SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

^{131}I-sodium-iodide ThyroTop 38-7400 MBq hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains 38-7400 MBq sodium iodide (^{131}I) at time of calibration.
Iodine-131 is produced by fission of uranium-235 or by neutron bombardment of stable tellurium in a nuclear reactor. Iodine-131 has a half-life of 8.02 days. It decays by emission of gamma radiations of 365 keV (81.7%), 637 keV (7.2%) and 284 keV (6.1%) and beta radiations of maximal energy of 606 keV to stable Xenon-131.
Excipient with known effect:
One hard capsule contains 115 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Colourless hard capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Radioiodide thyroid therapy is indicated in adults and children for:
- Hyperthyroidism: Treatment of Graves' disease, toxic multinodular goitre or autonomous nodules.
- Treatment of papillary and follicular thyroid carcinoma including metastatic disease:
  - Ablation of residual thyroid tissues following thyroid cancer surgery.
  - Treatment of recidivations and metastases.

Sodium iodide (^{131}I) therapy is often combined with surgical intervention and with antithyroid medicinal products.

4.2 Posology and method of administration

This medicinal product should be administered only by authorised healthcare professionals in designated clinical settings (see section 6.6).
Posology
The activity to be administered is a matter of clinical judgement. The therapeutic effect is only achieved after several weeks. The activity of the capsule should be determined before use.
Adults
Treatment of hyperthyroidism
In case of failure or impossibility to pursue the medical treatment, radioactive iodide may be administered to treat the hyperthyroidism.
Patients should be rendered euthyroid medically whenever possible before giving radioiodine treatment for hyperthyroidism.
The activity to be administered depends on the diagnosis, the size of the gland, thyroid uptake and iodine clearance. It is usually in the range of 200-800 MBq for a patient of average weight (70 kg) but repeated treatment up to a cumulative dose of 5,000 MBq may be necessary. Re-treatment after 6-12 months is indicated for persisting hyperthyroidism.
The activity to be administered may be defined by fixed dose protocols or may be calculated according to the following equation:

$$A\ (MBq) = \frac{\text{Target dose (Gy)} \times \text{target volume (ml)}}{\text{max. uptake I-131(\%)} \times \text{effective T ½ (days)}} \times K$$

under the following conditions

target dose	is the target absorbed dose in the whole thyroid gland or in an adenoma
target volume	is the volume of the whole thyroid gland (Graves' disease, multifocal or disseminated autonomy)
max. uptake I-131	is the max. uptake of I-131 in the thyroid gland or nodules in % of the administered activity as established in a test dose
effective T ½	is the effective half-life of I-131 in the thyroid gland expressed in days
K	is 24.67

The following target organ doses may be used:

Unifocal autonomy	300 – 400 Gy target organ dose
Multifocal and disseminated autonomy	150 – 200 Gy target organ dose
Graves' disease	200 Gy target organ dose

In the case of Graves' disease, multifocal or disseminated autonomy, the above mentioned target organ doses are related to the overall volume of the thyroid gland mass, however in the case of unifocal autonomy, the target organ dose is only related to the volume of the adenoma. For recommended doses to target organs, see section 11.
Other dosimetric procedures may also be used including sodium pertechnetate (^{99m}Tc) thyroid uptake tests to determine the appropriate target organ dose (Gy).
Thyroid ablation and treatment of metastases
The activities to be administered following total or subtotal thyroidectomy to ablate remaining thyroid tissue are in the range of 1,850-3,700 MBq. It depends on the remnant size and radioiodine uptake. For treatment of metastases, administered activity is in the range of 3,700-11,100 MBq.
Special populations
Renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in patients with reduced renal function. The therapeutic use of sodium iodide (^{131}I) in patients with significant renal impairment requires special attention (see section 4.4).
Paediatric population
The use of sodium iodide (^{131}I) in children and adolescents has to be considered carefully, based upon clinical needs and assessing the benefit/risk ratio in this patients group.
In certain cases the activity to be administered in children and adolescents should be determined after performing an individual dosimetry (see section 4.4).
In children and adolescents, treatment of benign thyroid defects with radioactive iodide is possible in justified cases, in particular in case of relapse after the use of antithyroid medicinal products or in case of severe adverse reaction to antithyroid medicinal products (see section 4.4).
Method of administration
^{131}I-sodium-iodide ThyroTop 38-7400 MBq hard capsules is for oral use. The capsules should be taken on an empty stomach. They should be swallowed whole with abundant drink to ensure clear passage into the stomach and upper small intestine.
In case of administration to children, especially to younger children, it must be ensured that the capsule can be swallowed whole without chewing. It is recommended to give the capsule with mashed food.
For patient preparation, see section 4.4.
Method of examination
Monitoring can be performed by imaging with gamma scanner 1–48 hours after administration. To prepare thyroid scintigram usually front-view is used, but right and left anterior oblique imaging (LAO, RAO) can also be useful.

4.3 Contraindications

- Hypersensitivity to active substance or to any of the excipients listed in section 6.1.
- Pregnancy and breast-feeding (see section 4.6).
- Patients with dysphagia, oesophageal stricture, oesophagal stenosis, oesophagus diverticulum, active gastritis, gastric erosions and peptic ulcer.
- Patients with suspected reduced gastrointestinal motility.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.
Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity to be administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.
There is little evidence of an increased incidence of cancer, leukaemia or mutations in patients after treatment with radioiodine for benign thyroid diseases, despite its extensive use. In the treatment of malignant thyroid diseases, in a study conducted on patients with doses of sodium iodide (^{131}I) higher than 3,700 MBq a higher incidence of bladder cancer was reported. Another study reported a slight increase in leukaemia in patients receiving very high doses. Therefore, total cumulative doses greater than 26,000 MBq are not recommended.
Gonadal function in males
The use of the sperm bank could be considered to compensate a potential reversible damage of gonadal function in males due to the high therapeutic dose of radioiodine, in the cases of patients with extensive disease.
Patients with renal impairment
Careful consideration of the benefit/risk balance in these patients is required since an increased radiation exposure is possible. In these patients it may be necessary to adjust the posology.
Paediatric population
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11). When treating children and young adults, account must be taken of the greater sensitivity of child tissue and the greater life expectancy of such patients. The risks should be weighed against those of other possible treatments (see sections 4.2 and 11).
The radioiodine treatment of benign thyroid diseases of children and adolescents may be performed only in justified cases, especially in relapse after use of antithyroid medicinal products or in case of serious adverse reactions to antithyroid medicinal products. There is no evidence of an increased incidence of cancer, leukemia or mutations in humans with respect to patients treated for benign thyroid disease with radioiodine, despite extensive use.
Persons who have received radiotherapy of the thyroid as children and adolescents, should be re-examined once a year.
Patient preparation
Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities e.g. for the treatment of thyroid carcinoma. Patients with bladder voiding problems should be catheterised after administration of high activities of radioiodine.
To reduce colon radiation exposure, mild laxatives (but not stool softeners which do not stimulate the bowel) may be necessary in patients having less than one bowel movement a day.
To avoid sialadenitis that may occur after high dose radioiodine administration, the patient should be advised to take sweets or drinks containing citric acid (lemon juice, vitamin C) to stimulate saliva excretion before therapy. Other pharmacological protection measures may be used additionally. Iodide overload from food or medicinal treatment should be investigated before administration of iodide (see section 4.5). A low iodine diet prior to therapy (3-10 days) is recommended to enhance uptake into functioning thyroid tissue.
Thyroid replacement should be stopped prior to radioiodide administration for thyroid carcinoma to ensure adequate uptake. It is recommended to stop triiodothyronine treatment for a period of 14 days and to stop thyroxine treatment for a period of 4 weeks. They should be restarted two days after treatment.
Carbimazole and propylthiouracil should be stopped 1 week prior to treatment of hyperthyroidism and restarted several days after treatment.
The radioiodine treatment of Graves' disease should be performed under concomitant treatment of corticosteroids, particularly when endocrine ophthalmopathy is present.
In patients with suspected gastrointestinal disease, great care should be taken when administering sodium iodide (^{131}I) capsules. Concomitant use of H_2 antagonists or proton pump inhibitors is advised.
After the procedure
Close contact with infants and pregnant women should be restricted for at least one week.
In case of vomiting, the risk of contamination has to be considered.
Patients receiving therapy of the thyroid should be re-examined at appropriate intervals.
Specific warnings
In patients with hypersensitivity to gelatine or its catabolic products, sodium (^{131}I) iodide solution should be preferred for the radioiodide therapy.
This medicinal product contains 115 mg sodium per capsule, equivalent to 5.75 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into account by patients on a controlled sodium diet.
Precautions with respect to environmental hazard are in section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Many pharmacologically active substances interact with radioiodide. Various interaction mechanisms exist which can affect the protein binding, the pharmacokinetics or the dynamic effects of labelled iodide. As a consequence, it should be considered that the thyroid uptake might be reduced. Therefore, a full drug history should be taken and relevant medicational products are required to be withheld prior to the administration of sodium iodide (^{131}I).
Clearance of radioiodide from thyroid can be delayed by administration of lithium carbonate or colchicin.
For example, the treatment with the following substances should be discontinued:

Active substances	**Withdrawal period before administration of sodium iodide (^{131}I)**
Antithyroid medicinal products (e.g. carbimazole, methimazole, propyluracil), perchlorate	1 week before starting treatment till several days after
Salicylates, corticosteroids, sodium nitroprusside, sodium sulfobromophthalein, anticoagulants, antihistamines, antiparasitics, penicillins, sulphonamides, tolbutamide, thiopental	1 week
Phenylbutazone	1-2 weeks
Containing iodine expectorants and vitamins	Approximately 2 weeks
Thyroid hormone preparations	Triiodothyronine 2 weeks
	thyroxine 6 weeks
Benzodiazepines, lithium	Approximately 4 weeks
Amiodarone*,	3-6 months
Containing iodine preparations for topical use	1-9 months
Water-soluble iodine-containing contrast media	6 to 8 weeks
Lipo-soluble iodine-containing contrast media	up to 6 months

* Due to the long half-life of amiodarone, iodine uptake in the thyroid tissue can be decreased for several months.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Women receiving sodium iodide (^{131}I) should be advised not to become pregnant within 6-12 months after administration.
Contraception in males and females
Contraception for 6 months (for patients with benign thyroid conditions) or 12 months (for patients with thyroid cancer) is recommended for both sexes after therapeutic administration of sodium iodide (^{131}I).
Men should not father a child for a time period of 6 months after radioiodine treatment to allow the replacement of irradiated by non-irradiated spermatozoa. Sperm banking should be considered for men who have extensive disease and therefore may need high sodium iodide (^{131}I) therapeutic doses.
Pregnancy
The use of sodium (^{131}I) iodide is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded because transplacental passage of sodium iodide (^{131}I) can cause severe and possibly irreversible hypothyroidism in neonates (the absorbed dose to the uterus for this medicinal product is likely to be in the range 11-511 mGy, and the foetal thyroid gland avidly concentrates iodine during the second and third trimesters) (see section 4.3).
If a differentiated thyroid carcinoma is diagnosed during pregnancy, sodium iodide (^{131}I) treatment should be postponed until after the childbirth.
Breast-feeding
Before administering a radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding must be discontinued at least 8 weeks before sodium iodide (^{131}I) administration and should not be resumed (see section 4.3).
For radioprotection reasons following therapeutic doses, it is recommended to avoid close contact between mother and infants for at least one week.
Fertility
After radioiodine therapy of thyroid carcinoma, a dose dependent impairment of fertility may occur in men and women. Depending on the activity dose, a reversible impairment of the spermatogenesis could occur in doses above 1,850 MBq. Clinical relevant effects including oligospermia and azoospermia and elevated serum FSH serum levels have been described after administration greater than 3,700 MBq.

4.7 Effects on ability to drive and use machines

Sodium iodide (^{131}I) has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The frequencies of reported adverse reactions were derived from the medical literature. The safety profile of sodium iodide (^{131}I) differs widely according to the doses administered, while the doses to be administered are dependent on the type of treatment (i.e. treatment of benign or malignant disease). Moreover, the safety profile depends on the cumulative doses administered and the dosing intervals which are used. Therefore, the reported adverse reactions were grouped by their occurrence in treatment of benign or malignant disease.
Frequently occurring adverse reactions are: hypothyroidism, transient hyperthyroidism, salivary and lacrimal gland disorders, and radiation local effects. In cancer treatment additionally gastro-intestinal adverse reactions and bone marrow suppression may frequently occur.
Tabulated list of adverse reactions
The following tables include reported adverse reactions sorted by system organ classes. Symptoms, which are rather secondary to a group-syndrome (e.g. sicca syndrome) are subsumed in parenthesis behind the respective syndrome.
The following table presents how the frequencies are reflected in this section:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions after treatment of benign disease

System organ class	***Adverse reaction***	***Frequency***
Immune system disorders	Anaphylactoid reaction	Not known
Endocrine disorders	Permanent hypothyroidism, hypothyroidism	Very common
	Transient hyperthyroidism	Common
	Thyreotoxic crisis, thyroiditis, hypoparathyroidism (blood calcium decreased, tetany)	Not known
Eye disorders	Endocrine ophthalmopathy (in Graves' disease)	Very common
	Sicca syndrome	Not known
Respiratory, thoracic and mediastinal disorders	Vocal cord paralysis	Very rare
Gastrointestinal disorders	Sialoadenitis	Common
Hepatobiliary disorders	Hepatic function abnormal	Frequency not know
Skin and subcutaneous tissue disorders	Iodide induced acne	Not known
Congenital, familial and genetic disorders	Congenital hypothyroidism	Not known
General disorders and administration site conditions	Local swelling	Not known

Adverse reactions after treatment of malignant disease

System organ class	***Adverse reaction***	***Frequency***
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Leukaemia	Uncommon
	Solid cancers, Bladder cancer, colon cancer, gastric cancer, breast cancer	Not known
Blood and lymphatic system disorders	erythropenia, bone marrow failure	Very common
	Leukopenia, thrombocytopenia	Common
	Aplastic anemia, Permanent or severe bone marrow suppression	Not known
Immune system disorders	Anaphylactoid reaction	Not known
Endocrine disorders	Thyreotoxic crisis, transient hyperthyroidism	Rare
	Thyroiditis (transient leucocytosis), hypoparathyroidism (blood calcium decreased, tetany), hypothyroidism, hyperparathyroidism	Not known
Nervous system disorders	Parosmia, anosmia	Very common
	Brain oedema	Not known
Eye disorders	Sicca syndrome (conjunctivitis, dry eyes, nasal dryness)	Very common
	Nasolacrimal duct obstruction (lacrimation increased)	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoe	Common
	Throat constriction*, Pulmonary fibrosis, respiratory distress, obstructive airways disorder, pneumonia, tracheitis, vocal cord dysfunction (vocal cord paralysis, dysphonia, hoarseness), oropharyngeal pain, stridor	Not known
Gastrointestinal disorders	Sialoadenitis (dry mouth, salivary gland pain, salivary gland enlargement, dental caries, tooth loss), radiation sickness syndrome, nausea, ageusia, anosmia, dysgeusia, decreased appetite	Very common
	Vomiting	Common
	Gastritis, dysphagia	Not known
Hepatobiliary disorders	Hepatic function abnormal	Not known
Renal and urinary disorders	Radiation cystitis	Not known
Reproductive system and breast disorders	Ovarian failure, menstrual disorder	Very common
	Azoospermia, oligospermia, decreased fertility male	Not known
Congenital, familial and genetic disorders	Congenital hypothyroidism	Not known
General disorders and administration site conditions	Flu-like illness, headache, fatigue, neck pain	Very common
	Local swelling	Common

* especially in existing tracheal stenosis

Description of selected adverse reactions
General advice
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. 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 those of the disease itself. The effective dose after therapeutic doses of sodium iodide (^{131}I) is 3.108 mSv when the maximal recommended activity of 11,100 MBq is administered (with thyroid uptake 0%). For this medicinal product the effective dose is 2.072 mSv when the highest possible activity of 7,400 MBq is administered (with thyroid uptake 0%).
Thyroid and parathyroid glands disorders
Hypothyroidism may occur, depending on the dose, as a delayed result of treatment for hyperthyroidism with radioiodine.
In the treatment of malignant disease, hypothyroidism is often reported as an adverse reaction; however, the treatment of malignant diseases with radioiodine generally follows thyroidectomy.
The destruction of thyroid follicles caused by the radiation exposure of sodium iodide (^{131}I) may lead to exacerbation of an already existing hyperthyroidism within 2 – 10 days or may cause a thyrotoxic crisis. Occasionally, an immune hyperthyroidism may appear after initial normalisation (latency period is 2-10 months). After 1-3 days of administration of high dose radioiodine, the patient may experience transient inflammatory thyroiditis and tracheitis, with a possibility of severe tracheal constriction, especially where there is existing tracheal stenosis.
In rare cases, a temporary hyperthyroidism could be observed even after treatment of a functional thyroid carcinoma.
Cases of transient hypoparathyroidism have been observed after radioiodine administration which should be appropriately monitored and treated with replacement therapy.
Late consequences
Dose dependent hypothyroidism may occur as a delayed result of radioiodine treatment of hyperthyroidism. This hypothyroidism may manifest itself weeks or years after the treatment, and monitoring of thyroid function and appropriate hormone replacement therapy are required. Hypothyroidism does not generally appear until 6 – 12 weeks after radioiodine administration.
Eye disorders
Endocrine ophthalmopathy may progress or new ophthalmopathy may occur after radioiodine therapy of hyperthyroidism or Graves' disease. Radioiodine treatment of Graves' disease should be associated with corticosteroids.
Local irradiation effects
Dysfunction and paralysis of vocal cords have been reported after administration of sodium iodide (^{131}I), however, in some cases it cannot be decided whether the dysfunction of the vocal cords was caused by radiation or by surgical treatment.
High tissue uptake of radioiodine can be associated with local pain, discomfort and local oedema, e.g. in case of radioiodine treatment of the remnant thyroid gland, a diffuse and severe soft tissue pain may occur in the head and neck region.
Radiation induced pneumonia and pulmonary fibrosis have been observed in patients with diffuse pulmonary metastases from differentiated thyroid carcinoma, due to destruction of metastatic tissue. This occurs mainly after high dose radioiodine therapy.
In the treatment of metastasing thyroid carcinomas with central nervous system (CNS) involvement, the possibility of local cerebral oedema and/or aggravation of existing cerebral oedema should also be considered.
Gastrointestinal disorders
High levels of radioactivity may also lead to gastrointestinal disturbance, usually within the first hours or days after administration. For prevention of gastrointestinal disorders, see section 4.4.

Salivary and lacrimal gland disorders
Sialoadenitis may occur, with swelling and pain in the salivary glands, partial loss of taste and dry mouth. Sialoadenitis is usually reversible spontaneously or with anti-inflammatory treatment but cases of dose-dependent persistent ageusia and dry mouth have occasionally been described. The lack of saliva may lead to infections, e.g. caries and this may result in loss of teeth. For prevention of salivary disorders, see section 4.4.
Malfunction of the salivary and/or lacrimal glands with resulting sicca syndrome may also appear with a delay of several months and up to two years after radioiodine therapy. Although sicca syndrome is a transient effect in most cases, the symptom may persist for years in some patients.
Bone marrow depression
As a late consequence, reversible bone marrow depression may develop, presenting with isolated thrombocytopenia or erythrocytopenia which may be fatal. Bone marrow depression is more likely to occur after one single administration of more than 5,000 MBq, or after repeat administration in intervals below 6 months.
Secondary malignancies
After higher activities, typically those used in the treatment of thyroid malignancies, an increased incidence of leukaemia has been observed. There is evidence of an increased frequency of solid cancers induced by administration of high activities (above 7.4 GBq).
Paediatric population
The type of undesirable effects expected in children are identical to the one in adults. Based on greater radiation sensitivity of child tissues (see section 11) and the greater life expectancy frequency and severity may be different.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system one of the contacts (in Hungary: www.ogyei.gov.hu).

4.9 Overdose
This product must be used by authorised personnel in a hospital setting. The risk of overdose is therefore theoretical.
In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and by forced diuresis and frequent bladder voiding. Additionally, the blockade of the thyroid gland should be recommended (e.g. with potassium perchlorate) in order to reduce the radiation exposure of the thyroid gland. To reduce the uptake of sodium iodide (^{131}I), emetics can be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Therapeutic radiopharmaceuticals; Iodine (^{131}I) compounds, ATC code: V10XA01
The pharmacological active substance is sodium iodide (^{131}I) in the form of sodium iodide that is taken up by the thyroid. The physical decay takes place essentially in the thyroid gland, where sodium iodide (^{131}I) has a long residence time, delivering a selective irradiation to this organ.
In the amount used for therapeutic indications, no pharmacodynamic effects of sodium iodide (^{131}I) are to be expected.
More than 90% of the radiation effects result from emitted beta-radiation which has a mean range of 0.5 mm. The beta-irradiation will dose dependently decrease cell function and cell division leading to cell destruction. The short range and almost absence of uptake of sodium iodide (^{131}I) outside the thyroid lead to a negligible amount of irradiation exposure outside the thyroid gland.

5.2 Pharmacokinetic properties
Absorption
After oral administration, sodium iodide (^{131}I) is absorbed rapidly from the upper gastrointestinal tract (90 % within 60 min). The absorption is influenced by gastric emptying. It is increased by hyperthyroidism and decreased by hypothyroidism.
Studies on the serum activities levels showed that after a fast increase, over 10 to 20 minutes, an equilibrium is reached after about 40 minutes. After oral administration of sodium iodide (^{131}I) solution an equilibrium is reached at the same time.
Distribution and organ uptake
The pharmacokinetics follows 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 that extracts approximately 20% of the iodide in one pass or excreted renally.
The iodide uptake in the thyroid reaches a maximum after 24-48 hours; 50% of the maximum peak is reached after 5 hours. The uptake is influenced by several factors: patient age, thyroid gland volume, renal clearance, plasmatic concentration of iodide and other drugs (see section 4.5). The iodide clearance by the thyroid gland is usually 5-50 mL/min. In case of iodine deficiency the clearance is increased to 100 mL/min and in case of hyperthyroidism can be up to 1,000 mL/min. In case of iodide overload the clearance can decrease to 2-5 mL/min. Iodide also accumulates in the kidneys.
Small amounts of sodium iodide (^{131}I) are taken up by salivary glands, gastric mucosa and they would also be localised in breast milk, the placenta and choroid plexus.
Biotransformation
The iodide that has been taken up by the thyroid follows the known metabolism of the thyroid hormones and is incorporated in the organic compounds from which the thyroid hormones are synthesised.
Elimination
Urinary excretion is 37-75%, faecal excretion is about 10%, with almost negligible excretion in sweat.
Urinary excretion is characterised by the renal clearance, which constitutes about 3% of the renal flow and is relatively constant from one person to another. The clearance is lower in hypothyroidism and in impaired renal function and higher in hyperthyroidism. In euthyroidic patients with normal renal function 50-75% of the administered activity is excreted in urine within 48 hours.
Half-life
The effective half-life of radioiodine in plasma is about 12 hours in blood plasma and about 6 days in the thyroid gland. Thus after administration of sodium iodide (^{131}I) about 40% of the activity has an effective half-life of 6 hours and the remaining 60% of 8 days.
Renal impairment
Patients with renal impairment may have a decrease in the radioiodine clearance, resulting in increased radiation exposure of sodium iodide (^{131}I) administered. One study showed, for example, that patients with impaired renal function undergoing continuous ambulatory peritoneal dialysis (CAPD) have a clearance of radioiodine 5 times lower than patients with normal kidney function.

5.3 Preclinical safety data
LD_{50} value, which expresses the acute toxicity of I-131 introduced orally into the body, is 1000 mg/kg body weight for mice and 760 mg/kg body weight for dogs. Optimal iodine intake for adults is 0.15-0.30 mg per day. Specific activity of ^{131}I-sodium iodide is not less than 1 GBq/mg. Since the radioactivity administered into the body is not more than 7.4 GBq, amount of iodine intake is not more than 7.4 mg, which is 2.4 – 4.9 % of the optimal daily iodine requirement of the human body.
Because of the small quantities of administered substance compared with the normal intake of iodine with food (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
Capsule content:
Disodium hydrogen phosphate dihydrate, sodium thiosulphate, sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, water for injection
Capsule shell: gelatine

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
21 days from the date of the manufacture.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original packaging to prevent from external radiation exposure. Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.
Protect from moisture, acid fumes and oxidative agents.

6.5 Nature and contents of container
High activity ^{131}I-sodium-iodide capsules are placed into lead container with wall thickness of 15-38 mm, in which a plastic insert with screwed cap (inner diameter 9.5 mm, height 32 mm) has been fixed. Bottom part of the insert is fixed in the bottom of the lead container while the upper part of the capsule is fixed in the upper part of the lead container. The packaging always contains one capsule.
The labelled lead container is packed into a labelled tin container which is closed with a tear-off cover. (Type'A' packaging)
Packaging:
38-7400 MBq at the date of calibration
Content of packaging:
Hard capsule. The ordered quantity of capsules.

6.6 Special precautions for disposal and other handling
General warning
Radiopharmaceuticals should 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 organisation. Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements.
Precautions to be taken before handling or administration of the medicinal product
The administration of sodium iodide (^{131}I) for therapy is likely to result in a relatively high radiation dose to most patients and may result in significant environmental hazard and creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. This 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 in accordance with national regulations should therefore be taken concerning the activity eliminated by the patients in order to avoid any contaminations.
Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.
When opening the container personnel should be aware that free radioactivity may be registered on monitors. This activity is due to Xe-131m which is formed for 1.17 % in the decay of I-131. Though visible on monitors this does not pose a relevant risk for personnel.
The effective dose rate by inhalation of the Xe-131m formed is 0.1% of the dose rate at 1 m from a lead-shielded capsule.
Precautions and activity data
1.3% of iodine (^{131}I) decays via xenon (^{131m}Xe) (half-life 12 days) and a small amount of xenon (^{131m}Xe) activity may be present in the packaging as a result of diffusion. It is therefore recommended that the transport container be opened in a ventilated enclosure and that, after removal of the capsule, the packaging materials are allowed to stand overnight before disposal to permit the release of absorbed xenon (^{131m}Xe).
Opening procedure of packaging of 38-7400 MBq activity capsules
- Tear off the cover of the tin container.
- Remove the upper part of the foam insert.
- If there is a protective lead container in the metal container, lift it out from the metal can.
- Lift the lead container containing the capsule out from the metal can or the protective lead container and put it on the working area.
- There are two ways of opening the lead container for two different purposes:
  - activity control with closed plastic insert without taking out the capsule or
  - opening the plastic insert with the same movement for taking out the capsule.

Opening of lead container for activity measurement
- Manipulate behind an appropriate radiation shielding.
- Hold the lower part of the lead container firmly with one hand and pull apart the upper part towards axial direction.
- The plastic insert will remain fixed in the upper part of the lead container but the lead shielding will not cover its lower part. In this position the activity measurement can be performed by a laboratory activity measuring unit (dose calibrator) without taking out the capsule from the vial.

After measuring, close the lead container.
Opening of lead container and insert at the same time
- Hold the container in vertical position.
- Screwing the upper part of the lead container counter-clockwise. Both lead container and plastic insert will open.
- The upper part of the plastic insert remains in the upper part of the lead container, while the lower part of the vial, containing the capsule, remains in the lower part of the lead container.
- The capsule can be easily taken out or the lower part of the lead container can be given to the patient in order to get the capsule.

The activity of a capsule at 12h00 GMT from calibration date can be calculated from the table 1.
Table 1

Day	Coefficient	Day	Coefficient
-6	1,677	5	0,650
-5	1,539	6	0,596
-4	1,412	7	0,547
-3	1,295	8	0,502
-2	1,188	9	0,460
-1	1,090	10	0,422
0	1,000	11	0,387
1	0,917	12	0,355
2	0,842	13	0,326
3	0,772	14	0,299
4	0,708		

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

7. MARKETING AUTHORISATION HOLDER

Institute Of Isotopes Co. Ltd.
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8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-9681/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16. August 1995.
Date of latest renewal: 27. July 2016.

10. DATE OF REVISION OF THE TEXT

06. September 2020.

11. DOSIMETRY

The data listed below are from ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals) publication 128. The biokinetic model is described as a compartment model including inorganic iodide as well as organically bound iodine released to the body tissues following discharge from the thyroid. The ICRP model refers to oral administration.
As part of the risk-benefit assessment it is advised that the effective dose and likely radiation doses to individual target organ(s) are calculated prior to administration. The activity might then be adjusted according to thyroid volume, 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.
Doses to the following target organs can be used

Unifocal autonomy	Target organ dose 300 – 400 Gy
Multifocal or disseminated autonomy	Target organ dose 150 – 200 Gy
Graves' disease (Morbus Basedow)	Target organ dose 200 Gy

The radiation exposure mainly affects the thyroid. The radiation exposure of the other organs is in the range of thousandths lower than that of the thyroid. It depends on the dietary intake of iodine (the uptake of radioiodine is increased up to 90% in iodine deficient areas and it is decreased to 5% in iodine rich areas). It further depends on the thyroid function (eu-, hyper-, or hypothyroidism) and on the presence of iodine accumulating tissues in the body (e.g. the situation after excision of the thyroid, the presence of iodine accumulating metastases and on thyroid blockade) The radiation exposure of all other organs is correspondingly higher or lower, depending on the degree of accumulation in the thyroid.

Thyroid blocked, uptake 0%, oral administration

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.044	0.054	0.086	0.14	0.25
Bone surfaces	0.030	0.037	0.059	0.092	0.18
Brain	0.021	0.026	0.043	0.071	0.14
Breast	0.020	0.025	0.042	0.069	0.13
Gallbladder Wall	0.037	0.048	0.085	0.13	0.21
GI-tract					
Stomach wall	0.87	1.1	1.6	2.8	5.9
Small intestine wall	0.035	0.044	0.070	0.11	0.19
Colon wall	0.14	0.18	0.30	0.50	0.92
Wall of upper large intestine	0.12	0.15	0.25	0.42	0.75
Wall of lower large intestine	0.17	0.22	0.37	0.61	1.2
Heart wall	0.062	0.080	0.13	0.20	0.37
Kidneys	0.62	0.32	0.46	0.69	1.2
Liver	0.050	0.065	0.10	0.16	0.30
Lungs	0.053	0.068	0.11	0.18	0.36
Muscles	0.026	0.032	0.051	0.080	0.15
Oesophagus	0.024	0.030	0.049	0.079	0.15
Ovaries	0.038	0.049	0.076	0.11	0.20
Pancreas	0.060	0.073	0.11	0.16	0.28
Red marrow	0.031	0.038	0.061	0.095	0.18
Salivary glands	0.27	0.33	0.44	0.59	0.86
Skin	0.019	0.023	0.038	0.062	0.12
Spleen	0.064	0.077	0.12	0.19	0.34
Testes	0.025	0.033	0.055	0.084	0.15
Thymus	0.024	0.030	0.049	0.079	0.15
Thyroid	2.2	3.6	5.6	13.0	25.0
Urinary bladder wall	0.54	0.7	1.1	1.4	1.8
Uterus	0.045	0.056	0.09	0.13	0.21
Remaining organs	0.029	0.037	0.060	0.10	0.18
Effective dose (mSv/MBq)	**0.28**	**0.40**	**0.61**	**1.2**	**2.3**

Thyroid low uptake, oral administration

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.051	0.067	0.12	0.20	0.44
Bone surfaces	0.089	0.10	0.14	0.22	0.40
Brain	0.093	0.10	0.13	0.18	0.30
Breast	0.038	0.050	0.10	0.17	0.32
Gallbladder wall	0.043	0.057	0.10	0.18	0.36
GI-tract					
Stomach wall	0.77	1.0	1.5	2.5	5.3
Small intestine wall	0.033	0.043	0.073	0.11	0.22
Colon wall	0.14	0.18	0.32	0.58	1.3
Wall of upper large intestine	0.12	0.15	0.27	0.49	1.0
Wall of lower large intestine	0.17	0.22	0.39	0.71	1.6
Heart wall	0.089	0.12	0.21	0.36	0.77
Kidneys	0.27	0.34	0.50	0.84	1.8
Liver	0.093	0.14	0.24	0.46	1.2
Lungs	0.10	0.13	0.22	0.38	0.79
Muscles	0.084	0.11	0.17	0.27	0.48
Oesophagus	0.10	0.15	0.30	0.58	1.1
Ovaries	0.037	0.049	0.080	0.13	0.28
Pancreas	0.064	0.080	0.13	0.21	0.41
Red marrow	0.072	0.086	0.12	0.19	0.37
Salivary glands	0.22	0.27	0.36	0.49	0.72
Skin	0.043	0.053	0.080	0.12	0.25
Spleen	0.069	0.089	0.15	0.26	0.55
Testes	0.024	0.032	0.056	0.095	0.20
Thymus	0.10	0.15	0.30	0.59	1.1
Thyroid	280	450	670	1400	2300
Urinary bladder wall	0.45	0.58	0.89	1.2	1.6
Uterus	0.042	0.054	0.090	0.15	0.28
Remaining organs	0.084	0.11	0.17	0.25	0.44
Effective dose (mSv/MBq)	**14**	**23**	**34**	**71**	**110**

Thyroid medium uptake, oral administration

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.055	0.074	0.13	0.24	0.55
Bone surfaces	0.12	0.14	0.19	0.30	0.52
Brain	0.13	0.14	0.18	0.24	0.39
Breast	0.048	0.063	0.13	0.23	0.43
Gallbladder wall	0.046	0.063	0.12	0.21	0.45
GI-tract					
Stomach wall	0.71	0.95	1.4	2.4	5.0
Small intestine wall	0.032	0.043	0.075	0.11	0.24
Colon wall	0.14	0.18	0.34	0.63	1.4
Wall of upper large intestine	0.12	0.15	0.28	0.53	1.2
Wall of lower large intestine	0.17	0.22	0.40	0.76	1.8
Heart wall	0.10	0.14	0.25	0.45	1.0
Kidneys	0.27	0.34	0.53	0.93	2.1
Liver	0.12	0.18	0.31	0.62	1.7
Lungs	0.13	0.16	0.28	0.50	1.0
Muscles	0.12	0.15	0.24	0.38	0.66
Oesophagus	0.14	0.22	0.45	0.87	1.7
Ovaries	0.036	0.049	0.082	0.15	0.33
Pancreas	0.066	0.084	0.14	0.24	0.49
Red marrow	0.095	0.11	0.15	0.24	0.48
Salivary glands	0.19	0.24	0.32	0.43	0.64
Skin	0.057	0.070	0.10	0.16	0.33
Spleen	0.072	0.096	0.16	0.29	0.68
Testes	0.023	0.032	0.056	1.0	2.3
Thymus	0.14	0.22	0.45	0.87	1.7
Thyroid	430	690	1000	2200	3600
Urinary bladder wall	0.39	0.51	0.79	1.1	1.5
Uterus	0.040	0.053	0.089	0.15	0.32
Remaining organs	0.11	0.15	0.23	0.33	0.58
Effective dose (mSv/MBq)	**22**	**35**	**53**	**110**	**180**

Thyroid high uptake, oral administration

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.059	0.082	0.15	0.28	0.66
Bone surfaces	0.16	0.18	0.24	0.37	0.65
Brain	0.17	0.18	0.23	0.30	0.49
Breast	0.058	0.077	0.17	0.28	0.54
Gallbladder wall	0.049	0.068	0.13	0.24	0.54
GI-tract					
Stomach wall	0.66	0.88	1.3	2.2	4.7
Small intestine wall	0.032	0.043	0.077	0.12	0.26
Colon wall	0.14	0.19	0.35	0.68	1.6
Wall of upper large intestine	0.12	0.16	0.30	0.58	1.4
Wall of lower large intestine	0.16	0.22	0.42	0.81	2.0
Heart wall	0.12	0.16	0.30	0.55	1.2
Kidneys	0.27	0.35	0.55	1.0	2.4
Liver	0.14	0.22	0.39	0.79	2.2
Lungs	0.15	0.20	0.35	0.61	1.3
Muscles	0.15	0.19	0.31	0.49	0.86
Oesophagus	0.19	0.28	0.59	1.2	2.3
Ovaries	0.035	0.049	0.084	0.16	0.37
Pancreas	0.068	0.088	0.15	0.27	0.57
Red marrow	0.12	0.14	0.19	0.29	0.59
Salivary glands	0.16	0.20	0.27	0.37	0.55
Skin	0.071	0.087	0.13	0.19	0.41
Spleen	0.075	0.10	0.18	0.33	0.80
Testes	0.22	0.031	0.057	0.11	0.27
Thymus	0.19	0.28	0.59	1.2	2.3
Thyroid	580	940	1400	3000	4900
Urinary bladder wall	0.34	0.44	0.68	0.95	1.3
Uterus	0.038	0.051	0.089	0.16	0.36
Remaining organs	0.15	0.19	0.29	0.42	0.74
Effective dose (mSv/MBq)	**29**	**47**	**71**	**150**	**250**

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The capsules are ready for use. Determine the activity before use.
Any unused product or waste material should be disposed of in accordance with local requirements.