blood cells :

e) **Cardiac and vascular scintigraphy**

- angiocardioscintigraphy for :
 - . evaluation of ventricular ejection fraction
 - . evaluation of global and regional cardiac wall motion
 - . myocardial phase imaging
- organ perfusion or vascular abnormalities imaging.

f) **Diagnosis and localisation of occult gastrointestinal bleeding**

Following instillation of sterile sodium pertechnetate [^{99m}Tc] into the eye :

- g) **Lachrymal duct scintigraphy** : to assess patency of tear ducts.

4.2. Posology and method of administration

Sodium pertechnetate [^{99m}Tc] is normally administered intravenously at activities which vary widely according to the clinical information required and the equipment employed. Pre-treatment of patients with thyroid blocking agents or reducing agents may be necessary for certain indications.

Recommended activities are as follows :

- Adults and the elderly :

Thyroid scintigraphy : 18.5 - 80 MBq (0.5 - 2.2 mCi)
Scintigraphy performed 20 minutes after intravenous injection.

Salivary gland scintigraphy : 40 MBq (1.1 mCi)
Scintigraphy performed immediately after intravenous injection and at regular intervals up to 15 minutes.

Meckel's diverticulum scintigraphy : 400 MBq (10.8 mCi)
Scintigraphy performed immediately after intravenous injection and at regular intervals up to 30 minutes.

Brain scintigraphy : 370 - 800 MBq (10 - 21.6 mCi)
Rapid sequential images are taken immediately within the first minute after intravenous administration; static images 1 to 4 hours later. Thyroid and choroid plexus should be blocked to avoid non-specific technetium-99m uptake.

Cardiac and vascular scintigraphy : 740 - 925 MBq (20 - 25 mCi)
Red cells are labelled in vivo or in vitro by pre-treating with a reducing agent. Dynamic images are taken in the first minute after intravenous administration, followed by regular images over 30 minutes.

Gastrointestinal bleeding : 740 - 925 MBq (20 - 25 mCi)
Red cells are labelled in vivo or in vitro by pre-treating with a reducing agent. Dynamic images are taken in the first minute after intravenous administration, followed by regular images at appropriate intervals for up to 24 hours.

Lachrymal duct scintigraphy : 2 - 4 MBq (0.05 - 0.11 mCi) each eye
Drops are instilled into the eye and dynamic images are taken over 2 minutes, followed by static images at appropriate intervals over 20 minutes.

- Children :

The activity for administration to children may be calculated from the recommended range of adult activity and adjusted according to body weight or surface area.

However, the Paediatric Task Group of EANM recommends that the activity to be administered to a child should be calculated from the body weight according to the following table :

Fraction of adult dose :

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

In very young children (up to 1 year) a minimum dose of 20 MBq (0.54 mCi) (10 MBq - 0.27 mCi - in thyroid scintigraphy) for direct administration or 80 MBq (2.2 mCi) for red blood cell labelling is necessary in order to obtain images of sufficient quality.

4.3. **Contra-indications**

None known.

4.4. **Special warnings and special precautions for use**

Radiopharmaceutical agents should be used only by qualified personnel with the appropriate government authorisations for the use and manipulations of radionuclides.

This radiopharmaceutical may be received, used and administered only by authorised personnel in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of local competent official organisations.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken complying with the requirements of Good Pharmaceutical Manufacturing Practice for radiopharmaceuticals.

4.5. **Interaction with other medicaments and other forms of interaction**

Drug interactions have been reported in brain scintigraphy where there can be increased uptake of pertechnetate [^{99m}Tc] in the walls of cerebral ventricles as a result of methotrexate-induced ventriculitis. In abdominal imaging, drugs such as atropine, isoprenaline and analgesics can result in a delay in gastric emptying and redistribution of pertechnetate.

4.6. Pregnancy and lactation

Technetium-99m (as free pertechnetate) has been shown to cross the placental barrier.

Where it is necessary to administer radioactive medicinal products to a woman 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 particularly important that the radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiations should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus. Direct administration of 800 MBq (21.6 mCi) sodium pertechnetate [^{99m}Tc] to a patient results in an absorbed dose to the uterus of 6.5 mGy. Following pre-treatment of patients with a blocking agent, administration of 800 MBq (21.6 mCi) sodium pertechnetate [^{99m}Tc] results in an absorbed dose to the uterus of 5.3 mGy. Administration of 925 MBq (25 mCi) ^{99m}Tc-labelled red blood cells results in an absorbed dose to the uterus of 4.3 mGy. Doses above 0.5 mGy should be regarded as a potential risk to the foetus.

Before administering a radioactive medicinal product to a woman who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made. If the administration is considered necessary, breast feeding should be interrupted and the expressed feeds discarded. Breast feeding can be restarted when the activity level in the milk will not result in a radiation dose to the child greater than 1 mSv.

4.7. Effects on ability to drive and use machines

Effects on ability to drive and use machines have not been described.

4.8. Undesirable effects

Allergic reactions have been reported following intravenous injection of sodium pertechnetate [^{99m}Tc] and include urticaria, facial oedema, vasodilatation, pruritus, cardiac arrhythmia and coma.

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

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

For most diagnostic investigations using a nuclear medicine procedure, the radiation dose delivered is less than 20 mSv (EDE). Higher doses may be justified in some clinical circumstances.

4.9. Overdose

In the event of the 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. Measures to reduce possible harmful effects include frequent voiding of urine and promotion of diuresis and faecal excretion.

Very little supportive treatment can be undertaken in the event of an overdose of ^{99m}Tc -labelled red blood cells since elimination is dependent on the normal haemolytic process.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

5.2. Pharmacokinetic Properties

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 released 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. Technetium-99m is selectively excluded from the cerebrospinal fluid.

Following intravenous administration, pertechnetate [^{99m}Tc] is distributed throughout the vascular system from which it is cleared by three main mechanisms :

- . rapid removal, depending on the diffusion equilibrium with interstitial fluid,
- . intermediate rate of removal, depending on the concentration of the pertechnetate in glandular tissues, mainly thyroid, salivary and gastric fundus glands which have an ionic pump mechanism,
- . slow removal, by glomerular filtration by the kidneys, dependent on rate of urinary excretion.

Plasma clearance has a half-life of approximately 3 hours.

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 pre-administration of blocking agents, excretion follows the same pathways but there is a higher rate of renal clearance.

When pertechnetate [^{99m}Tc] is administered in association with pre-treatment with reducing agents such as stannous medronate or stannous pyrophosphate which cause a "stannous loading" of red blood cells, up to approximately 95 % of the administered activity is taken up by the red blood cells where it becomes bound within the cells. Any unbound pertechnetate [^{99m}Tc] is cleared by the kidneys; radioactivity in the plasma normally constitutes less than 5 % of the intravascular activity.

The fate of the technetium-99m follows that of the labelled erythrocytes themselves and the activity is cleared very slowly. A small level of elution of activity from the circulating red cells is thought to occur.

5.3. Preclinical safety data

- a) There is no information on acute, subacute and chronic toxicity from single or repeated dose administration.
- b) Reproductive toxicity

Placental transfer of technetium-99m from intravenous administered sodium pertechnetate [^{99m}Tc] has been studied in mice. The pregnant uterus was found to contain as much as 60 % of the injected technetium-99m 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.

5.4. Radiation dosimetry

According to ICRP 53, the radiation doses absorbed by a patient following direct administration of sodium pertechnetate [^{99m}Tc] are as follows :

(i) Without pre-treatment with blocking agent :

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	3.6×10^{-3}	4.7×10^{-3}	7.1×10^{-3}	1.1×10^{-2}	1.9×10^{-2}
Bladder wall	1.9×10^{-2}	2.3×10^{-2}	3.4×10^{-2}	5.1×10^{-2}	9.1×10^{-2}
Bone surfaces	3.9×10^{-3}	4.7×10^{-3}	6.9×10^{-3}	1.0×10^{-2}	1.9×10^{-2}
Breast	2.3×10^{-3}	2.3×10^{-3}	3.5×10^{-3}	5.7×10^{-3}	1.1×10^{-2}
Gastro-intestinal tract					
Stomach wall	2.9×10^{-2}	3.6×10^{-2}	5.0×10^{-2}	8.1×10^{-2}	1.5×10^{-1}
Small intestine	1.8×10^{-2}	2.2×10^{-2}	3.4×10^{-2}	5.2×10^{-2}	9.0×10^{-2}
Upper large intestine wall	6.2×10^{-2}	7.7×10^{-2}	1.3×10^{-1}	2.1×10^{-1}	3.9×10^{-1}
Lower large intestine wall	2.2×10^{-2}	2.8×10^{-2}	4.6×10^{-2}	7.4×10^{-2}	1.4×10^{-1}
Kidneys	5.0×10^{-3}	6.0×10^{-3}	8.7×10^{-3}	1.3×10^{-2}	2.1×10^{-2}
Liver	3.9×10^{-3}	4.8×10^{-3}	8.0×10^{-3}	1.3×10^{-2}	2.2×10^{-2}
Lungs	2.7×10^{-3}	3.4×10^{-3}	5.1×10^{-3}	7.9×10^{-3}	1.4×10^{-2}
Ovaries	1.0×10^{-2}	1.3×10^{-2}	1.9×10^{-2}	2.7×10^{-2}	4.5×10^{-2}
Pancreas	5.9×10^{-3}	7.2×10^{-3}	1.1×10^{-2}	1.6×10^{-2}	2.7×10^{-2}
Salivary glands	9.3×10^{-3}	1.2×10^{-2}	1.7×10^{-2}	2.4×10^{-2}	3.9×10^{-2}
Red marrow	6.1×10^{-3}	7.1×10^{-3}	9.8×10^{-3}	1.3×10^{-2}	2.0×10^{-2}
Spleen	4.4×10^{-3}	5.3×10^{-3}	7.9×10^{-3}	1.2×10^{-2}	2.1×10^{-2}
Testes	2.7×10^{-3}	3.7×10^{-3}	5.9×10^{-3}	9.3×10^{-3}	1.7×10^{-2}
Thyroid	2.3×10^{-2}	3.7×10^{-2}	5.6×10^{-2}	1.2×10^{-1}	2.3×10^{-1}
Uterus	8.1×10^{-3}	1.0×10^{-2}	1.6×10^{-2}	2.4×10^{-2}	4.0×10^{-2}
Other tissue	3.4×10^{-3}	4.0×10^{-3}	6.0×10^{-3}	9.3×10^{-3}	1.7×10^{-2}
Effective Dose Equivalent (mSv/MBq)	1.3×10^{-2}	1.6×10^{-2}	2.5×10^{-2}	4.0×10^{-2}	7.3×10^{-2}

The effective dose equivalent resulting from an administered activity of 800 MBq (21.6 mCi) sodium pertechnetate [^{99m}Tc] is 10.4 mSv.

(ii) With pre-treatment with blocking agent :

Organ	Absorbed dose per unit activity (mGy/MBq) when blocking agents are given				
	Adult	15 years	10 years	5 years	1 year
Adrenals	3.3×10^{-3}	4.1×10^{-3}	6.3×10^{-3}	9.5×10^{-3}	1.7×10^{-2}
Bladder wall	3.2×10^{-2}	3.9×10^{-2}	5.7×10^{-2}	8.4×10^{-2}	1.5×10^{-1}
Bone surfaces	3.8×10^{-3}	4.5×10^{-3}	6.7×10^{-3}	1.0×10^{-2}	1.8×10^{-2}
Breast	2.5×10^{-3}	2.5×10^{-3}	3.6×10^{-3}	5.7×10^{-3}	1.1×10^{-2}
Gastro-intestinal tract					
Stomach wall	3.2×10^{-3}	4.1×10^{-3}	6.6×10^{-3}	9.3×10^{-3}	1.7×10^{-2}
Small intestine	4.1×10^{-3}	4.9×10^{-3}	7.6×10^{-3}	1.1×10^{-2}	2.0×10^{-2}
Upper large intestine wall	3.8×10^{-3}	4.9×10^{-3}	7.1×10^{-3}	1.1×10^{-2}	1.9×10^{-2}
Lower large intestine wall	4.5×10^{-3}	5.9×10^{-3}	9.2×10^{-3}	1.3×10^{-2}	2.3×10^{-2}
Kidneys	4.7×10^{-3}	5.7×10^{-3}	8.2×10^{-3}	1.2×10^{-2}	2.1×10^{-2}
Liver	3.1×10^{-3}	3.8×10^{-3}	5.9×10^{-3}	9.0×10^{-3}	1.6×10^{-2}
Lungs	2.8×10^{-3}	3.5×10^{-3}	5.2×10^{-3}	7.9×10^{-3}	1.4×10^{-2}
Ovaries	4.7×10^{-3}	6.0×10^{-3}	8.9×10^{-3}	1.3×10^{-2}	2.3×10^{-2}
Pancreas	3.5×10^{-3}	4.4×10^{-3}	6.7×10^{-3}	1.0×10^{-2}	1.8×10^{-2}
Red marrow	4.5×10^{-3}	5.4×10^{-3}	7.8×10^{-3}	1.1×10^{-2}	1.8×10^{-2}
Spleen	3.2×10^{-3}	3.9×10^{-3}	5.9×10^{-3}	9.0×10^{-3}	1.6×10^{-2}
Testes	3.2×10^{-3}	4.4×10^{-3}	6.8×10^{-3}	1.1×10^{-2}	1.9×10^{-2}
Thyroid	2.1×10^{-3}	3.5×10^{-3}	5.7×10^{-3}	9.0×10^{-3}	1.6×10^{-2}
Uterus	6.6×10^{-3}	7.9×10^{-3}	1.2×10^{-2}	1.8×10^{-2}	3.0×10^{-2}
Other tissue	2.9×10^{-3}	3.5×10^{-3}	5.3×10^{-3}	8.2×10^{-3}	1.5×10^{-2}
Effective Dose Equivalent (mSv/MBq)	5.3×10^{-3}	6.6×10^{-3}	9.8×10^{-2}	1.5×10^{-2}	2.6×10^{-2}

Following pre-treatment of patients with a blocking agent, administration of 800 MBq (21.6 mCi) sodium pertechnetate [^{99m}Tc] results in an effective dose equivalent of 4.24 mSv.

- (iii) The radiation doses absorbed by a patient following intravenous injection of ^{99m}Tc -labelled red blood cells are as follows :

Organ	Absorbed dose per unit activity (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	8.7×10^{-3}	1.1×10^{-2}	1.7×10^{-2}	2.7×10^{-2}	4.9×10^{-2}
Bladder wall	9.2×10^{-3}	1.2×10^{-2}	1.7×10^{-2}	2.5×10^{-2}	4.6×10^{-2}
Bone surfaces	9.2×10^{-3}	1.3×10^{-2}	2.3×10^{-2}	3.9×10^{-2}	7.8×10^{-2}
Breast	4.3×10^{-3}	4.5×10^{-3}	7.2×10^{-3}	1.1×10^{-2}	1.9×10^{-2}
Gastrointestinal tract					
Stomach wall	4.8×10^{-3}	6.1×10^{-3}	9.5×10^{-3}	1.4×10^{-2}	2.4×10^{-2}
Small intestine	4.4×10^{-3}	5.3×10^{-3}	8.1×10^{-3}	1.2×10^{-2}	2.2×10^{-2}
Upper large intestine wall	4.3×10^{-3}	5.5×10^{-3}	7.9×10^{-3}	1.3×10^{-2}	2.1×10^{-2}
Lower large intestine wall	3.9×10^{-3}	5.3×10^{-3}	8.0×10^{-3}	1.1×10^{-2}	2.1×10^{-2}
Heart	2.3×10^{-2}	2.8×10^{-2}	4.1×10^{-2}	6.2×10^{-2}	1.1×10^{-1}
Kidneys	1.0×10^{-2}	1.2×10^{-2}	1.9×10^{-2}	3.0×10^{-2}	5.5×10^{-2}
Liver	7.5×10^{-3}	8.8×10^{-3}	1.4×10^{-2}	2.1×10^{-2}	3.8×10^{-2}
Lungs	1.4×10^{-2}	1.8×10^{-2}	2.9×10^{-2}	4.5×10^{-2}	8.5×10^{-2}
Ovaries	4.2×10^{-3}	5.4×10^{-3}	7.9×10^{-3}	1.2×10^{-2}	2.1×10^{-2}
Pancreas	6.2×10^{-3}	7.5×10^{-3}	1.1×10^{-2}	1.7×10^{-2}	2.9×10^{-2}
Red marrow	7.3×10^{-3}	8.8×10^{-3}	1.3×10^{-2}	2.0×10^{-2}	3.5×10^{-2}
Spleen	1.5×10^{-2}	1.8×10^{-2}	2.8×10^{-2}	4.4×10^{-2}	8.4×10^{-2}
Testes	2.7×10^{-3}	3.7×10^{-3}	5.4×10^{-3}	8.3×10^{-3}	1.5×10^{-2}
Thyroid	4.9×10^{-3}	7.1×10^{-3}	1.2×10^{-2}	1.9×10^{-2}	3.5×10^{-2}
Uterus	4.7×10^{-3}	5.7×10^{-3}	8.5×10^{-3}	1.3×10^{-2}	2.2×10^{-2}
Other tissue	3.7×10^{-3}	4.4×10^{-3}	6.4×10^{-3}	9.8×10^{-3}	1.8×10^{-2}
Effective Dose Equivalent (mSv/MBq)	8.5×10^{-3}	1.1×10^{-2}	1.6×10^{-2}	2.5×10^{-2}	4.6×10^{-2}

The effective dose equivalent resulting from an administration of 925 MBq (25 mCi) ^{99m}Tc -labelled red blood cells is 7.86 mSv.

- (iv) The radiation dose absorbed by the lens of the eye following administration of sodium pertechnetate [^{99m}Tc] for lachrymal 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 (0.11 mCi).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Elution solution containing 0.9 % sodium chloride and 0.005 % sodium nitrate.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date for this product is 20 days from the date of manufacture. The expiry date is indicated on the label.

Once eluted, store the sodium pertechnetate (^{99m}Tc) injection in a refrigerator (2°C – 8°C) and use within 10 hours after elution.

6.4 Special precautions for storage

The generator ELUMATIC III should be stored at a temperature ranging between +15 °C and +25 °C, preferably inside the specific lead shielding for storage and elution "PROTEC-ELU" (available on request), or behind a lead shielding of appropriate thickness.

Storage should be in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

ELUMATIC III is supplied with a packet of ten 15 ml, colourless, European Pharmacopoeia type I, drawn glass vials, closed with chlorobutyl rubber stoppers and aluminium capsules.

These vials are sterile, pyrogen-free and under partial vacuum allowing elution of 5 ml.

On request, it is possible to obtain kits containing 50 or 150 vials of 15 ml :

- either under partial vacuum, allowing elution of 5 ml (Ref. TC-ELU-5-50 or TC-ELU-5-150) ;
- either under partial vacuum, allowing elution of 10 ml (Ref. TC-ELU-10-50 or TC-ELU-10-150) ;
- either under vacuum, allowing elution of 15 ml (Ref. TC-ELU-15-50 or TC-ELU-15-150).

6.6 Instructions for use / handling

Elution

During transport, and between two elutions of the generator, needle is secured by the container B.

When starting using the generator, OPEN the safety valve (n° 0 : ☉), BEFORE putting the elution vial in place. NEVER turn off the valve between two elutions. Turn it off only when the generator is not being used any more.

To elute the generator, just replace the container (B) by the elution container (A) with a vacuum vial corresponding to the elution volume required (13).

Usual precautions regarding sterility and radiation safety should be respected. To maintain aseptic conditions, surfaces in contact with the needle (8) should be disinfected. Do not spray ethanol or ethylic ether on the needle or on the cap of the collection vial, as this could perturbate the elution process.

The elution may be observed through the lead glass window (14) of container (A). Wait for two minutes until the elution is total.

Before use, check the clarity of the eluate.

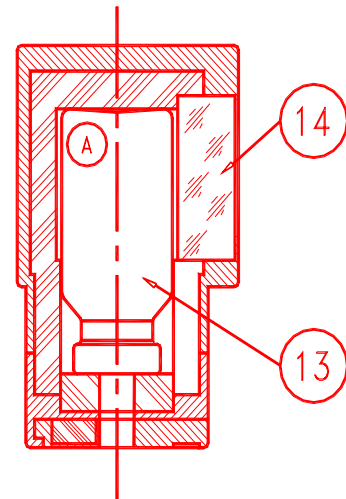
After elution, put the container (B) back in place immediately in order to preserve the sterility of the needle.

N.B. : The bacteriostatic solution should not be injected.

The elution container is supplied free of charge with the first order and is available on request (Ref. : CONT-ELU, or : CONT-ELU-SP).

Elution volumes

The generator ELUMATIC III is designed to elute all the available technetium-99m activity in 5 ml. Fractionated elutions are therefore unnecessary. On the other hand, elution may be performed in larger volumes such as 10 or 15 ml.



Possibilities of use

The activity quoted on the label of the ELUMATIC III is expressed in available technetium-99m at the calibration time (12 h CET).

The available activity of technetium-99m depends on :

- the molybdenum-99 activity at the time of elution ;
- the time elapsed since the last elution was performed.

Activities of technetium-99m available with elutions performed every 24 hours can be calculated with table 4 :

Previous days								Calibration date
-8	-7	-6	-5	-4	-3	-2	-1	0
751	584	454	353	274	213	166	129	100
Available activity in percent of ^{99m} Tc at the calibration date (round values)								

Calibration date	Following days														
0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	
100	78	60	47	36	28	22	17	13	10	8	6	5	4	3	
Available activity in percent of ^{99m} Tc at the calibration date (round values)															

TABLE 4

It is also possible, to elute the ELUMATIC III before 24 hours have elapsed thus performing "partial time" elutions. Table 5 shows the percentage of activity in technetium-99m which can be collected after times varying from 0 to 23 hours :

Time elapsed since the last elution was performed (hours)	0	1	2	3	4	5	6	8	10	12	14	16	18	20	22	23
Corrective factor	0.00	0.11	0.21	0.30	0.39	0.45	0.51	0.62	0.71	0.79	0.85	0.89	0.93	0.96	0.99	1.00
Decay of ⁹⁹ Mo (see decay table inside cover)	100	98.95	97.92	96.90	95.89	94.88	93.97	91.94	90.03	88.16	86.33	84.53	82.78	81.05	79.37	78.54
% of ^{99m} Tc available (round values)	0	11	21	29	37	43	48	57	64	70	73	75	77	78	79	79
Available activity in percent of ^{99m} Tc activity at the time of previous elution (if performed about 24 hours after the previous one)																

TABLE 5

Examples

- a) A 10 GBq (270 mCi) generator is eluted 24 hours after the calibration date. The technetium-99m activity collected is (table 4) :

$$10 \times \frac{78}{100} = 7.8 \text{ GBq} \quad 270 \times \frac{78}{100} = 211 \text{ mCi}$$

- b) The same generator is eluted 6 hours later. The technetium-99m activity collected is (tables 4 and 5) :

$$7.8 \times \frac{48}{100} = 3.7 \text{ GBq} \quad 211 \times \frac{48}{100} = 101 \text{ mCi}$$

- c) The same generator is eluted 18 hours later i.e. 48 hours after the calibration date. The 24 hours needed to reach the ^{99}Mo - $^{99\text{m}}\text{Tc}$ equilibrium have not elapsed and the technetium-99m activity collected will be instead of 6.0 GBq (162 mCi) (tables 4 and 5 : corrective factor) :

$$6.0 \times \frac{93}{100} = 5.6 \text{ GBq} \quad 162 \times \frac{93}{100} = 151 \text{ mCi}$$

This is summarised in the following table :

	Monday	Tuesday	Wednesday		Thursday		Friday
Time of elution	8 a.m.	8 a.m.	8 a.m.		8 a.m.		8 a.m.
Radioactivity eluted 10 GBq on Tuesday 270 mCi on Tuesday	13 350	10 270	7.8 211		6.0 162		4.7 127
Time of elution	8 a.m.	8 a.m.	8 a.m.	2 p.m.	8 a.m.	12 a.m.	8 a.m.
Same generator eluted at different times (GBq) (mCi)	13 350	10 270	7.8 211	3.7 101	5.6 151	2.1 56	4.5 122

TABLE 6

N.B. :

In case the user waits for 48 hours or more between two elutions, he will obtain the activity indicated in table 4 multiplied by 1.1 (this factor accounts for the "rate equilibrium" which appears after 48 hours between molybdenum-99 and technetium-99m). This remark applies mainly :

- to the first elution : the previous elution was performed in the production laboratory, several days before ;
- when the generator has a high activity.

Interest of partial time elutions

The potential utilisation of a generator can be notably increased by partial time elutions. The ELUMATIC III has the advantage of a small elution volume. When choosing an appropriate volume for the elution vial, the desired volumic activity can be obtained even when the period of time between two elutions is of a few hours.

Example :

An elution of 10 GBq (270 mCi) has been performed at 10 a.m. in 15 ml. The volumic activity is 0.67 GBq/ml (18 mCi/ml). A new elution performed at 2 p.m., 4 hours after the first one, will give 3.7 GBq (100 mCi). If this activity is collected in 5 ml instead of 15 ml as previously, the volumic activity, 0.74 GBq/ml (20 mCi/ml) will be higher than in the morning.

Table 7 shows that a comparatively constant volumic activity can be obtained all along the week :

		Calibration date	Elutions on following days				
		0	+ 1	+ 2	+ 3	+ 4	+ 5
Eluted activity	GBq mCi	10 270	7.8 211	6.0 162	4.7 127	3.6 97	2.8 76
Elution volume	ml	15	15	10	8*	5	5
Volumic activity	GBq/ml mCi/ml	0.67 18	0.52 14	0.60 16.2	0.59 15.9	0.72 19.4	0.56 15.2

TABLE 7

* To reach a final volume of 8 ml, 3 ml of 0.9 % sodium chloride injection are added to the 5 ml eluted in a vial TC-ELU-5.

Quality control

The user laboratory should control : clarity of the solution, pH, radioactivity, gamma spectrum.

To obtain an approximate estimate of molybdenum-99, prior to use of the injection, take a volume of eluate equivalent to 37 MBq (1 mCi) and determine the gamma-ray spectrum using a sodium iodide detector with a shield of lead, of thickness 6 mm, interposed between the sample and the detector. The response in the region corresponding to the 0,740 MeV photon of molybdenum-99 does not exceed that obtained using 37 kBq (1 µCi) of a standardised solution of molybdenum-99 measured under the same conditions, when all measurements are calculated with reference to the date and hour of administration.

Warning :

The maximal radioactivity contained in the generator at the time of reception can be higher than that indicated on the label on the corresponding calibration date. Refer to table 3, showing the maximal radioactivity of elutable sodium pertechnetate [^{99m}Tc] for each content of generator, to determine the maximal radioactivity contained in the generator at the time of reception.

Weight of (^{99m}Tc + ⁹⁹Tc) in the eluate

The molybdenum-99 is transformed into technetium-99m (87.6 % of the molybdenum-99 disintegrations) and technetium-99 (12.4 % of the molybdenum-99 disintegrations). Thus, the eluted solution is not "carrier free". The calculation of the total weight (⁹⁹Tc + ^{99m}Tc) expressed in µg present in the eluate can be done with the following simplified formula :

$$W (\mu\text{g}) = \frac{{}^{99\text{m}}\text{Tc activity in the eluate} \times k}{F}$$

k = 5.161.10⁻³ when activity is expressed in GBq.

k* = 1.909.10⁻⁴ when activity is expressed in mCi.

F is the ratio between the number of technetium-99m (N_{99m}) and the total number of technetium atoms (Nt) :

$$F = \frac{N_{99\text{m}}}{N_t}$$

The values of this ratio in terms of time elapsed between two elutions are given in the table hereunder :

Hours	Days						
	0	1	2	3	4	5	6
0	-	0.277	0.131	0.076	0.0498	0.0344	0.0246
3	0.727	0.248	0.121	0.072	0.0474	0.0329	0.0236
6	0.619	0.223	0.113	0.068	0.0452	0.0315	0.0227
9	0.531	0.202	0.105	0.064	0.0431	0.0302	0.0218
12	0.459	0.184	0.098	0.061	0.0411	0.0290	0.0210
15	0.400	0.168	0.092	0.058	0.0393	0.0278	0.0202
18	0.352	0.154	0.086	0.055	0.0375	0.0266	0.0194
21	0.311	0.141	0.081	0.052	0.0359	0.0256	0.0187

TABLE 8

Examples :

- 1) The technetium-99m from an ELUMATIC III has been eluted in 5 ml ; the activity measured is 10 GBq (270 mCi) ; the previous elution was performed 27 hours earlier. The weight of technetium carrier will be :

$$W (\mu\text{g}) = \frac{10 \times 5.161 \cdot 10^{-3}}{0.248} = 0.208 \mu\text{g}$$

corresponding to 0.042 $\mu\text{g/ml}$.

- 2) The technetium-99m is eluted from an ELUMATIC III 4 days after the preparation, this being the first elution for the user. For an activity of 10 GBq (270 mCi) eluted in 5ml, the weight of technetium carrier is :

$$W (\mu\text{g}) = \frac{10 \times 5.161 \cdot 10^{-3}}{0.0498} = 1.036 \mu\text{g}$$

corresponding to 0.207 $\mu\text{g/ml}$, which is 5 times as much carrier as in the former example. However small, this amount of technetium may affect the labelling yield of some compounds.

This remark applies not only to the ELUMATIC III but to all technetium-99m generators.

Table 9 shows the variation in the weight of technetium carrier on a 10 GBq (270 mCi) generator from Tuesday and eluted every day at an interval of 24 hours, assuming that the first elution was performed 3 days after that performed on Monday.

	Monday	Tuesday	Wednesday	Thursday	Friday
Radioactivity eluted GBq mCi	13 350	10 270	7.8 210	6.0 162	4.7 127
Weight of technetium carrier in μg for the whole eluate	0.883	0.186	0.145	0.112	0.088

TABLE 9

General precautions

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.

Waste must be disposed of in accordance with national regulations for radioactive materials.

7. MARKETING AUTHORISATION HOLDER

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