DRN 4920 **OctreoScan Singapore**

DATASHEET/DIRECTIONS FOR USE

1. TRADE NAME OF THE MEDICINAL PRODUCT

OctreoScan
(Curium catalogue number: DRN 4920)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OctreoScan is supplied as two vials which cannot be used separately.

Contents of vial **4920/A**:
^{111}In as $InCl_3$ 122 MBq/1.1 ml at activity reference time/date

Contents of vial **4920/B**:
Pentetreotide 10 µg

After reconstitution and labelling the solution contains ^{111}In-pentetreotide.

3. PHARMACEUTICAL FORM

Vial A: Precursor solution.
Vial B: Powder for solution for injection.

4. CLINICAL PARTICULARS

I. Indications

^{111}In pentetreotide specifically binds to receptors for somatostatin.
OctreoScan is indicated for use as adjunct in the diagnosis and management of receptor bearing gastro-entero-pancreatic neuroendocrine (GEP) tumours and carcinoid tumours, by aiding in their localisation. Tumours which do not bear receptors will not be visualised.
In a number of patients suffering from GEP or carcinoid tumours the receptor density is insufficient to allow visualisation with OctreoScan. Notably in approximately 50% of patients suffering from insulinoma the tumour cannot be visualised.

II. Posology and method of administration

The dose for planar scintigraphy is 110 MBq in one single intravenous injection. Careful administration is necessary to avoid paravasal deposition of activity. For single photon emission tomography the dose depends on the available equipment. In general, an activity dose of 110 to 220 MBq in one single intravenous injection should be sufficient. No special dosage regimen for elderly patients is required.

There is limited experience on administrations in paediatric patients, but when the use in a child is considered to be necessary, the amount of activity administered should be reduced according to standard body weight or body surface calculations. A practical approach is to adopt the recommendations of the Paediatric Task Group, European Association of Nuclear Medicine.

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

Scintigraphy takes place approx. 24 hours after administration. When activity in the abdomen is observed at 24 hours which cannot be interpreted with certainty as uptake in tumour or activity in bowel contents, scintigraphy should be repeated at 48 hours. In some cases, scintigraphy after 4 hours gives acceptable results. Physiologic uptake occurs in spleen, liver, kidneys and bladder. Thyroid, pituitary and intestines are visible in most patients.

III. Contraindications
No specific contraindications have been identified.

IV. Special warnings and special precautions for use
Because of the potential hazard of the ionizing radiation ^{111}In-pentetreotide should not be used in children under 18 years of age, unless the value of the expected clinical information is considered to outweigh the possible damage from radiation.

Administration of a laxative is necessary in patients not suffering from diarrhoea, to differentiate stationary activity accumulations in lesions in, or adjacent to, the intestinal tract from moving accumulations in the bowel contents.

In patients with significant renal failure administration of ^{111}In-pentetreotide is not advisable because the reduced or absent function of the principal route of excretion will lead to delivery of an increased radiation dose (E.D.E. 1.9E-01 mSv/MBq). Administration should be considered only when the possible damage from radiation is outweighed by the potential diagnostic information. Interpretable scintigrams may be obtained after haemodialysis during which the high background activity can at least partially be removed. Prior to dialysis images are non-diagnostic because of activity in the circulation. After dialysis a higher than usual uptake in liver, spleen and intestinal tract, and a higher than usual activity in circulation, were observed.

^{111}In-pentetreotide not bound to receptors, and non-peptide bound ^{111}In, are rapidly eliminated through the kidneys. To enhance the process of excretion, in order to reduce background noise and to reduce the radiation dose to kidneys and bladder, a liberal fluid intake is required for 2 or 3 days following administration.

In diabetic patients, receiving high doses of insulin, the administration of pentetreotide may cause paradoxical hypoglycaemia via a temporary inhibition of glucagon secretion.

Regarding patients on octreotide therapy it is recommended to withdraw this

therapy temporarily to avoid a possible blockade of somatostatin receptors. This recommendation is given on empirical grounds, the absolute need for such measure has not been demonstrated. In some patients the withdrawal of therapy might be not tolerated and may cause rebound effects. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome.
If the clinician responsible for the patients therapeutic management considers withdrawal of octreotide therapy tolerable a three days withdrawal period is recommended.
Positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of tissue somatostatin receptors rather than a malignant disease. Furthermore positive uptake is not specific for GEP- and carcinoid-tumours. Positive scintigraphic results require evaluation of the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. An increase in somatostatin receptor density can also occur in the following pathological conditions: tumours arising from tissue embryologically derived from the neural crest, (paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas), tumours of the pituitary gland, endocrine neoplasms of the lungs (small-cell carcinoma), meningiomas, mamma-carcinomas, lympho-proliferative disease (Hodgkin's disease, non-Hodgkin lymphomas), and the possibility of uptake in areas of lymphocyte concentrations (subacute inflammations) must be considered.
Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the 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 Manufacturing Practice for pharmaceuticals.

V. Interaction with other medicaments and other forms of interaction
No drug interactions have been reported to date.

VI. Pregnancy and lactation
There are no data available from studies in animals or man to assess the possible risks during pregnancy and lactation. 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 have to be

considered. Radionuclide procedures carried out on pregnant women also involve the delivery of radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when likely benefit exceeds the risks incurred by mother and foetus.
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 administration is considered necessary, breast feeding should be interrupted and the expressed feeds must be discarded. Breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv.

VII. Effects on the ability to drive and use machines
^{111}In-pentetreotide does not affect the ability to drive or to use machines.

VIII. Undesirable effects
Adverse effects attributable to the administration of OctreoScan are rare. Specific effects have not been observed. The symptoms reported are suggestive of vasovagal reactions or of anaphylactoid drug effects.
The withdrawal of octreotide therapy as a preparatory step to scintigraphy might provoke severe adverse effects, generally of the nature of a return of the symptoms seen before this therapy was started.

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 radiation doses delivered (EDE) is less than 20 mSv. However, with this product when performing SPECT this level might be exceeded. The EDE in a 70 kg individual with normal renal function is maximally 26 mSv. The higher dose may be justified under some clinical circumstances.

IX. Overdose
The pharmaceutical form (monodose injection) makes inadvertent overdosing improbable. The renal elimination of ^{111}In-pentetreotide, not bound to receptors, and of non-peptide bound ^{111}In can be enhanced by administration of fluids.

5. PHARMACOLOGICAL PROPERTIES
I. Pharmacodynamic properties
OctreoScan attaches to somatostatin receptors in tissues where, as consequence of disease, the cell-surfaces contain these receptors in a more

than physiologic density. In individual patients, where the disease did not lead to an increased receptor density, scintigraphy will not be successful. In carcinoids and GEP-tumours the prevalence of increased receptor density in the tumour-tissue in general is rather high.
Only limited studies of pharmacodynamic effects have been performed. The in vitro biological activity is approximately 30% of the biological activity of natural somatostatin. The in vivo biological activity, measured in rats, is less than that of equal amounts of octreotide. Intravenous administration of 20 μg of pentetreotide resulted in some patients in a measurable but very limited decrease of serum gastrin and serum glucagon levels of less than 24 hours duration.

II. Pharmacokinetic properties
Approximately 80% (resp. 90%) of intravenously administered radiolabelled pentetreotide is eliminated through the urinary system in 24 (resp. 48) hours. ^{111}In-pentetreotide is taken up by the following organs: liver (approx. 2% at 24 hours) and spleen (approx. 2.5% at 24 hours).
Uptake in thyroid and pituitary occurs but not reproducibly.
The uptake in kidneys is partly a reflection of ongoing elimination through the urine and partly due to delayed excretion by the kidney. The elimination via the gallbladder and subsequently the faeces is approx. 2% of the administered activity dose in patients with normal intestinal function.
Up to 6 hours post-administration radioactivity in urine is predominantly intact ^{111}In-pentetreotide. Thereafter, increasing amounts of non-peptide-bound activity are excreted.

III. Preclinical safety data
Preclinical safety testing did not yield remarkable findings. No testing has been done on carcinogenic potential nor of the influence of pentetreotide on fertility or on embryotoxicity.

IV. Radiation dosimetry

The following radiation dosimetry is based on external measurements in humans. The calculations were done according to the MIRD system. In the calculation of the effective dose equivalent the seven obligatory organs have been incorporated, and those five other organs which receive the highest organ dose (indicated by a preceding asterisk).

Radiation dose estimates for ^{111}In-pentetreotide, including the contribution from 0.1% ^{114m}In.

Target organ	**mGy/MBq**	**(rad/mCi)**
Adrenals	6.7E-02	(2.5E-01)
Brain	1.2E-02	(4.5E-02)
Breasts	1.3E-02	(4.7E-02)
Gallbladder wall	5.5E-02	(2.0E-01)
*LLI wall	8.6E-02	(3.2E-01)
Small intestine	4.5E-02	(1.7E-01)
Stomach	4.1E-02	(1.5E-01)
ULI wall	5.7E-02	(2.1E-01)
Heart wall	2.5E-02	(9.2E-02)
*Kidneys	6.6E-01	(2.4E+00)
Liver	6.7E-02	(2.5E-01)
Lungs	2.2E-02	(8.2E-02)
Muscle	2.6E-02	(9.7E-02)
Ovaries	4.7E-02	(1.7E-01)
*Pancreas	6.8E-02	(2.5E-01)
Red marrow	3.0E-02	(1.1E-01)
Bone surfaces	3.4E-02	(1.2E-01)
Skin	1.4E-02	(5.1E-02)
*Spleen	3.8E-01	(1.4E+00)
Testes	2.7E-02	(1.0E-01)
Thymus	1.7E-02	(6.1E-02)
Thyroid	5.5E-02	(2.0E-01)
*Urinary bladder wall	4.8E-01	(1.8E+00)
Uterus	6.8E-02	(2.5E-01)
Pituitary	7.6E-02	(2.8E-01)
EFFECTIVE DOSE EQUIVALENT (E.D.E)	**mSv/MBq** **1.2E-01**	**(rem/mCi)** **(4.5E-01)**

The E.D.E. for the recommended activity dosage in adults is 13 mSv for 110 MBq and 26 mSv for 220 MBq of ^{111}In (including the contribution from ^{114m}In).

For children, when the activity dose adjustments as recommended by the Paediatric Task Group of the EANM are applied, the actual effective dose equivalents for the stated activity dosages for the different age/weight groups are:

Age	E.D.E (mSv/MBq)	Recommended activity dose	E.D.E. for recommended dose
15-year-old/58 kg	1.55E-01	100 MBq	16 mSv
10-year-old/34 kg	2.21E-01	75 MBq	17 mSv
5-year-old/22 kg	3.23E-01	55 MBq	18 mSv
1-year-old/8 kg	5.72E-01	25 MBq	14 mSv
Newborn/3 kg	1.32E+00	11 MBq	15 mSv

6. PHARMACEUTICAL PARTICULARS

I. Excipients

After reconstitution and labelling the solution contains trisodium citrate dihydrate, citric acid monohydrate, inositol, gentisic acid, ferric chloride hexahydrate and hydrochloride acid 0.02 M. No preservatives.

II. Incompatibilities

Major incompatibilities: not known. After reconstitution and labeling OctreoScan may be diluted with 0.9% saline solution. Do not mix the injectate with any other solution in order to avoid possible incompatibilities.

III. Special precautions for storage

No special storage conditions are required, except for adequate shielding of the radiation that is emitted. Refer to outer carton for storage condition.

IV. How supplied

OctreoScan is supplied as two separate vials, of which one has a lead shielding. Both vials are packed in a closed, folded tin.

V. Instructions for use/handling

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

VI. Instructions for labelling

1. Add the contents of vial A (^{111}In) Indium chloride to vial B (lyophilised pentetreotide) to obtain (^{111}In) pentetreotide; only the Sterican (0.90 x 70) needle supplied with the patient dose should be used to remove (^{111}In) indium chloride from its vial.
2. Observe an incubation period of 30 minutes following the reconstitution.
3. The preparation may be diluted with 2-3 mL of 0.9% sodium chloride solution if a larger volume is desired for easier handling in the syringe.
4. The solution must be clear and colourless, this can be checked behind a lead wall containing a lead glass window. If the solution does not comply it should be discarded.
5. Use a tiny sample of this (diluted or not) volume for the quality control, which is described in the following section.

For the reconstitution do not use other ^{111}In-chloride solutions but the one

supplied in the same container together with the lyophilized pentetreotide.

VII. Instructions for quality control
Analysis of ^{111}In-bound peptides versus ^{111}In-bound non-peptide compounds may be done on silicagel impregnated glass fiber strips (iTLC). Prepare a thoroughly dried strip, approx. 10 cm long and 2.5 cm wide by marking a starting line at 2 cm, with additional marks at 6 and 9 cm. Apply 5 to 10 µl of the reconstituted and labelled solution to the starting line and develop in freshly prepared sodium citrate solution 0.1M, adjusted with HCl to pH 5. In approximately 2-3 min the front will have reached the 9 cm mark. Cut the strip at the 6 cm mark and measure the activity of both halves. Non-peptide bound ^{111}In moves with the front.
Requirement: The lower end of the chromatogram should contain ≥ 98% of the applied activity.

VIII. Instructions for waste disposal
Unused ^{111}In activity or unused OctreoScan should be allowed to decay until the activity has dropped to such a low level that, according to local regulations, it is no longer considered radioactive. Then it may be disposed of as harmless waste. Unused vials with lyophilized pentetreotide may be disposed of as harmless waste. Waste must be disposed of according to national regulations for radioactive material.

7. NAME AND ADDRESS OF PRODUCT OWNER
Manufactured and released by:
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8. LICENCE NUMBER
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9. LAST REVISED DATE

22 Aug 2023