12/2023

תראקאפ 131 Theracap 131

מרכיבים פעילים:
SODIUM IODIDE (^{131}I) 37 - 5550 MBQ
צורת מינון:
HARD CAPSULE

רופא/ה, רוקח/ת נכבד/ה,
חברת אלדן ציוד אלקטרוני בע"מ מבקשת להודיע על עדכון העלון לרופא של התכשיר שבנדון .
העלון עודכן בתאריך מאי 2023 .

ההתוויה הרשומה לתכשיר בישראל:
Theracap 131 is a radioiodine thyroid therapy indicated for:
1. Treatment of Grave's disease, toxic multinodular goitre or autonomous nodules.
2. Treatmernt of papilary and follicular thyroid carcinoma including metastastic desease.

בהודעה זו מצוינים השינויים המהותיים בלבד.

מקראה לעדכונים המסומנים:
מידע שהוסר - מסומן בקו אדום חוצה ~~XXX~~
תוספת - כתב **כחול**
תוספת חמרה - כתב **כחול** -מסומן בצהוב מרקר
מידע שעבר מקום - כתב ירוק
הקלה – כתב **כחול** - מסומן בירוק מרקר

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא:

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Excipient(s) with known effect
One hard capsule~~**. This medicinal product**~~ contains~~:~~ not more than ~~**1.9 mmol**~~ ~~**(44**~~ **50** mg~~)~~ of sodium ~~**per capsule.**~~
For ~~**a**~~ **the** full list of excipients, see section 6.1.

(…)

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients **listed in section 6.1**.
- Pregnancy **and breast-feeding (see section 4.6).**
- ~~**For diagnostic purposes in children under 10 years of age.**~~
- ~~**Thyroid scanning except in the follow-up of malignant disease or when iodine-123 or technetium-99m is not available.**~~
- Patients with dysphagia, oesophageal stricture**, oesophagal stenosis, oesophagus diverticulum**, active gastritis, gastric erosions and peptic ulcer.
- Patients with suspected reduced gastrointestinal motility.

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4.4 Special warnings and ~~special~~ precautions for use

Potential for ~~The possibility~~ of hypersensitivity **~~including~~ or** anaphylactic**~~/ anaphylactoid~~** 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 (131I) higher than 3700 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 26000 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).
~~should always be considered. Advanced life support facilities should be readily available.~~
~~For radioprotection reasons following therapeutic doses, it is recommended to avoid close contact between mother and child for at least one week.~~
~~The risk of second primary malignancies in thyroid cancer survivors treated with radioactive iodine is slightly increased compared to thyroid cancer survivors not treated with radioiodine.~~
~~This medicinal product contains not more than 1.9 mmol (44 mg) of sodium in each capsule. To be taken into consideration by patients on a controlled sodium diet .~~
~~The administration of high dose radioiodine may result in significant environmental hazard. Suitable precautions should be taken concerning the activity eliminated by the patients in order to avoid any contamination .~~
~~The therapeutic administration of sodium [131I] iodide in patients with significant renal impairment requires special attention with regards to administered activity.~~
~~There is inconclusive evidence of a beneficial effect of saliva stimulation to avoid sialadenitis.~~
A low-iodine 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 catheterized 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 sialoadenitis 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 prior to therapy ~~will~~ is recommended to enhance uptake into functioning thyroid tissue. Thyroid replacement ~~therapy~~ should be stopped prior to radioiodine 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.
Hyponatraemia: Serious manifestations of hyponatraemia have been reported after sodium iodide (~~[~~^{131}I)~~]~~ therapy in elderly patients who have undergone total thyroidectomy. Risk factors include older age, female sex, use of thiazide diuretics and hyponatraemia at the start of sodium iodide (~~[~~^{131}I)~~]~~ therapy. Regular serum electrolytes measurements shall be considered for these patients.
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 H2- 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 after therapeutic doses.
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
This medicinal product contains 50 mg of sodium per capsule., equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
For precautions with respect to environmental hazard see section 6.6.
~~Sperm banking should be considered for young men who have extensive disease and therefore may need high radioiodine therapeutic doses.~~
~~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 [131I] 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.~~

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 ~~A~~ full drug history should be taken and relevant medicainal~~tion~~ products are required to ~~including the ones mentioned below should~~ be withheld prior to the administration of sodium [131I] iodide.
For example, the treatment with the following substances should be discontinued:

Active substances	Withdrawal period prior to administration of sodium [131I] iodine.
Antithyroid agents (e.g. carbimazole, methimazole, propyluracil), perchlorate	1 week before starting treatment till several days after

	~~2 – 5 days before until several days after administration~~
Salicylates, steroids, sodium nitroprusside, sodium sulfobromophthalein, anticoagulants, antihistamines, antiparasitics, penicillins, sulphonamides, tolbutamide, thiopental	1 week.
Phenylbutazone	1 **to** 2 weeks.
Containing iodine expectorants and vitamins	~~**approx.**~~ **approximately** 2 weeks.
Thyroid hormone preparations	**Triiodothyronine 2 weeks** **Thyronine 6 weeks.** 2-6 weeks.
Benzodiazepines, lithium	Approximately 4 weeks.
Amiodarone*	**3 to 6 months**
Containing iodine preparations for topical use	1 **to** 9 months.
Water-soluble iodine-containing contrast media	**6 to 8 weeks** ~~**up to 3 months**~~
Lipo-soluble iodine-containing contrast media	**up to 6 months**
~~**Oral cholecystographic agents**~~	~~**for a period of up to 1 year.**~~

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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 [^{131}I] iodide should be advised not to become pregnant within 6-12 months of administration.

Contraception in males and females

Contraception for **a period of** 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) ~~iodide~~.

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 ~~young~~ men who have extensive disease and therefore may need high **sodium iodide (^{131}I)** ~~radioiodine~~ therapeutic doses.

Pregnancy

The use of s~~**S**~~odium iodide **[^{131}I]** ~~iodide~~ is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded **because transplacental passage of sodium iodine (^{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.

~~**The absorbed dose to the uterus for this agent is likely to be in the range 11-511 mGy, and the foetal thyroid gland avidly concentrates iodine during the second and third trimesters. When it is necessary to**~~

~~administer radioactive 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 [131I] iodide should be advised not to become pregnant within 6-12 months of administration.~~

Breastfeeding
~~Breastfeeding should be discontinued after sodium [131I] iodide administration .~~
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 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.

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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 undesirable effects are recognised for sodium [131I] iodide :**~~
The following table presents how the frequencies are reflected in this section: ~~**The frequencies of undesirable effects are defined as follows:**~~
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	Hypersensitivity including 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
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 the lymphatic system disorders	Erythrocytopenia, bone marrow failure	Very common
	Leukopenia, thrombocytopenia,	Common
	Aplastic anemia, permanent or severe bone marrow suppression	Not known

Immune system disorders	Hypersensitivity including anaphylactoid reaction	Not known
Endocrine disorders	Thyreotoxic crisis, transient hyperthyroidism Thyroiditis (transient leukocytosis), hypoparathyroidism (blood calcium decreased, tetany), hypothyroidism, hyperparathyroidism	Rare Not known
Nervous system disorders	Parosmia, anosmia Brain oedema	Very common Not known
Eye disorders	Sicca syndrome (conjunctivitis, dry eyes, nasal dryness) Nasolacrimal duct obstruction (lacrimation increased)	Very common Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea Throat constriction*, Pulmonary fibrosis, respiratory distress, obstructive airways disorder, pneumonia, tracheitis, vocal cord dysfunction (vocal cord paralysis, dysphonia, hoarseness), oropharyngeal pain, stridor	Common 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 Vomiting Gastritis, dysphagia	Very common Common Not known
Hepatobiliary disorders	Hepatic function abnormal	Frequency not known**
Renal and urinary disorders	Radiation cystitis	Not known
Reproductive system and breast disorders	Ovarian failure, menstrual disorder Azoospermia, oligospermia, decreased fertility male	Very common 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

** this effect may be seen with other similar products but has not been observed with Theracap I-131

~~Blood and the lymphatic system disorders~~

~~Not known: Bone marrow depression, including serious thrombcytopenia, erythrocytopenia and/or leukopenia~~

~~Eye disorders~~

~~Common: Sicca syndrome, endocrine ophthalmopathy~~

~~Not known: acquired dacryostenosis~~

~~Gastrointestinal disorders~~

~~Very common: Transient or persistent sialadenitis, including dry mouth, Nausea, vomiting Endocrine disorders~~

~~Endocrine disorders~~

~~Very common: Hypothyroidism~~

~~Not known: Aggravated hyperthyroidism, Basedow's (Graves') disease, hypoparathyroidism, hyperparathyroidism~~

~~Neoplasms benign, malignant and unspecified (including cysts and polyps)~~

~~Uncommon: leukaemia~~

~~Not known: Gastric cancer, bladder and breast cancer~~

~~Immune system disorders~~

~~Not known: Hypersensitivity~~

~~Injury, poisoning and procedural complications~~

~~Very common: Radiation injury, including radiation thyroiditis, radiation associated pain, tracheal obstruction~~

~~Reproductive system and breast disorders~~

~~Not known: Impairment of fertility in man and woman~~

~~Congenital, familial and genetic disorders~~

~~Not known: Congenital thyroid disorders~~

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 from the disease itself.

For therapeutic use, 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 Effective Dose 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 physiology.

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 (131I), 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 5000 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.

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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 radiationoverdose, 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.
~~High radiation exposure through overdose can be reduced by means of administration of thyroid blocking agent, such as potassium perchlorate, the use of emetics and promoting a diuresis with frequent voiding of urine.~~

(...)

קיימים עדכונים נוספים . למידע נוסף יש לעיין בעלון לרופא המעודכן.

בברכה,

עוז וולך

רוקח ממונה