TECHNICAL LEAFLET: SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CAPSION
Sodium iodide [^{131}I] capsule for therapy.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The capsule contains as active substance sodium iodide [^{131}I], with activities of 50 to 3700 MBq per capsule at calibration date.
[^{131}I] iodine is produced by fission of [^{235}U]uranium and by neutron bombardment of stable tellurium in a nuclear reactor. [^{131}I] iodine has a half-life of 8.04 days. It decays by emission of gamma radiation of 365 keV (81 %), 637 keV (7.3 %) and 284 keV (6.0 %) and beta radiation of 606 keV to stable [^{131}Xe] xenon.

3 PHARMACEUTICAL FORM

Capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Radioiodine 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 [^{131}I] therapy is often combined with surgical intervention and with antithyroid medications.

4.2 Posology and method of administration

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. 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 subtotal 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.

The activity to be administered in children and adolescents should be a fraction of the adult dose calculated from the body weight/surface area methods according to the following equations :

$$\textit{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq)} \times \text{child weight (kg)}}{70\ \text{(kg)}}$$

$$\textit{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq)} \times \text{child surface } (m^2)}{1.73\ (m^2)}$$

Correction factors given for guidance are proposed below.

Fraction of adult dose :

3 kg = 0.10	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)

The capsule is administered orally together with a drink. It should be swallowed whole.

In patients with suspected gastrointestinal disease, great care should be taken when administering [^{131}I] capsules. The capsules should be swallowed whole with sufficient fluid to ensure clear passage into the stomach and upper small intestine. Concomitant use of H_2 antagonists or proton pump inhibitors is advised.

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.

4.3 Contraindications

- Pregnancy.
- For diagnostic purpose children under 10 years of age.
- Thyroid scanning except in the follow-up of malignant disease or when [^{123}I] or [^{99m}Tc] are not available.
- Patients with dysphagia, oesophageal stricture, active gastritis, gastric erosions and peptic ulcer.
- Patients with suspected reduced gastrointestinal motility.

4.4 Special warnings and precautions for use

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

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiological and pharmaceutical quality requirements.

This preparation is likely to result in relatively a high radiation dose to most patients (see section 4.8 and 5.4).

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 contaminations.

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 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 more than 3700 MBq [^{131}I]. Another study has reported a small excess leukaemia in patients receiving very high doses. A cumulative total activity higher than 26000 MBq is therefore not advisable.

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

To avoid sialadenitis which may complicate high dose radioiodine administration, the patient may be advised to take sweets or drinks containing citric acid which will stimulate saliva excretion.

To compensate a potential transient impairment of male gonadal function by high radioiodine therapeutic dose, sperm banking should be considered for men who have extensive disease.

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.

In patients with a known hypersensitivity for gelatine or their metabolites, sodium iodide [^{131}I] solution should be preferred for the radioiodine therapy.

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 [^{131}I].
For example antithyroid agents, carbimazole (or other imidazole derivatives such as propylthiouracil), salicylates, steroids, sodium nitroprusside, sodium sulfobromophthalein, perchlorate, miscellaneous agents (anticoagulants, anti-histamines, antiparasitics, penicillins, sulphonamides, tolbutamide, thiopentone), are normally withheld for 1 week ; phenylbutazone for 1-2 weeks, expectorants, vitamins for 2 weeks ; natural or synthetic thyroid preparations (sodium thyroxine, 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 periods up to 1 year.

4.6 Pregnancy and lactation

Sodium iodide [^{131}I] is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (the absorbed dose to the uterus for this agent is likely to be in the range 11-511 mGy, and 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. 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 Sodium iodide [^{131}I] should be advised NOT to become pregnant within four months of 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 activity in breast milk. Breast feeding should be discontinued indefinitely after Sodium iodide [^{131}I] administration.

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.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary effects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself. The radiation dose delivered (EDE) after therapeutic doses of Sodium iodide [^{131}I] is higher than 20 mSv.

Some cases of adverse reactions have been reported following the administration of sodium iodide [^{131}I], including nausea, vomiting and unspecified possible allergic phenomena. Nausea and vomiting are more frequent after administration by oral route especially after therapeutic doses and the risks of contamination following the occurrence of vomiting have to be considered.

Some cases of adverse reactions of the allergic type following the administration of sodium iodide [^{131}I] have been reported (European system for reporting of adverse reactions and drug defects). It is very probable that these reactions occur due to a hypersensitivity against the gelatine of the capsules or their metabolites.

Early consequences

Therapeutic quantities of sodium iodide [^{131}I] may worsen existing hyperthyroidism temporarily. In the course of a toxic multinodular goitre treatment, (^{131}I) may induce Graves' disease or thyroid associated ophtalmopathy (incidence 1 to 5 %).

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 as 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 antiinflammatory 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.

Malfunction of the lachrymal glands, such as ocular dryness and nasolachrymal duct obstruction may occur after radioiodine treatment. Although these symptoms are in the majority of cases transient, they may persist for a longer period or appear late in some patients.

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.

Transient impairment of male gonadal function may occur after high radioiodine therapeutic dose or in the presence of pelvic metastasis.

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 born in mind.

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 2-70 %.
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 erythrocytopenia, which may be fatal.

Transient leucocytosis is frequently observed.

Epidemiological studies report a higher incidence of stomach cancer in patients receiving [^{131}I].

After higher 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 are 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

Iodide in the amount used for 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 0.5 mm.

5.2 Pharmacokinetic properties

After oral administration sodium iodide [^{131}I] is absorbed rapidly from the upper gastrointestinal tract (90 % in 60 minutes). The pharmacokinetics follow that of unlabelled iodide. After entering the blood stream it is distributed in the extra thyroidal compartment. From here it is predominantly taken up by the thyroid or excreted renally. Small amounts of iodide [^{131}I] are taken up by salivary glands, gastric mucosa and would also be localised in breast milk, the placenta and choroid plexus. 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 [^{131}I] approximately 40 % of the activity has an effective half-life of 0.4 days and the remaining 60 %, 8 days. Urinary excretion is 37-75 %, faecal excretion is about 10 % with almost negligible excretion in the sweat.

5.3 Preclinical safety data

Because of the small quantities of substance administered compared with the normal food intake of iodine (40-500 µg/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

Anhydrous sodium pyrophosphate

Sodium thiosulphate

Gelatine capsule

6.2 Incompatibilities

None known

6.3 Shelf life

21 days following manufacture.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.
Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of container

15 mL colourless glass (type I of European Pharmacopoeia) penicillin-type vial, closed with polypropylene device (centring element and perforator), and sealed with aluminium flip-off capsule.

6.6 Special precautions for disposal

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.

The disposal of radioactive waste should be in accordance with relevant national and international regulations.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL/11876/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 October 2000

10 DATE OF REVISION OF THE TEXT

12/2008

11 DOSIMETRY

Tabulated radiation dosimetry data, as reported in ICRP publication No. 53 (1987) are reported hereafter.

The ICRP model refers to intravenous administration. Since absorption of radioiodide is rapid and complete, this model is applicable in case of oral administration also but there is a further radiation dose to the stomach wall in addition to that due to gastric and salivary excretion. Assuming that the mean residence time in the stomach is 0.5 hours, the absorbed dose to the stomach wall increases by about 30 % for [^{131}I] iodine.

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process.

As part of the risk-benefit assessment it is advised that the EDE and likely radiations doses to individual target organ(s) be calculated prior to administration. The activity might then be adjusted according to thyroid mass, biological half-life and the "re-cycling" factor which takes into account the physiological status of the patient (including iodine depletion) and the underlying pathology.

Radiation exposure (Thyroid blocked, uptake 0 %)

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.037	0.042	0.067	0.11	0.20
Bladder wall	0.61	0.75	1.1	1.8	3.4
Bone surfaces	0.032	0.038	0.061	0.097	0.19
Breast	0.033	0.033	0.052	0.085	0.17
GI-tract					
Stomach wall	0.034	0.040	0.064	0.10	0.19
Small intest	0.038	0.047	0.075	0.12	0.22
ULI wall	0.037	0.045	0.070	0.12	0.21
LLI wall	0.043	0.052	0.082	0.13	0.23
Kidneys	0.065	0.080	0.12	0.17	0.31
Liver	0.033	0.040	0.065	0.10	0.20
Lungs	0.031	0.038	0.060	0.096	0.19
Ovaries	0.042	0.054	0.084	0.13	0.24
Pancreas	0.035	0.043	0.069	0.11	0.21
Red marrow	0.035	0.042	0.065	0.10	0.19
Spleen	0.034	0.040	0.065	0.10	0.20
Testes	0.037	0.045	0.075	0.12	0.23
Thyroid	0.029	0.038	0.063	0.10	0.20
Uterus	0.054	0.067	0.11	0.17	0.30
Other tissue	0.032	0.039	0.062	0.10	0.19
Effective dose equivalent (mSv/MBq)	**0.072**	**0.088**	**0.14**	**0.21**	**0.4**

Bladder wall contributes to 50.8 % of the effective dose equivalent.

Incomplete blockage

Effective dose equivalent (mSv/MBq) at small uptake in the thyroid

uptake : 0.5 %	0.3	0.45	0.69	1.5	2.8
uptake : 1.0 %	0.52	0.81	1.2	2.7	5.3
uptake : 2.0 %	0.97	1.5	2.4	5.3	10

Radiation exposure (Thyroid uptake : 15 %)

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adults	15 years	10 years	5 years	1 year
Adrenals	0.036	0.043	0.071	0.11	0.22
Bladder wall	0.52	0.64	0.98	1.5	2.9
Bone surfaces	0.047	0.067	0.094	0.14	0.24
Breast	0.043	0.043	0.081	0.13	0.25
GI-tract					
Stomach wall	0.46	0.58	0.84	1.5	2.9
Small intest	0.28	0.35	0.62	1.0	2.0
ULI wall	0.059	0.065	0.10	0.16	0.28
LLI wall	0.042	0.053	0.082	0.13	0.23
Kidneys	0.060	0.075	0.11	0.17	0.29
Liver	0.032	0.041	0.068	0.11	0.22
Lungs	0.053	0.071	0.12	0.19	0.33
Ovaries	0.043	0.059	0.092	0.14	0.26
Pancreas	0.052	0.062	0.10	0.15	0.27
Red marrow	0.054	0.074	0.099	0.14	0.24
Spleen	0.042	0.051	0.081	0.12	0.23
Testes	0.028	0.035	0.058	0.094	0.18
Thyroid	210	340	510	1100	2000
Uterus	0.054	0.068	0.11	0.17	0.31
Other tissue	0.065	0.089	0.14	0.22	0.40
Effective dose equivalent(mSv/MBq)	**6.6**	**10**	**15**	**34**	**62**

Radiation exposure (Thyroid uptake : 35 %)

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.042	0.050	0.087	0.14	0.28
Bladder wall	0.40	0.50	0.76	1.2	2.3
Bone surfaces	0.076	0.12	0.16	0.23	0.35
Breast	0.067	0.066	0.13	0.22	0.40
GI-tract					
Stomach wall	0.46	0.59	0.85	1.5	3.0
Small intest	0.28	0.35	0.62	1.0	2.0
ULI wall	0.058	0.065	0.10	0.17	0.30
LLI wall	0.040	0.051	0.080	0.13	0.24
Kidneys	0.056	0.072	0.11	0.17	0.29
Liver	0.037	0.049	0.082	0.14	0.27
Lungs	0.090	0.12	0.21	0.33	0.56
Ovaries	0.042	0.057	0.090	0.14	0.27
Pancreas	0.054	0.069	0.11	0.18	0.32
Red marrow	0.086	0.12	0.16	0.22	0.35
Spleen	0.046	0.059	0.096	0.15	0.28
Testes	0.026	0.032	0.054	0.089	0.18
Thyroid	500	790	1200	2600	4700
Uterus	0.050	0.063	0.10	0.16	0.30
Other tissue	0.11	0.16	0.26	0.41	0.71
Effective dose equivalent(mSv/MBq)	**15**	**24**	**36**	**78**	**140**

Radiation exposure (Thyroid uptake : 55 %)

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.049	0.058	0.11	0.17	0.34
Bladder wall	0.29	0.36	0.54	0.85	1.6
Bone surfaces	0.11	0.17	0.22	0.32	0.48
Breast	0.091	0.089	0.19	0.31	0.56
GI-tract					
Stomach wall	0.46	0.59	0.86	1.5	3.0
Small intest	0.28	0.35	0.62	1.0	2.0
ULI wall	0.058	0.067	0.11	0.18	0.32
LLI wall	0.039	0.049	0.078	0.13	0.24
Kidneys	0.051	0.068	0.10	0.17	0.29
Liver	0.043	0.058	0.097	0.17	0.33
Lungs	0.13	0.18	0.30	0.48	0.80
Ovaries	0.041	0.056	0.090	0.15	0.27
Pancreas	0.058	0.076	0.13	0.21	0.38
Red marrow	0.12	0.18	0.22	0.29	0.46
Spleen	0.051	0.068	0.11	0.17	0.33
Testes	0.026	0.031	0.052	0.087	0.17
Thyroid	790	1200	1900	4100	7400
Uterus	0.046	0.060	0.099	0.16	0.30
Other tissue	0.16	0.24	0.37	0.59	1.0
Effective dose equivalent (mSv/MBq)	**24**	**37**	**56**	**120**	**220**

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Capsules ready for use.

Any unused product or waste material should be disposed of in accordance with local requirements.

Detailed information on this medicinal product is available on the website of MHRA.