SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MON.IYOT-131 0.37 - 7400 MBq (10 μCi – 200 mCi) oral capsule
0.37 - 7400 MBq / Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

One capsule contains 131I as sodium iodide (^{131}I): 0,37-7400 MBq (10 μCi – 200 mCi) at activity reference date and time.

Iodine-131 has a half-life of 8.02 days. During the reduction of activity, it emits beta (β) and gamma (γ) radiations. 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.

Excipients:

	Amount that 1 capsule contains	
	Diagnostic (D)	Therapeutic (T)
Disodium hydrogen phosphate anhydrous	400 mg	400 mg
Sodium thiosulphate	0.1 -1 mg	0.1 -1 mg
Sodium carbonat decahydrate	0.02 – 1.1 mg	0.0 – 0.7 mg
Sodium bicarbonate	0.05 – 2.8 mg	0.0 – 1.7 mg
Sodium hydroxide 1M	0.00 – 0.01 mL	0.00 – 0.01mL

See section 6.1 for a full list of excipients

3. PHARMACEUTICAL FORM

Oral capsule
Transparent, colorless hard gelatin capsule containing white to light brown powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapeutic indications:

- Graves' disease, Toxic Multinodular Goiter and Toxic adenoma treatment
- Papillary and Follicular Thyroid cancer ablation treatment and metastatic disease treatment

Diagnostic indications:

- Radioactive iodine uptake test, Thyroid scintigraphy and whole body scanning with radioactive iodine

4.2 Posology and method of administration

Posology / administration frequency and duration

Administration for therapeutic purposes:
The activity to be administered for treatment depends on the iodine retention in the thyroid gland. The therapeutic effect is only achieved after a few months.

Radioactive iodine can be administrated for the treatment of hyperthyroidism in patients with medical treatment fails or cannot be applicable. In persistent hyperthyroidism, treatment can be applied again after 6-12 months.

For the treatment of hyperthyroidism
The activity administered depends on the diagnosis, the size of the gland, thyroid uptake, and iodine clearance. 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 Graves` disease, multifocal and disseminated autonomy, the above mentioned target organ doses are related to the overall weight of the thyroid gland, however in the unifocal autonomy, the target organ dose is only related to the weight of the adenoma.

The activity administered is usually in the range of 200-800 MBq but repeated treatment may be necessary.

If it is possible patients should be rendered euthyroid medically before giving radioiodine treatment for hyperthyroidism.

The activity to be administered may be calculated according to the following equation:

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

In this equation:
target dose = is the target absorbed dose in the whole thyroid gland or in an adenoma

target volume = volume of the whole thyroid gland (Graves`disease, multifocal or disseminated autonomy)

max. uptake 131I = 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 = effective half-life of I-131 in the thyroid gland

K = 24.67

Other dosimetry procedures may also be used including sodium pertechnetate (Tc-99m) thyroid uptake tests to determine the appropriate target organ dose (Gy).
Fixed dose protocols may also be used.

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

Administration for diagnosis purpose:
The following doses are used for adult patients (70 kg).

- Thyroid uptake study: 0.2- 3.7 MBq
- After thyroid ablation (for metastasis and thyroid remnant): Maximum dose: 400 MBq
- For thyroid imaging: 7.4- 11 MBq

Scanning is generally completed in 4 hours and repeated between 18-24 hours. However, scintigraphy studies are conducted in 72 hours.

Paediatric population
The activity to be administered in children and adolescents should be determined after performing individual dosimetry (see section 4.4).

Method of administration
Application by oral swallowing.

The capsule should be swallowed whole, on an empty stomach with plenty of water.
Before giving the capsule to children, in particular to young children, it should be ensured that the capsule can be swallowed whole. Giving it with mashed food is recommended.

In patients with suspected gastrointestinal disease, great care should be taken when administering Sodium [^{131}I] iodide. The capsules should be swallowed whole with sufficient

amount of water to ensure complete passage into the stomach and upper small intestine. Concurrent use with H2 antagonists or proton pump inhibitors is recommended.

For instructions on what do before administration, see section 12.

Additional information on special populations

Renal/hepatic impairment:
It may increase the risk of potential adverse effects as patients with renal disease may extend the duration of stay of I-131 within the body. The therapeutic administration of 131I capsules in patients with significant renal impairment, in which an activity adjustment is necessary, requires special attention.

Pediatric population:
The activity to be administered in children and adolescents should be determined after performing an individual dosimetry (see section 4.4).

The quantity of dose (activity) to be administered to a children over the age of 10 and adolescents is calculated based on the adult dose using the formulas based on the child's body weight or surface area of the child.

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

or

$$\text{Child dose (MBq)} = \frac{\text{Adult dose (MBq)} \times \text{Child body surface } (m^2)}{1.73\ m^2}$$

The table stated in below includes suggested correction factors for guidance.

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, European Association of Nuclear Medicines)

Geriatric population
It is not necessary to adjust dose for old patients.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Lactation
- During pregnancy or if there is a suspicion of pregnancy, or if the possibility of pregnancy has not been excluded (see section 4.6.)
- For diagnostic purposes in children under the age of 10.
- Thyroid scanning except in the follow-up of malignant disease or when ^{123}I or ^{99m}Tc are not available.
- Patients with dysphagia, esophageal stricture, esophageal stenosis, esophagus diverticulum, active gastritis, gastric erosions and peptic ulcer.
- Patients with suspected reduced gastrointestinal motility.

4.4 Special warnings and precautions for use

RADIOPHARMACEUTICALS SHOULD BE ADMINISTERED ONLY BY NUCLEAR MEDICINE PHYSICIANS IN NUCLEAR MEDICINE CENTERS.

This product is likely to result in a relatively high radiation dose to most patients (see sections 4.8 and section 11).

Appropriate precautions should be taken concerning the activity eliminated by the patient in order to avoid any contamination.

Iodine-131 has not been used in diagnostic studies in children younger than 10 years of age and is not suitable for administration to children over 10 years old and adolescents unless exceptional circumstances prevail, due to significantly higher radiation exposure compared with the adult.

There is no evidence of an increased incidence of malignancies (cancer, leukaemia or mutations) in human with patients treated for diagnostic purpose with sodium [^{131}I] iodide.

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 reasonable achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

<u>Potential for hypersensitivity or anaphylactic reactions</u>
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.

<u>Renal impairment</u>

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

Hyponatremia
Incidence of severe hyponatremia has been reported in thyroid cancer patients, administered radioactive iodine therapy. The mechanism is described as multifactorial in the scientific literature: risk factors include hyperthyroidism due to discontinuation of thyroid hormone replacement before starting radioactive iodine treatment, old age, female gender, use of thiazide group diuretics, and when starting sodium iodine ^{131}I treatment hyponatremia. Serum electrolytes should be measured regularly in these patients.

Paediatric population
In the treatment of children and adolescents, the radioiodine therapy can be used in the treatment of benign thyroid diseases may be performed in justified cases, such as recurrence after the use of antithyroid medicinal products or 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 its common use in these patients. However, in the treatment of children and young people, the high sensitivity of children's tissue and the longer life expectancy of these patients must be taken into account. The risks must also be discussed against those of other possible treatments. See sections 4.2 and 11.

Patient preparation
Patients should be encouraged to increase oral fluid intake and urinate as frequently as possible to reduce bladder radiation, especially after high activities, such as for the treatment of thyroid carcinoma. Patients with bladder voiding problems should be catheterized after administration of high activities of radioiodine.

The capsules should be swallowed whole with adequate amount of water to ensure complete passage into the stomach and upper small intestine. Concomitant use of H2 antagonists or proton pump inhibitors is recommended.
In case of vomiting, the risk of contamination has to be considered.

Specific warnings
The radiation exposure of the salivary glands can be reduced by stimulating saliva excretion with acidic substances. Other pharmacological protection measures may be used additionally.

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 14 days is recommended for triiodothyronine

and 4-5 weeks for thyroxine. These medicines should be restarted two days after treatment. Similarly, carbimazole and propylthiouracil should be stopped five days prior to treatment of hyperthyroidism and restarted several days later.

The radioiodine treatment of Graves' disease should be performed under concomitant treatment of corticosteroids, when endocrine ophthalmopathy is present.

Patients receiving therapy of the thyroid should be re-examined at appropriate intervals.

In patients with known hypersensitivity to gelatin and/ or its metabolites the use of sodium iodide [^{131}I] solution should be preferred for radioiodine treatment.

This medicinal product contains 129.68 mg sodium in each capsule. To be taken into consideration for patients on a controlled sodium diet.

For precautions regarding environmental hazards, see Section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Many active substances are known to interact pharmacologically with radioiodine. These interactions can occur through a variety of mechanisms which can affect the dynamic effects of labelled iodide or alter protein binding, pharmacokinetics. Consequently, it should be considered that the thyroid uptake might be reduced. Therefore, complete medication history should be obtained and ensure that no medications are used that need to be discontinued before administering sodium iodide I-131.

For example, the treatment with the following substances should be discontinued:

Active ingredients	**Period of the medication should not be used before administration of I-131**
antithyroid agents (e.g. carbimazole, methimazole, propyluracil), perchlorate	withheld 1 week before starting treatment and do not use until a few days after treatment
salicylates, steroids, sodium nitroprusside, sodium sulfobromophthalein, anticoagulants, antihistamines, antiparasitics, penicillins, sulphonamides, tolbutamide, thiopentone	1 week
Phenylbutazone	1 – 2 weeks
containing iodine expectorants and vitamins	approx. 2 weeks

thyroid hormone preparations	Triiodothyronine 14 days thyroxine 4-5 weeks
amiodarone*, benzodiazepines, lithium	approx. 4 weeks
containing iodine preparations for topical use	1 – 9 months
containing iodine contrast media	up to 1 year

* In case of amiodarone, a reduced uptake in the thyroid gland during several months is possible due to the long half-life of this agent.

Additional information on special population
There is no additional information on special population

Paediatric population
Interaction study specific to children has not been conducted.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: X

Women of childbearing potential
Administration of sodium iodide I-131 to a woman during pregnancy can cause serious birth anomalies.
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.

Contraception
Woman of a childbearing potential must be use effective contraception method during treatment (and following the treatment for 6 to 12 months).
As a precaution, men should not have children for 6 months after radioiodine treatment to allow the irradiated spermatozoa to be replaced by non-irradiated spermatozoa.

Pregnancy
MON.IYOT-131 oral capsule is contraindicated during pregnancy (see Section 4.3).

Sodium iodide I-131 should not be used during confirmed or suspected pregnancy or when possibility of pregnancy has not been excluded, due to transplacental passage of sodium iodide I-131 which can cause severe and possibly irreversible hypothyroidism in neonates (the absorbed dose to the uterus for this medication is likely to be in the range 11-511 mGy, and the foetal thyroid gland readily concentrates iodine during the second and third trimesters) (see section 4.3).

When differential thyroid cancer needs to be treated during pregnancy, radioactive iodine treatment must be postponed until after the pregnancy.

Breast-feeding
Before administering 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 radiopharmaceutical, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be discontinued after Sodium Iodide I-131 administration.

Fertility
There may be a decrease in fertility after therapy of thyroid cancer with radioiodine on women and men. Temporary spermatogenesis may occur depending on the dose. Furthermore, it may cause change in the menstruation period.

4.7 Effects on ability to drive and use machines
MON.IYOT-131 oral capsule has no influence on the ability to drive and use machines or degree of this effect can be neglected.

4.8 Undesirable effects

The frequencies of reported adverse reactions are based on medical literature. The safety profile of sodium iodide I-131 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 local radiation effects. In cancer treatment additionally gastro-intestinal adverse reactions and bone marrow suppression may frequently occur.
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.

Undesirable effects are listed below in order of frequencies.
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); not known (cannot be estimated from the available data).

Adverse Reactions after Diagnostic Use:

System Organ Class	Symptom	Frequency
Immune system disorders	Hypersensitivity	Not known
Gastrointestinal disorders	Nausea, vomiting	Not known
Congenital and hereditary/genetic disorders	Congenital thyroid disorders	Not known

Adverse Reactions after Treatment of Benign Disease:

System Organ Class	Symptom	Frequency
Immune system disorders	Anaphylactoid reaction	Not known
Endocrine disorders	Permanent hypothyroidism, hypothyroidism	Very common
	Permanent hyperthyroidism	Common
	Thyreotoxic crisis, thyroiditis, hypoparathyroidism (blood calcium decreased, tetany)	Not known
Eye disorders	Endocrine ophthalmopathy (in Graves' disease)	Common
	Sicca syndrome	Not known
Respiratory thoracic and mediastinal disorders	Vocal cord paralysis	Very rare
Skin and subcutaneous disorders	Iodo acne (acne-like rash)	Not known
Gastrointestinal Disorders	Salivary gland inflammation-Sialadenitis	Common
General disorders and administration site conditions	Local swelling	Not known

Adverse reactions after Treatment of Malignant Disease:

System Organ Class	Symptom	Frequency
Benign, malignant and unspecified neoplasms (including cysts and polyps)	Leukemia	Common
	Solid cancers e.g. bladder cancer, colon cancer, gastric cancer	Not known
Blood and lymphatic system disorders	Aplastic anemia, erythropenia, bone marrow failure	Very common
	Leukopenia, thrombocytopenia	Common
	Permanent or severe bone marrow suppression	Not known
Immune system disorders	Anaphylactoid reaction	Not known

System Organ Class	Symptom	Frequency
Endocrine disorders	Thyrotoxic crisis, transient hyperthyroidism	Rare
	Thyroiditis (leukocytosis transient), hypoparathyroidism (blood calcium decreased, tetany), hypothyroidism	Not known
Nervous system disorders	Parosmia	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	Dyspnea	Common
	Throat constriction*, Pulmonary fibrosis, respiratory distress, obstructive airways disorder, pneumonitis, tracheitis, vocal cord dysfunction (vocal cord paralysis, dysphonia, hoarseness), oropharyngeal pain, stridor	Not known
Gastrointestinal Disorders	Sialadenitis (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
Hepato-biliary disorders	Abnormal liver function	Not known
Renal and urinary disorders	Cystitis radiation	Not known
Reproductive system and breast disorders	Ovarian failure	Very common

System Organ Class	Symptom	Frequency
Reproductive system and breast disorders	Azoospermia, oligospermia, decreased fertility on male, menstrual disorder	Not known
Congenital, heredit and genetic disorders	Congenital hypothyroidism	Not known
General disorders and administration site conditions	Influenza like illness, headache, fatigue, neck pain	Very common
	Local swelling	Common

*: especially in existing tracheal stenosis

Detailed description of undesirable effects:

Thyroid and parathyroid gland disorders
Dose dependent hypothyroidism may occur as a late consequence of radioiodine treatment of hyperthyroidism. This may occur weeks or years after treatment, requiring well-timed measurement of thyroid function and appropriate thyroid replacement. Hypothyroidism does generally not occur until 6-12 weeks after sodium iodide I-131 administration.
In treatment of malignant disease hypothyroidism is frequently reported as an adverse reaction, which, however, is being accounted for by the preceding 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 after 2 – 10 days or even to thyrotoxic crisis. Occasionally, an immune hyperthyroidism may develop after initial normalisation (latency period 2 – 10 months). With high dose radioiodine treatment, the patient may experience transient inflammatory thyroiditis and tracheitis 1-3 days after administration, with a possibility of severe tracheal constriction, especially where there is existing tracheal stenosis.

In rare cases, a transient hyperthyroidism could be occur even after treatment of functional thyroid carcinoma.

Cases of transient hypoparathyroidism have been observed after radioiodine; they must be monitored accordingly and treated with replacement therapy.

Eye disorders
Endocrine ophthalmopathy may progress or new ophthalmopathy may occur after radioiodine therapy of hyperthyroidism or Graves` disease

Local irradiation effects
Vocal cord dysfunction and paralysis have been reported after administration of sodium iodide I-131, 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 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 differential thyroid carcinoma, due to destruction of metastatic tissue. This occurs mainly after high dose radioiodine therapy.

In the treatment of metastasising thyroid carcinomas with central nervous system (CNS) involvement, the possibility of local cerebral oedema and/or an increasing existing cerebral oedema should also be considered.

Gastrointestinal disorders
High levels of radioactivity may lead to gastrointestinal disorders, usually within the first hours or days after administration. For prevention of gastrointestinal disorders see section 4.4.

Salivary and lacrimal gland disorders
Sialadenitis may occur, with swelling and pain in the salivary glands, loss of taste and dry mouth. Sialadenitis is usually reversible spontaneously or with anti-inflammatory treatment, but cases have occasionally been described of dose-dependent persistent ageusia and dry mouth. The lack of saliva may lead to infections, e.g. caries and this may result in loss of teeth. For prevention of salivary gland disorders see section 4.4.

Malfunction of the salivary and/or lacrimal glands with resulting in 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, presented with isolated thrombocytopenia or erythrocytopenia which may be fatal. Bone marrow depression is more likely to occur after one single administration of more than 5000 MBq, or after repeat administration in intervals below 6 months.

Secondary cancers
After higher activities, typically those used in the treatment of thyroid cancers, an increased incidence of leukemia has been observed. There is also evidence for an increased incidence of secondary solid cancers at high activities (more than 7.4 GBq).

<u>Fertility impairment</u>
After radioiodine therapy of thyroid carcinoma, a dose dependent impairment of fertility may occur in men and women. Depending on the activity dose, reversible impairment of the spermatogenesis could be verified in doses above 1850 MBq; relevant clinical effects such as

oligospermia and azoospermia and elevated serum FSH levels have been described after administration higher than 3700 MBq.

General advice
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 increased incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than risk of the disease. The effective radiation dose equivalent (EDE) after therapeutic doses of sodium iodide I-131 is higher than 20 mSv.

Paediatric population
Types of adverse reactions in children are expected to be the same as in adults. Based on higher radiation sensitivity of paediatric tissue (see section 11) and the longer life expectancy, the 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 listed Appendix V.

4.9 Overdose
In case of overdose by mistake, laxatives should be administered and gastric lavage should be performed.

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 urination and by forced diuresis. Additionally, the blockade of the thyroid gland should be recommended (e.g. with potassium iodide or perchlorate) immediately following suspected overexposure in order to reduce the radiation exposure of the thyroid gland. To reduce the uptake of I-131, emetics can be given.

5. PHARMACOLOGICAL PROPERTIES

It is used for diagnosis and treatment purposes.

Pharmacotherapeutic group:
ATC Code: V09FX03: Diagnostic radiopharmaceutical

ATC Code: V10XA01: Therapeutic Radiopharmaceutical

Mechanism of action

The pharmacological active substance is iodine -131 in the form of sodium iodide that is taken up by the thyroid. It decays mainly there during its long retention time and in this manner induces a selective irradiation of this organ.

5.1 Pharmacodynamic properties

In the small amounts of substance used for diagnostic and therapeutic procedures no pharmacodynamic effects of sodium iodide (^{131}I) are to be expected. More than 90% of the radiation effects result from emitted β radiation which has a mean range of 0.5 mm. The β 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 characteristics

Absorption:

After oral administration sodium iodide I-131 is absorbed rapidly from the upper gastrointestinal tract (90% in 60 minutes). The absorption is influenced by gastric emptying. It is increased by hyperthyroidism and decreased by hypothyroidism.

Dissolution studies of ^{131}I sodium iodide capsule, it has been shown that radioactivity is distributed homogeneously in gastric mucosa and dissolution occurs within 5-12 minutes.

Studies on the serum activities levels showed that after a fast increase, -persisting 10 – 20 minutes-, equilibrium was reached after approximately 40 minutes. After oral administration of a ^{131}I sodium iodide solution the equilibrium was measured to be at the same time.

Distribution and Organ uptake:

The pharmacokinetics are same as unlabeled iodide. After entering the bloodstream, it is distributed in the extra thyroidal compartment. From here it is predominantly taken up by the thyroid gland. The thyroid extracts approximately 20 % of the iodide in one pass or is excreted renally. The uptake of iodide in the thyroid reaches a maximum after approximately 24-48 hours and reaches 50 % of the maximum peak after 5 hours. The uptake is affected by several factors: the age of the patient, the volume of the thyroid, renal clearance, the level of circulating iodide and may be affected by other medicinal products (see section 4.5). The iodide clearance by the thyroid is usually 5- 50 ml/min. However, it can increase up to 100 ml/min in case of iodine deficiency and during hyperthyroidism up to 1000 ml/min. In case of iodine overload, it can be decreased to 2 – 5 ml/min. Iodide accumulates also in the kidneys.

Small amounts of iodide I-131 are taken up by salivary glands, gastric mucosa and may also be localized in breast milk, the placenta and choroid plexus.

The iodide that has been taken up by the thyroid follows the known metabolism of the thyroid hormones and is incorporated into the organic compounds from which the thyroid hormones are synthesised.

Elimination:
The main elimination occurs through urine. It is excreted mainly through the thyroid gland and kidneys. 37-75% of the administrated dose is excreted through urine, 10% faecal and negligible amount is excreted through sweat. Renal excretion is characterised by the renal clearance, which constitutes approximately 3 % of the renal flow and is relatively constant from one person to another. It is lower in hypothyroidism and in impaired renal function and higher in hyperthyroidism. The mean urinary excretion in healthy subjects (24 hours urine was investigated) was 2.8 mg/kg in men and 2.7 mg/kg in women.
In euthyroid 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 in 12 hours. However, for radioiodine uptaken in the thyroid gland is approximately 6 days. Thus, after administration of sodium iodide (I^{131}) approximately 40% of the activity has an effective half-life of 0.4 days and the remaining 60% has 8 days.

5.3 Preclinical safety data
Because of the small quantities of substance administered compared with the normal dietary intake of iodine (40-500 mcg/day) no acute toxicity is to be 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
Disodium hydrogen phosphate anhydrous
Sodium thiosulphate
Sodium carbonate decahydrate
Sodium bicarbonate
Sodium hydroxide
Hydrochloric acid
Hard gelatin capsule

6.2 Incompatibilities
There is no known incompatibility with MON.IYOT-131 oral capsule.

6.3 Shelf life
30 days from the date of production.

6.4 Special precautions for storage
It should be stored at room temperature below 25 ºC in the original packaging.
Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and content of container

Inner packaging: Polypropylene plastic tube
Outer packaging: Plastic covered lead shield in a tin box in a cardboard box for transportation or plastic covered lead shield in a cardboard box for transportation.

Content of package for MON.IYOT-131 oral capsule produced in microcurie activity:
1 Capsule / Package
6 Capsules / Package
20 Capsules / Package

Content of package for MON.IYOT-131 oral capsule produced in 1 mCi- 200 mCi activity:
1 Capsule / Package

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

General warnings
Radiopharmaceuticals should be received, used and administered only by authorised people in specified clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the local authorised organizations.
Radiopharmaceuticals should be prepared in a manner both radiation safety and pharmaceutical quality requirements.

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

This product is likely to result in relatively high radiation dose to most patients (see sections 4.8 and 11). The administration of high dose radioiodine may result in significant environmental hazard. This may be of concern to the immediate family of those individuals undergoing treatment or the public depending on the level of activity administered.

Appropriate precautions should be taken concerning the activity eliminated by the patients in order to avoid any contamination.

When opening the packaging 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.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

223/93

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15.03.2010
Date of last renewal: 07.02.2017

10. DATE OF REVISION OF THE TEXT

06.2025

11. DOSIMETRY

Tabulated radiation dosimetry as reported in ICRP publication n° 128.

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 radiation 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 is mainly affecting the thyroid. The radiation exposure of the other organs is in the range of thousands of times lower than that of the thyroid. It is dependant on the dietary intake of iodine (the uptake of radioactive iodine is in iodine deficient areas increased by up to 90 % and is decreased in iodine rich areas to 5 %). It is further dependant on the thyroid function (Eu-, hyper-, or hypothroid) 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 blockade of the thyroid. The radiation exposure of all other

organs is correspondingly higher or lower, depending on the degree of accumulation in the thyroid.

Blocked thyroide

Absorbed dose (mGy/MBq)

Organ	**Adult**	**15 years old**	**10 years old**	**5 years old**	**1 years old**
Adrenals	0,044	0,054	0,086	0,14	0,25
Bladder wall	0,54	0,7	1,1	1,4	1,8
Bone surface	0,03	0,037	0,059	0,092	0,18
Brain	0,021	0,026	0,043	0,071	0,14
Breast	0,02	0,025	0,042	0,069	0,13
Gallbladder wall	0,037	0,048	0,085	0,13	0,21
Gastrointestinal System					
Stomach wall	0,87	1,1	1,6	2,8	5,9
Small intestine	0,035	0,044	0,07	0,11	0,19
Colon wall	0,14	0,18	0,3	0,5	0,92
Upper colon wall	0,12	0,15	0,25	0,42	0,75
Lower colon wall	0,17	0,22	0,37	0,61	1,2
Heart wall	0,062	0,08	0,13	0,2	0,37
Kidneys	0,27	0,32	0,46	0,69	1,2
Liver	0,05	0,065	0,1	0,16	0,3
Lungs	0,053	0,068	0,11	0,18	0,36
Muscles	0,026	0,032	0,051	0,08	0,15
Esophagus	0,024	0,03	0,049	0,079	0,15
Ovaries	0,038	0,049	0,076	0,11	0,2
Pancreas	0,06	0,073	0,11	0,16	0,28
Red bone marrow	0,031	0,038	0,061	0,095	0,18
Salivary gland	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
Timus	0,024	0,03	0,049	0,079	0,15
Thyroid	2,2	3,6	5,6	13	25
Uterus	0,045	0,056	0,09	0,13	0,21
Other organs	0,029	0,037	0,06	0,1	0,18
Effective dose (mSv/MBq)	**0,28**	**0,4**	**0,61**	**1,2**	**2,3**

Thyroid, low uptake

Absorbed dose (mGy/MBq)

Organ	**Adult**	**15 years old**	**10 years old**	**5 years old**	**1 years old**
Adrenals	0,051	0,067	0,12	0,2	0,44
Bladder wall	0,45	0,58	0,89	1,2	1,6
Bone surface	0,089	0,1	0,14	0,22	0,4
Brain	0,093	0,1	0,13	0,18	0,3
Breast	0,038	0,05	0,1	0,17	0,32
Gallbladder wall	0,043	0,057	0,1	0,18	0,36
Gastrointestinal System					
Stomach wall	0,77	1,0	1,5	2,5	5,3
Small intestine	0,033	0,043	0,073	0,11	0,22
Colon wall	0,14	0,18	0,32	0,58	1,3
Upper colon wall	0,12	0,15	0,27	0,49	1,0
Lower colon wall	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	0,5	0,84	1,8
Liver	0,093	0,14	0,24	0,46	1,2
Lungs	0,1	0,13	0,22	0,38	0,79
Muscles	0,084	0,11	0,17	0,27	0,48
Esophagus	0,1	0,15	0,3	0,58	1,1
Ovaries	0,037	0,049	0,08	0,13	0,28
Pancreas	0,064	0,08	0,13	0,21	0,41
Red bone marrow	0,072	0,086	0,12	0,19	0,37
Salivary gland	0,22	0,27	0,36	0,49	0,72
Skin	0,043	0,053	0,08	0,12	0,25
Spleen	0,069	0,089	0,15	0,26	0,55
Testes	0,024	0,032	0,056	0,095	0,2
Timus	0,1	0,15	0,3	0,59	1,1
Thyroid	280	450	670	1400	2300
Uterus	0,042	0,054	0,09	0,15	0,28
Other organs	0,084	0,11	0,17	0,25	0,44
Effective dose (mSv/MBq)	**14**	**23**	**34**	**71**	**110**

Thyroid, mid-uptake

Absorbed dose (mGy/MBq)

Organ	**Adult**	**15 years old**	**10 years old**	**5 years old**	**1 years old**
Adrenals	0,055	0,074	0,13	0,24	0,55
Bladder wall	0,39	0,51	0,79	1,1	1,5
Bone surface	0,12	0,14	0,19	0,3	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
Gastrointestinal System					
Stomach wall	0,71	0,95	1,4	2,4	5
Small intestine	0,032	0,043	0,075	0,11	0,24
Colon wall	0,14	0,18	0,34	0,63	1,4
Upper colon wall	0,12	0,15	0,28	0,53	1,2
Lower colon wall	0,17	0,22	0,4	0,76	1,8
Heart wall	0,1	0,14	0,25	0,45	1
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	0,5	1
Muscles	0,12	0,15	0,24	0,38	0,66
Esophagus	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 bone marrow	0,095	0,11	0,15	0,24	0,48
Salivary gland	0,19	0,24	0,32	0,43	0,64
Skin	0,057	0,07	0,1	0,16	0,33
Spleen	0,072	0,096	0,16	0,29	0,68
Testes	0,023	0.032	0,056	0,1	0,23
Timus	0,14	0,22	0,45	0,87	1,7
Thyroid	430	690	1000	2200	3600
Uterus	0,04	0,053	0,089	0,15	0,32
Other organs	0.11	0,15	0,23	0,33	0,58
Effective dose (mSv/MBq)	**22**	**35**	**53**	**110**	**180**

Thyroid, high uptake
Absorbed dose (mGy/MBq)

Organ	**Adult**	**15 years old**	**10 years old**	**5 years old**	**1 years old**
Adrenals	0,059	0,082	0,15	0,28	0,66
Bladder wall	0,34	0,44	0,68	0,95	0,13
Bone surface	0,16	0,18	0,24	0,37	0,65
Brain	0,17	0,18	0,23	0,3	0,49
Breast	0,058	0,077	0,17	0,28	0,54
Gallbladder wall	0,49	0,068	0,13	0,24	0,54
Gastrointestinal System					
Stomach wall	0,66	0,88	1,3	2,2	4,7
Small intestine	0,032	0,043	0,077	0,12	0,26

Colon wall	0,14	0,19	0,35	0,68	1,6
Upper colon wall	0,12	0,16	0,3	0,58	1,4
Lower colon wall	0,16	0,22	0,42	0,81	2,0
Heart wall	0,12	0,16	0,3	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	0,2	0,35	0,61	1,3
Muscles	0,15	0,19	0,31	0,49	0,86
Esophagus	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 bone marrow	0,12	0,14	0,19	0,29	0,59
Salivary gland	0,16	0,2	0,27	0,37	0,55
Skin	0,071	0,087	0,13	0,19	0,41
Spleen	0,075	0,1	0,18	0,33	0,8
Testes	0,22	0,031	0,057	0,11	0,27
Timus	0,19	0,28	0,59	1,2	2,3
Thyroid	580	940	1400	3000	4900
Uterus	0,038	0,051	0,089	0,16	0,36
Other 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 RADIOPHARMEUTICALS

Capsules are provided with its application apparatus like pipette in a cardboard box, in the form of ready to use.