IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0240/020/001
Case No: 2067523

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

GE Healthcare Limited

Amersham Place, **Little Chalfont**, **Buckinghamshire**, **HP7 9NA**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Chromium [51Cr] EDTA Injection ,Chromium [51Cr] EDTA 3.7MBq/ml Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/11/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Chromium [^{51}Cr] EDTA Injection
Chromium [^{51}Cr] EDTA 3.7MBq/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chromium [^{51}Cr] EDTA	37MBq/vial (3.7 MBq/ml at the activity reference date

The formulation contains 0.64 mg/ml chromium edetate.

Chromium-51 has a physical half-life of approximately 28 days and decays by gamma emisision with a principal energy of 0.32 MeV.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

Chromium-51 edetate is indicated for the determination of glomerular filtration rate in the assessment of renal function.

4.2 Posology and method of administration

The normally recommended dose for adults and the elderly is 1.1-6.0 MBq 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 11 MBq may be appropriate for use in conjunction with external counting techniques.

The activity to be administered to children may be calculated approximately by correcting on a weight, body surface area or age basis the activity to adults. For children under about one year of age, the target organ size in relation to the whole body must also be taken into consideration. Chromium (^{51}Cr) EDTA contains benzyl alcohol. It must not be given to premature babies or neonates.

The following methods of administration are recommended:

Single intravenous injection

Because of the complexities of the infusion technique (see below) a single injection technique is normally used. This method obviates the need for urine collection. However, it is not suitable for use with patients with oedema since, in

such patients**;** equilibration of the administered chromium-51 edetate between the plasma and interstitial fluid may take up to 12 hours.

The single injection plasma clearance is calculated from the injected amount of chromium-51 edetate and the decrease of activity in plasma samples as a function of time. A number of different methods are available for analysis of the plasma disappearance curve, one of which is presented below.

A single intravenous administration of 3.7 MBq of chromium-51edetate is given. Venous samples are taken at appropriate intervals (for example, two, three, and four hours after administration) with another at 24 hours if renal failure is suspected. The venous samples are spun and the plasma separated and counted, together with an aliquot of the given dose. The net plasma activities are then expressed in terms of fractional dose and plotted against time on a log-linear plot. A regression line is then fitted to the data and the line extrapolated back to the ordinate axis. The turnover rate *k* is determined from the slope of the line. The apparent distribution volume of the tracer *V* is obtained by dividing the count rate due to the administered dose by the plasma concentration given by the intercept on the ordinate axis. The plasma clearance *C* is then given by:

$$C = kV$$

In order to correlate the chromium-51 edetate values with standard inulin clearance values, a correction factor may be applied to the final result if this is required.

Continuous intravenous infusion

A priming administration of 1.85 MBq is given intravenously followed by the infusion of a solution containing 37 kBq/ml at a rate of 0.5 ml/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 separation and counting of the plasma radioactivity until constant plasma activity is observed in two successive samples. The values of the urine and the plasma concentrations and the urine flow are then substituted into the equation

$$C = \frac{UV}{P}$$

(where *C* = vol. of plasma cleared per unit time, *U* = urine concentration, *V* = urinary flow, *P* = plasma concentration) to give the clearance. When the urinary flow is low, it may be necessary to catheterise the bladder in order to remove the whole of the urine sample for a particular time period.

Alternative methods for determining glomerular filtration rate (GFR) using chromium-51 edetate may be used in certain centres.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Must not be given to premature babies or neonates.

4.4 Special warnings and precautions for use

This medicinal product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

To reduce the radiation dose to the bladder and an accumulation of radioactivity in it, the patient should be asked to drink additional fluids and to void the bladder as often as possible in the hours following administration.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction-studies have been performed.

4.6 Pregnancy and lactation

No data are available on the use of this product in human pregnancy. Animal reproduction studies have not been performed.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus.

Avoidance of pregnancy following administration of chromium-51 edetate is not necessary for a woman of child-bearing potential because of the low absorbed radiation dose associated with such an administration.

Before administering a radioactive medicinal product to a mother 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, bearing in mind the secretion of activity in breast milk. If the administration of chromium-51 edetate is considered necessary, breast feeding should be interrupted for 4 hours and the expressed feeds discarded, after which time the level of activity 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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Unwanted effects have been reported infrequently after single or repeated intravenous administrations of chromium-51 edetate such that the incidence of individual reactions cannot be quantified. Limited details are available, but mild allergic phenomena have been described. The causation of the adverse events reported to date has not been firmly established.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely 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 diagnostic 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 effective dose is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

In the event of an accidental administration of an overdose of chromium-51 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, renal system, chromium (^{51}Cr) edetate, ATC code: V09CXO4

Chromium-51 edetate is a chemically stable, hydrophilic metal chelate. It is metabolically inert. Renal function is unaffected even by large amounts of chromium edetate. At the chemical concentrations and activities used, chromium-51 edetate does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Following intravenous administration, the chromium-51 edetate complex is excreted almost exclusively by the kidneys via the glomerular membrane (less than 1% faecal excretion in 24 hours reported for an anuric patient). Less than 0.5% plasma protein binding occurs. In patients with normal or near-normal glomerular filtration rate the recovery of unchanged chelate in the urine during the first 24 hours after administration is close to 100% of the injected activity, cumulative faecal clearance accounting for less than 0.1%. There is no significant tubular secretion or re-absorption of chromium-51 edetate. However, a small amount of tubular re-absorption, some whole body retention or complex dissociation have each been postulated to explain the known but small underestimation of inulin clearance by chromium-51 edetate.

After intravenous administration**;** the chromium-51 edetate equilibrates within the intra- and extravascular spaces, a process taking between 30 and 90 minutes. Beyond this period a constant percentage of the chromium-51 edetate present in 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 the normal adult is approximately 130 ml/min in men and 120 ml/min in women (normalised for body surface area of 1.73 m^2).

5.3 Preclinical safety data

It has been reported that no toxic effects were noted in dogs following intravenous infusion for a period of 36 hours of 1.5 g chromium edetate/kg.

Intravenous administration of a formulation of chromium-51 edetate to rats and mice has indicated that the average lethal dose is more than 1000 times the maximum recommended dose to humans. Repeat dose studies with the same formulation revealed no detrimental clinical or histological effects when the equivalent of more than 50 times the maximum recommended human dose was administered to rats and dogs over a two week period. Chromium-51 edetate is not intended for regular or continuous administration.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium EDTA
Benzyl alcohol
Water for Injections

6.2 Incompatibilities

None known

6.3 Shelf Life

The shelf-life of the product is not more than 90 days after the date of release.
The reference date of the product is 60 days before expiry.

6.4 Special precautions for storage

The product should be stored below 25^{o}C. Do not freeze.
Storage procedures should be in accordance with national regulations for radioactive substances.

6.5 Nature and contents of container

The product is supplied in a 10 ml Type I Ph. Eur., clear, colourless, borosilicate glass vial sealed with a PTFE faced rubber closure and oversealed with an aluminium overseal with an aperture. Each vial is packed within a radiation shielding container of lead metal.
Pack sizes: 37 MBq

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The administration of radiopharmaceuticals creates risks for other persons from external radiation on contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Storage procedures and the disposal of waste should be in accordance with national guidelines.

7 MARKETING AUTHORISATION HOLDER

GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire
HP7 9NA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0240/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 February 1999

Date of last renewal: 05 February 2009

10 DATE OF REVISION OF THE TEXT

November 2009

11 DOSIMETRY

Data on absorbed dose following administration of chromium [^{51}Cr] edetate are taken from ICRP 53, International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1988.

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	8.1E-04	9.1E-04	1.4E-03	2.2E-03	4.0E-03
Bladder wall	2.3E-02	3.2E-02	4.6E-02	7.0E-02	1.3E-01
Bone surfaces	7.0E-04	8.2E-04	1.2E-03	1.9E-03	3.5E-03
Breast	5.6E-04	5.6E-04	8.3E-04	1.3E-03	2.6E-03
GI-tract					
Stomach wall	7.3E.04	8.4E-04	1.3E-03	2.1E-03	3.6E-03
Small intest	1.1E-03	1.4E-03	2.1E-03	3.3E-03	5.8E-03
ULI wall	1.0E-03	1.2E-03	1.9E-03	3.0E-03	5.1E-03
LLI wall	1.6E-03	2.1E-03	3.0E-03	4.5E-03	7.6E-03
Kidneys	1.8E-03	2.2E-03	3.2E-03	4.6E-03	8.1E-03
Liver	6.8E-04	8.3E-04	1.3E-03	2.1E-03	3.8E-03
Lungs	5.7E-04	7.2E-04	1.1E-03	1.7E-03	3.2E-03
Ovaries	1.6E-03	2.0E-03	3.0E-03	4.5E-03	7.6E-03
Pancreas	7.8E-04	9.4E-04	1.5E-03	2.3E-03	4.1E-03
Red marrow	8.7E-04	1.0E-03	1.5E-03	2.1E-03	3.5E-03
Spleen	7.2E-04	8.6E-04	1.3E-03	2.0E-03	3.8E-03
Testes	1.2E-03	1.6E-03	2.8E-03	4.2E-03	7.8E-03
Thyroid	5.3E-04	7.3E-04	1.2E-03	1.9E-03	3.5E-03
Uterus	2.8E-03	3.4E-03	5.3E-03	7.9E-03	1.3E-02
Other tissue	8.0E-04	9.5E-04	1.5E-03	2.2E-03	4.1E-03
Effective dose equivalent (mSv/MBq)	**2.3E-03**	**3.1E-03**	**4.6E-03**	**7.0E-03**	**1.3E-02**

The data presented above assume a body retention half-time of 100 minutes and a renal transit time of 5 minutes. Data are also presented for abnormal renal function in which the retention half-time is 1000 minutes and the renal transit time is increased to 20 minutes.

Abnormal renal function

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	4.5E-03	5.0E-03	7.7E-03	1.2E-02	2.1E-02
Bladder wall	2.1E-02	2.9E-02	4.2E-02	6.4E-02	1.2E-01
Bone surfaces	3.6E-03	4.2E-03	6.4E-03	9.8E-03	1.8E-02
Breast	3.2E-03	3.2E-03	4.8E-03	7.6E-03	1.4E-02
GI-tract					
Stomach wall	4.1E-03	4.7E-03	7.2E-03	1.1E-02	1.9E-02
Small intest	4.5E-03	5.5E-03	8.4E-03	1.3E-02	2.3E-02
ULI wall	4.3E-03	5.2E-03	7.7E-03	1.2E-02	2.1E-02
LLI wall	4.6E-03	5.7E-03	8.8E-03	1.3E-02	2.3E-02
Kidneys	8.3E-03	1.0E-02	1.4E-02	2.1E-02	3.6E-02
Liver	3.8E-03	4.6E-03	7.2E-03	1.1E-02	2.0E-02
Lungs	3.3E-03	4.2E-03	6.3E-03	9.7E-03	1.8E-02
Ovaries	4.6E-03	6.0E-03	9.1E-03	1.4E-02	2.5E-02
Pancreas	4.3E-03	5.2E-03	8.1E-03	1.2E-02	2.2E-02
Red marrow	4.0E-03	4.8E-03	7.1E-03	1.0E-02	1.8E-02
Spleen	4.0E-03	4.8E-03	7.3E-03	1.1E-02	2.0E-02
Testes	3.7E-03	4.6E-03	7.2E-03	1.1E-02	2.1E-02
Thyroid	3.1E-03	4.3E-03	6.8E-03	1.1E-02	2.0E-02
Uterus	5.8E-03	7.1E-03	1.1E-02	1.7E-02	2.9E-02
Other tissue	3.4E-03	4.1E-03	6.3E-03	9.9E-03	1.8E-02
Effective dose equivalent (mSv/MBq)	**5.2E-03**	**6.5E-03**	**9.7E-03**	**1.5E-02**	**2.7E-02**

For this product, the effective dose equivalent to a 70kg adult resulting from an administered activity of 1.1 to 6MBq is typically 0.0025 to 0.014mSv in the case of normal kidney function and is 0.0057 to 0.031mSv under conditions of abnormal renal function.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

They may 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 local competent official organisations (see section 6.6).

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.