AUSTRALIAN PRODUCT INFORMATION

ANSTO (CHROMIUM [^{51}Cr] EDETATE) INJECTION

1 NAME OF THE MEDICINE

Chromium [^{51}Cr] Edetate Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Description
Chromium [^{51}Cr] Edetate Injection BP is single dose clear purple coloured sterile pyrogen free aqueous isotonic solution for intravenous administration. Each 3 mL vial contains 8 MBq of chromium [^{51}Cr], ≤1mg of Chromium element and ≤15mg of EDTA in 1 mL of 0.9%w/v sodium chloride solution at a pH of between 3.5 and 6.5.

Physical Characteristics of Chromium 51
Chromium-51 has a physical half-life of 27.71 days, and has 9.9% disintegration's with a single gamma photon at 320 keV.

To correct for the effect of decay multiply the activity on the calibration date by the appropriate factor from the table -1 below:

Table-1
Physical Decay Chart

Day	Factor	Day	Factor
-5	1.133	14	0.705
-4	1.105	15	0.687
-3	1.078	16	0.670
-2	1.051	17	0.654
-1	1.025	18	0.637
0	1.000	19	0.622
1	0.975	20	0.606
2	0.951	21	0.591
3	0.928	22	0.577
4	0.905	23	0.563
5	0.882	24	0.549
6	0.861	25	0.535
7	0.839	26	0.522
8	0.819	27	0.509
9	0.798	28	0.496
10	0.779	29	0.484
11	0.759	30	0.472
12	0.741	31	0.461
13	0.722		

External Radiation
The attenuation coefficient (μ) in lead[1] is ~ 3.6 cm^{-1} and the attenuation factors for lead are given in Table 2:

Table-2
Radiation Attenuation by Lead Shielding

Shield Thicknesses - Pb (in cm)	Coefficient of Attenuation (approx.)
0.18	0.5
0.64	10^{-1}
1.28	10^{-2}

Excipient(s) with known effect:
Each mL of Chromium [^{51}Cr] Edetate solution contains ≤1mg of Chromium and ≤15mg of EDTA.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

A clear purple coloured sterile pyrogen free aqueous isotonic solution for intravenous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chromium [^{51}Cr] Edetate Injection BP is indicated for the determination of glomerular filtration rate in the assessment of renal function.

4.2 DOSE AND METHOD OF ADMINISTRATION

Chromium [^{51}Cr] Edetate Injection should be used without dilution. Product is for one dose in one patient only. Discard any remaining contents appropriately. Contains no antimicrobial agent.

Dose handling
Radiation exposure to staff must be minimised. For each patient, exposure to ionising radiation must be justified on the basis of likely benefit. The normally recommended dose for adults is 1.1 to 6.0 MBq by intravenous injection or continuous infusion. Higher doses up to 11
MBq may be appropriate for the use in conjunction with external counting techniques. The dosage for children may be calculated as a proportion of adult body weight or surface area. For newborn or children under one year the target organ's size should be taken into consideration.

Adults
The normal recommended dose for adults is 1.1 to 6.0MBq (30 - 160 μCi) by intravenous injection or continuous infusion. The actual activity administered will depend on the technique, used to determine the renal clearance and on that used for radioactivity detection. Higher activities up to a maximum of 11MBq (300 μCi) may be appropriate for use in conjunction with external counting techniques.

Because of the complexities of the infusion technique, a single injection technique is normally used. This method obviates the need for urine collection, but is not suitable for patients with oedema. A single intravenous dose of 3.7 MBq of Chromium [^{51}Cr] Edetate Injection BP is normally given and the plasma clearance is calculated from the injected amount of Chromium [^{51}Cr] Edetate BP and the decrease of activity in the plasma samples as a function of time.

For continuous intravenous infusion a priming dose of 1.85 MBq is given intravenously followed by the infusion of a solution containing 37 kBq per mL at a rate of 0.5 mL per minute. After about
40 minutes, the plasma concentration becomes constant. A urine collection lasting about 15 minutes is then started and a venous sample taken at the mid time. This process is repeated with rapid separations and counting of the plasma radioactivity until constant plasma activity is observed in two successive samples. The GFR is then calculated.

Paediatric administration
The dosage to be administered to children may be calculated approximately by correcting on a weight or body surface area basis the dosage to adults. For the newborn and children under about one year of age, the target organ size in relation to the whole body must also be taken into consideration.

Radiation Dosimetry
Radiation dose to specific organs, which may not be the target organ, can be influenced significantly by pathophysiological changes induced by any disease processes. This should be taken into consideration when using the following information.
This data assumes a body retention half-life of 100 minutes and a transit time of 5 minutes. (Considered normal). For abnormal renal function, refer Table 4.

Table 3
Absorbed dose per unit activity administered[2] (mGy MBq^{-1})

Intravenous administration, normal renal function					
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	7.3E-4	9.1E-4	1.4E-3	2.1E-3	3.9E-3
Bone surfaces	8.2E-4	1.0E-3	1.5E-3	2.1E-3	3.8E-3
Brain	4.8E-4	6.0E-4	9.8E-4	1.6E-3	2.9E-3
Breast	4.3E-4	5.6E-4	8.2E-4	1.3E-3	2.5E-3
Gallbladder wall	7.9E-4	1.3E-3	1.7E-3	2.3E-3	3.4E-3
Gastrointestinal tract -					
Stomach wall	6.9E-4	8.5E-4	1.3E-3	2.0E-3	3.4E-3
Small intestine wall	1.1E-3	1.4E-3	2.1E-3	3.1E-3	4.8E-3
Colon wall	1.3E-3	1.6E-3	2.4E-3	3.4E-3	4.8E-3
Upper large intestine wall	9.7E-4	1.2E-3	1.9E-3	2.8E-3	4.3E-3
Lower large intestine wall	1.7E-3	2.1E-3	3.0E-3	4.1E-3	5.5E-3
Heart wall	6.4E-4	8.1E-4	1.3E-3	1.9E-3	3.4E-3
Kidneys	1.8E-3	2.2E-3	3.1E-3	4.7E-3	8.2E-3
Liver	6.6E-4	8.3E-4	1.3E-3	2.0E-3	3.6E-3
Lungs	5.6E-4	7.2E-4	1.1E-3	1.7E-3	3.1E-3
Muscles	7.7E-4	9.5E-4	1.5E-3	2.1E-3	3.6E-3
Oesophagus	5.8E-4	7.3E-4	1.1E-3	1.7E-3	3.2E-3
Ovaries	1.6E-3	2.0E-3	3.0E-3	4.0E-3	5.8E-3
Pancreas	7.6E-4	9.4E-4	1.5E-3	2.3E-3	3.9E-3
Red marrow	7.5E-4	9.2E-4	1.4E-3	1.9E-3	3.2E-3
Skin	4.8E-4	5.8E-4	9.1E-4	1.4E-3	2.5E-3
Spleen	6.8E-4	8.6E-4	1.3E-3	2.0E-3	3.6E-3
Testes	1.2E-3	1.6E-3	2.7E-3	3.8E-3	5.4E-3
Thymus	5.8E-4	7.3E-4	1.1E-3	1.7E-3	3.2E-3
Thyroid	5.7E-4	7.3E-4	1.1E-3	1.9E-3	3.4E-3
Urinary bladder wall	2.4E-2	3.1E-2	4.5E-2	5.7E-2	6.6E-2
Uterus	2.8E-3	3.4E-3	5.2E-3	6.9E-3	8.7E-3
Remaining organs	7.8E-4	9.7E-4	1.4E-3	2.1E-3	3.5E-3

Effective dose (mSv MBq^{-1})	**2.0E-3**	**2.6E-3**	**3.9E-3**	**5.2E-3**	**7.0E-3**

Table 4
Absorbed dose per unit activity administered[2] (mGy MBq^{-1})

Intravenous administration, abnormal renal function					
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	3.9E-3	4.9E-3	7.4E-3	1.1E-2	2.1E-2
Bone surfaces	4.2E-3	5.1E-3	7.5E-3	1.1E-2	2.1E-2
Brain	2.9E-3	3.6E-3	5.8E-3	9.6E-3	1.7E-2
Breast	2.6E-3	3.3E-3	4.8E-3	7.6E-3	1.5E-2
Gallbladder wall	4.2E-3	5.2E-3	8.3E-3	1.2E-2	1.8E-2
Gastrointestinal tract -					
Stomach wall	3.8E-3	4.7E-3	7.2E-3	1.1E-2	1.9E-2
Small intestine wall	4.4E-3	5.5E-3	8.4E-3	1.3E-2	2.2E-2
Colon wall	4.5E-3	5.4E-3	8.3E-3	1.3E-2	2.1E-2
Upper large intestine wall	4.2E-3	5.2E-3	7.8E-3	1.2E-2	2.1E-2
Lower large intestine wall	4.8E-3	5.7E-3	8.9E-3	1.3E-2	2.2E-2
Heart wall	3.7E-3	4.7E-3	7.3E-3	1.1E-2	2.0E-2
Kidneys	4.8E-3	5.9E-3	8.7E-3	1.3E-2	2.4E-2
Liver	3.7E-3	4.6E-3	7.2E-3	1.1E-2	2.0E-2
Lungs	3.3E-3	4.2E-3	6.3E-3	9.7E-3	1.8E-2
Muscles	3.4E-3	4.1E-3	6.4E-3	9.8E-3	1.8E-2
Oesophagus	3.4E-3	4.3E-3	6.5E-3	1.0E-2	1.9E-2
Ovaries	4.9E-3	6.1E-3	9.0E-3	1.4E-2	2.3E-2
Pancreas	4.2E-3	5.2E-3	7.8E-3	1.2E-2	2.2E-2
Red marrow	3.6E-3	4.4E-3	6.7E-3	9.9E-3	1.7E-2
Skin	2.4E-3	2.9E-3	4.6E-3	7.4E-3	1.4E-2
Spleen	3.7E-3	4.7E-3	7.2E-3	1.1E-2	2.0E-2
Testes	3.7E-3	4.6E-3	7.2E-3	1.1E-2	1.9E-2
Thymus	3.4E-3	4.3E-3	6.5E-3	1.0E-2	1.9E-2
Thyroid	3.4E-3	4.3E-3	6.8E-3	1.1E-2	2.0E-2
Urinary bladder wall	2.2E-2	2.8E-2	4.1E-2	5.4E-2	6.9E-2
Uterus	5.9E-3	7.2E-3	1.1E-2	1.6E-2	2.6E-2
Remaining organs	3.4E-3	4.2E-3	6.5E-3	1.0E-2	1.8E-2
Effective dose (mSv MBq^{-1})	**4.7E-3**	**5.8E-3**	**8.8E-3**	**1.3E-2**	**2.2E-2**

4.3 CONTRAINDICATIONS

There are no known contraindications.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Precautions

Patients should be encouraged to drink fluids and void the bladder frequently in the hours following administration of Chromium [^{51}Cr] Edetate Injection BP to minimise radiation dose to the bladder.

Chromium [^{51}Cr] Edetate Injection BP is not suitable for use in patients with oedema as in such patients equilibration of the administered chromium [^{51}Cr] edetate between the plasma and interstitial fluid may take up to 12 hours.

General

Radiopharmaceuticals should be administered by medical practitioners who are qualified and licensed to handle radioisotopes.

Disposal of all radioactive wastes should be carried out in accordance with the ARPANSA's *"Code for the Disposal of Radioactive Waste by the User - Radiation Protection Series, C-6*, S*eptember 2018".*

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine. Radiation protection precautions in accordance with national regulations must therefore be taken.

Check the following before use
The following should be checked prior to administration:

- Verification of the dose to be administered and patient identification.
- An inspection visually for colour (violet) and an absence of particulate matter.
- The expiry date.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, mutagenicity or reproductive toxicity studies have been conducted with chromium [^{51}Cr] edetate.

Patient care
Care should be taken to minimise unwanted radiation exposure to patients, consistent with proper patient management.

Use in the elderly
See Section 4.2 Dose and method of administration.

Paediatric use
See Section 4.2 Dose and method of administration.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Decreased glomerular filtration rate has been noted in patients treated with a variety of drugs such as aminoglycosides (gentamicin) and amphoyericin B. This is believed to be an effect of the nephrotoxicity associated with the use of such drugs.

This product should not be administered together with other medications unless this is in the context of a simultaneous investigation of renal function.

Long-term effects
None known.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No data available.
Use in pregnancy - Pregnancy Category B2
Only imperative investigations should be carried out during pregnancy and only when the likely benefit exceeds the risk incurred by the mother and the foetus. When it is necessary to administer radioactive medicinal products to a woman of childbearing potential the radiation exposure should be the minimum consistent with achieving the desired clinical information, whether or not the woman is known to be pregnant.

Administration of 6 MBq chromium [^{51}Cr] edetate results in an absorbed dose to the uterus of 0.017mGy for normal renal function and 0.039mGy for abnormal renal function. Whenever

possible, alternative techniques that do not involve ionising radiation should be employed. Any woman who has missed a period should be assumed to be pregnant until proven otherwise.

Use in lactation
Breast feeding need not be discontinued, however it is recommended that it be interrupted for four hours post administration the end of which period the milk is expressed and discarded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Reactions
Unwanted effects have been reported infrequently after single or repeated intravenous administrations of chromium[^{51}Cr] edetate such that the incidence of individual reactions cannot be quantified. Limited details are available, but mild allergic phenomena have been described.

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

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at – *www.tga.gov.au/reporting-problems*

4.9 OVERDOSE

In the event of an accidental administration of an overdose of chromium [^{51}Cr] edetate, the absorbed radiation dose to the patient should be reduced by increasing the elimination of the radionuclide from the body. This may be done by more frequent emptying of the urinary bladder by hydration, diuretics and catheterisation.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Chromium [^{51}Cr] Edetate Injection BP is a chemically stable, hydrophilic metal chelate. It is metabolically inert and exhibits no pharmacological properties. Renal function is unaffected, even by large amounts of Chromium [^{51}Cr] Edetate Injection BP.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
No data available.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Following intravenous administration, the Chromium [^{51}Cr] Edetate complex is excreted almost exclusively by the kidneys via the glomerular membrane. Less than 0.5% plasma protein binding occurs in patients, with normal glomerular filtration rate, the recovery of unchanged

chelate is close to 100% during the first 24 hours post injection. Tubular secretion and reabsorption, as well as external excretion, are negligible.

After intravenous administration, the Chromium [^{51}Cr] Edetate equilibrates within the intra- and extra-vascular spaces, a process taking between 30 and 90 minutes. Beyond this period, a constant percentage of the Chromium [^{51}Cr] edetate present on the extracellular fluid is excreted by the kidneys per unit time. Total body retention is described by a double exponential function.

The mean value of the glomerular filtration rate in a normal adult is approximately 130 mL/min in men and 120 mL/min in women. (Normalised for body surface area of 1.73 m2).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
See Section 4.2 Special warnings and precautions for use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Chromium
Ethylenediaminetetraacetic acid (EDTA)
Sodium Chloride, BP
Water for Injections, BP

Refer to Section 2 Qualitative and Quantitative composition.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except with those as required to achieve therapeutic indications given in Section 4 of this Product Information document.
Interaction of this medicine with others is also given in Section 4.5 of this Product Information document.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage
Store in an airtight container in a place that is sufficiently shielded to protect personnel from Irradiation by primary or secondary emission and that complies with national and international regulations concerning the storage of radioactive substances.

Store below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Chromium [^{51}Cr] Edetate Injection BP is contained in a 3 ml glass vial, sealed with a rubber stopper and a gold coloured aluminium cap. It is transported in a labelled pill packs.

The pack size is 8 MBq at calibration, 0900hours (Eastern Standard Time) the first day of each calendar month.

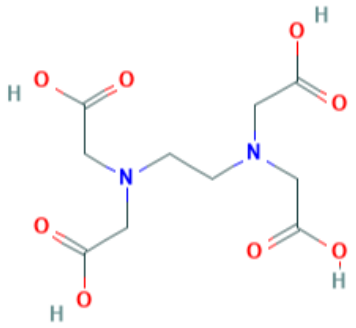
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Disposal of all radioactive wastes should be carried out in accordance with the ARPANSA's *"Code for the Disposal of Radioactive Waste by the User - Radiation Protection Series, C-6, September 2018".*

Refer to Section 4.4 - Special warnings and precautions for use.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number:
11063-42-6.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled.

8 SPONSOR

ANSTO
Locked Bag 2001
Kirrawee, DC NSW 2232

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Facsimile: 02 9543 6511

Australian Registration Number:
AUST R 22779

9 DATE OF FIRST APPROVAL

15 October 1991

10 DATE OF REVISION

26 march 2020.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Update to new TGA PI format.
2	Updated quantity of excipients.
4	Addition of the following: - effects on laboratory tests - effects on fertility - effects on ability to drive and use machines - reporting suspected adverse effects - information on the management of overdose Updated the "radiation absorbed dose" in tables 3 and 4 as per updated ICRP publication 128.
5	Addition of the following: - Mechanism of action - Clinical trials - Genotoxicity
6	Addition of the following: - List of excipients - Chemical structure and CAS number Updated the shelf-life information.
7	Included 'medicine schedule'.

References:
[1]The Health Physics and Radiological Health Handbook, (eds. Schleien, B, Terpilak, M.S.), Nucleon Lectern Associates, Olney, 1984.
[2]ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances.