IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0240/018/001
Case No: 2041908

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

SODIUM IODIDE [131I] Injection 37 MBq/ml

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 **08/11/2007** until **12/04/2012**.

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

Sodium Iodide [^{131}I] Injection 74 MBq/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium iodide [^{131}I]: 37-740MBq/vial (74MBq/ml)
at the activity reference date

0.925-9.25GBq/vial (925MBq/ml) at the activity reference date

The specific activity of the sodium iodide [^{131}I] is not less than 222GBq/mgI at the activity reference date.

Physical characteristics

Iodine-131 is produced by fission of uranium-235 or by neutron bombardment of stable tellurium in a nuclear reactor. It decays by emission of gamma radiations of 365 keV (81%), 637 keV (7.3%) and 284 (6.1%) and beta radiations of maximal energy of 0.606MeV to stable Xenon 131. Iodine-131 has a half-life of 8.04 days.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

4.1.1 **Diagnostic indications**

- Sodium iodide may be given as a “tracer” dose to study radioiodine kinetics. An estimation of the thyroid uptake and effective half-life obtained with a tracer amount, can be used to calculate the activity required for radioiodine therapy.
- In the management of thyroid carcinoma, sodium iodide is used to identify thyroid remnant and metastases (after ablation).
- Thyroid scanning for benign conditions with 131I can be performed but only where circumstances do not allow for radiopharmaceuticals with more favourable dosimetry to be used.

4.1.2 **Therapeutic indications**

Radioiodide thyroid therapy is indicated for :

- treatment of Graves disease, toxic multinodular goitre or autonomous nodules.
- treatment of papillary and follicular thyroid carcinoma including metastatic disease.

Sodium iodide [131I] therapy is often combined with surgical intervention and with antithyroid medications.

4.2 Posology and method of administration

Diagnostic use

The recommended activities for an adult patient (70 kg) are as follows:

1. For the thyroid uptake studies: 0.2-3.7 MBq

2. For post thyroid ablation (for metastases and thyroid remnant): a maximum dose of 400 MBq.

3. For thyroid imaging: 7.4-11 MBq

Scans are usually performed at 4 hours, and then again at 18 - 24 hours (for scintigraphy also at 72 hours).
The diagnostic activity to be administered to a child and adolescent should be a fraction of the adult dose calculated from the body weight/surface area methods or 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

(Paediatric Task Group, EANM)

Therapeutic use

The activity administered is a matter for clinical judgement. The therapeutic effect is only achieved after several months.

- For the treatment of hyperthyroidism

The activity administered is usually in the range of 200 - 800 MBq but repeated treatment may be necessary, with cumulative activities of up to 5,000MBq. The dose required depends on the diagnosis, the size of the gland, thyroid uptake and iodine clearance. Patients should be rendered euthyroid medically whenever possible before giving radioiodine treatment for hyperthyroidism.

- For thyroid ablation and treatment of metastases

The administered activities following total or sub total thyroidectomy to ablate remaining thyroid tissue are in the range of 1850 - 3700 MBq. It depends on the remnant size and radioiodine uptake. In subsequent treatment for metastases, administered activity is in the range 3700-11100 MBq.

After high doses used, e.g. for the treatment of thyroid carcinoma, patients should be encouraged to increase oral fluids to have frequent bladder emptying to reduce bladder radiation.

The therapeutic activity to be administered to a child over 10 years and adolescent should be a fraction of the adult dose, calculated from body weight or surface area.

4.3 Contraindications

^{131}I is contraindicated during pregnancy. ^{131}I should only be used for thyroid scanning in the follow up of malignant disease. The high radiation dose to the thyroid gland precludes its use for scanning in benign thyroid conditions, unless there are exceptional circumstances, where ^{123}I is not available.

4.4 Special warnings and precautions for use

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

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

There is little evidence of an increased incidence of cancer, leukaemia or mutations in man with respect to patients treated for benign thyroid disease with radioiodine, despite extensive use. In the treatment of children over 10 years old and young people however, account must be taken of the greater sensitivity of child tissue and the greater life expectancy of such patients. The risks must also be weighed up against those of other possible treatments.

In the treatment of malignant thyroid disease, a higher incidence of bladder cancer has been reported in one study of patients receiving greater than 3,700 MBq iodine-131. Another study has reported a small excess leukaemia in patients receiving very high doses. A cumulative total dose higher than 25900 MBq is therefore not advisable.

The therapeutic administration of sodium iodide [^{131}I] in patients with significant renal impairment, in which an activity adjustment is necessary, requires special attention.

A low iodine diet prior to therapy will enhance uptake into functioning thyroid tissue.

Thyroid replacement should be stopped prior to radioiodine administration for thyroid carcinoma to ensure adequate uptake. A period of ten days is recommended for triiodothyronine and six weeks for thyroxine. They should be restarted two weeks after treatment. Similarly carbimazole and propylthiouracil should be stopped five days prior to treatment of hyperthyroidism and restarted several days later.

The administration of high dose radioiodine may result in significant environmental hazard. These may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered. Suitable precautions should be taken concerning the activity eliminated by the patients in order to avoid any contamination.

4.5 Interaction with other medicinal products and other forms of interaction

Many pharmacological agents are known to interact with radioiodide. These may do so by a variety of mechanisms which can affect the protein binding, the pharmacokinetics or influence the dynamic effects of labelled iodide. It is therefore necessary to take a full drug history and ascertain whether any medications are required to be withheld prior to the administration of sodium iodide [131I].
For example dynamic, antithyroidal agents, carbimazole (or other imidazole derivatives such as propylthiouracil), salicylates, steroids, sodium nitroprusside, sodium sulfobromophtalein, perchlorate, miscellaneous agents (anticoagulants, anti-histamines, antiparasities, penicillins, sulphonamides, tolbutamide, thiopental), are normally withheld for 1 week; phenylbutazone for 1-2 weeks; expectorants, vitamines for two weeks, natural or synthetic thyroid

preparations (levothyroxine sodium, sodium liothyronine, thyroid extract) for 2-3 weeks; amiodarone, benzodiazepines, lithium for 4 weeks; topical iodides for 1-9 months; and for intravenous contrast agents, oral cholecystographic agents, iodine containing contrast media for period up to 1 year.

4.6 Pregnancy and lactation

Sodium iodide [131I] is contra-indicated during established pregnancy (the absorbed dose to the uterus exceeds 0.5mGy for this agent and is in the range of 11-511 mGy). The foetal thyroid gland avidly concentrates iodine during the second and third trimesters.

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.

In the case of differentiated thyroid carcinoma diagnosed in pregnancy therefore, radioiodine treatment should be postponed until after the pregnancy has ended.

Women receiving activities of sodium iodide [^{131}I] greater than 1000MBq should be advised NOT to become pregnant within four months of administration.

Breast feeding should be discontinued after administration of sodium iodide [^{131}I].

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or to operate machinery are to be expected after use of the drug.

4.8 Undesirable effects

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.

For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (effective dose/EDE) is less than 20mSv. These levels are usually exceeded for this compound. The radiation dose resulting from therapeutic exposure may also result in higher incidence of cancer and mutations (see “late consequences” described below). In such cases it is necessary to ensure that the risks of the radiation are less than from the disease itself.

- Early consequences

Therapeutic quantities of 131I may worsen existing hyperthyroidism temporarily. High levels of radioactivity may lead to gastrointestinal disturbance, usually within the first hours or days after administration.

The incidence of gastrointestinal upset can be as high at 67%. This can easily be prevented or counteracted by means of symptomatic treatment.

With high dose radioiodine treatment, 1 - 3 days after administration, the patient may experience transient inflammatory thyroiditis and tracheitis, with a possibility of severe tracheal constriction, especially where there is existing tracheal stenosis. Sialadenitis may occur, with swelling and pain in the salivary glands, partial loss of taste and dry mouth. Incidence varies from 10% (with precautions and 60% (without precautions). Sialadenitis is usually reversible spontaneously or with anti inflammatory treatment but cases have occasionally been described of dose dependent persistent loss of taste and dry mouth, followed by loss of teeth. The radiation exposure of the salivary glands should be reduced by stimulating saliva excretion with acidic substances.

High levels of uptake of radioiodine given to the patients can be associated with local pain, discomfort and oedema in the tissue taking up the radionuclide

In the treatment of metastasising thyroid carcinomas with CNS involvement, the possibility of local cerebral oedema and/or an increasing existing cerebral oedema must also be borne in mind.

Some cases of adverse reactions have been reported following the administration of sodium iodide [^{131}I], including nausea, vomiting and unspecified possible allergic phenomena.

- Late consequences

Dose dependent hypothyroidism may occur as a late consequence of radioiodine treatment of hyperthyroidism. This may manifest itself weeks or years after treatment, requiring suitable timed measurement of thyroid function and appropriate thyroid replacement. The incidence of hypothyroidism, generally not seen until 6-12 weeks, following radioiodine has been variously reported as between 2 and 70%.

Occasionally cases of transient hypoparathyroidism have been observed after radioiodine, they must be monitored accordingly and treated with replacement therapy. As a late consequence a single administration of over 5000 MBq or in interval of below 6 months are more likely to be associated with reversible or in very rare cases irreversible bone marrow depression may develop, with isolated thrombocytopenia or erytrocytopenia, which may be fatal. Transient leucocytosis is frequently observed.

Epidemiological studies carried out for the periods 1950 - 1975 report a higher incidence of stomach cancer in patients receiving 131I.

After high activities, typically those used in the treatment of thyroid malignancies, an increased incidence of leukaemia has been observed. There may also be a small increase in bladder and breast cancers.

4.9 Overdose

This agent is intended for use by competent personnel within a hospital setting. As such the risk of overdose is theoretical. The risks related to the inadvertent administration of excess radioactivity. High radiation exposure through overdose can be reduced by means of administration of thyroid blocking agent, such as potassium perchlorate, the use of the emetics and promoting a diuresis with frequent voiding of urine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Codes: V09F X03 V10X A01

Iodide in the amount used for diagnostic and therapeutic indications, is not known to have any pharmacological effect. More than 90% of the radiation effects result from beta radiation which has a mean range of 0.5mm.

5.2 Pharmacokinetic properties

Following injection, about 20% of blood iodide is extracted in a single passage through the thyroid gland. Peak thyroid accumulation occurs within 24 - 48 hours of dosing with about 50% of the maximum at 5 hours. This kinetic profile provides the rationale for the diagnostics procedures at 24 and 72 hours after dosing.

The effective half-life of radioiodine in plasma is in the order of 12 hours whereas that for radioiodine taken up by the thyroid gland is about 6 days. Thus after administration of sodium iodide [131I] approximately 40% of the activity has an effective half-life of 0.4 days and the remaining 60%, 8 days. Elimination is mainly via the urine. Small amounts of iodide [131I] are taken up by salivary glands, gastric mucosa and would also be localised in breast milk, the placenta

and choroid plexus. Urinary excretion is 37 - 75%, faecal excretion is about 10% with almost negligible excretion in sweat.

5.3 Preclinical safety data

Because of the small quantities of substance administered compared with the normal food intake of iodine (40-500 mcg/day) no acute toxicity is expected or observed.

There are no data available on the toxicity of repeated doses of sodium iodide nor on its effects on reproduction in animals or its mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium thiosulphate
Sodium dihydrogen phosphate
Disodium hydrogen phosphate.
Sodium chloride
Water for Injections

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf Life

The shelf-life for this product is 39 days from the activity reference date stated on the label.

6.4 Special precautions for storage

The product should be stored below 25^{o}C. Do not freeze.

6.5 Nature and contents of container

Since the product does not contain an antimicrobial preservative and is marketed for multidose use, all doses from a single vial should be taken within a single working day and the product stored at 2-8^{o}C after removal of the first aliquot.

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.

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

Since the product does not contain an antimicrobial preservative and is marketed for multidose use, all doses from a single vial should be taken within a single working day and the product stored at 2-8^{o}C after removal of the first aliquot.

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.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 240/18/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 13th April 2007.

10 DATE OF REVISION OF THE TEXT

November 2007