HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 December 2009

THERACAP ^{131} capsules
1 capsule in a polycarbonate cup (CIP: 571 495-1)

Applicant: GE HEALTHCARE SA

Sodium iodide (^{131}I) for therapy

ATC Code (2009): V10XA01

List I – For hospital use only.
Radiopharmaceuticals must only be used by qualified persons. They may only be supplied to practitioners who have obtained the special authorisation provided for under Article R 1333-24 of the Public Health Code.

Date of (national) MA: 4 August 2009

Reason for request: Inclusion on the list of medicinal products approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sodium iodide (^{131}I for therapy)

1.2. Indication

“Iodine-131 is indicated for the treatment of the following thyroid conditions:

- Hyperthyroidism: Basedow’s disease, toxic multinodular goitre or autonomous nodules.

Sodium iodide (^{131}I) therapy is frequently combined with surgery or synthetic anti-thyroid medications.”

- Papillary and/or follicular thyroid carcinoma, including metastases and residual thyroid tissue.

1.3. Dosage

“The activity administered is a matter for clinical judgement. Treatment only takes effect after several months.

Adults:

- Treatment of hyperthyroidism

The activity administered is generally between 200 and 800 MBq, but it may be necessary to repeat treatment to a maximum accumulated activity of 5,000 MBq. The activity required depends on the cause of hyperthyroidism, the size of the gland, thyroid uptake and iodine clearance.

Patients should be rendered euthyroid medically whenever possible before giving radioiodine treatment for hyperthyroidism.

- Thyroid ablation and treatment of metastases

After total or partial thyroidectomy, the activities given to eliminate remaining thyroid tissue are in the range of 1850 - 3700MBq.

This will depend on the remnant size and radioiodine uptake.

In subsequent treatment for metastases, administered activity is in the range of 3,700 – 11,000MBq.

Children and adolescents: the activity to be administered should be a fraction of the adult dose. This is calculated from the body weight/surface area methods according to the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

X : Various
X10 : Therapeutic radiopharmaceuticals
X10X : Other therapeutic radiopharmaceuticals
X10XA : Iodine compounds
X10XA01 : Sodium iodide (^{131}I)

2.2. Medicines in the same therapeutic category

Other therapeutic radiopharmaceuticals containing iodine-131 and with the same indications as THERACAP, administered:

in capsule form:

- IODURE DE SODIUM POUR THERAPIE MALLINCKRODT France, capsules
- CAPSION capsules

in the form of solution for IV infusion:

- IODURE DE SODIUM CIS BIO INTERNATIONAL, solution for injection

2.3. Medicines with a similar therapeutic aim

Treatment of hyperthyroidism: synthetic anti-thyroid drugs, thiourea derivatives:

- NEOMERCAZOLE 5 and 20 mg tablets (INN: carbimazole)
- BASDENE 25 mg tablets (INN: benzylthiouracile)
- PRORACYL 25 mg tablets / PROPYLTHIOURACILE 50 mg tablets

3 ANALYSIS OF AVAILABLE DATA

No clinical studies have been submitted by the company[1]. The efficacy of iodine-131 in its MA indications has been firmly established.
According to the SPC, early and late adverse effects are possible:

- transient worsening of hyperthyroidism; digestive disorders (with a risk of contamination not be ignored in the event of vomiting); thyroiditis and inflammatory tracheitis. The salivary glands' exposure to radiation to stimulate secretion by way of acid substances is advisable to avoid sialitis and rare cases of loss of taste and dryness of the mouth that are persistent and dose-dependent, then tooth loss.
- late hypothyroidism, transient hypoparathyroidism.

Epidemiological studies concerning the period from 1950 to 1975 have demonstrated an increase in the frequency of stomach cancer after treatment with iodine-131. Cases of leukaemia and bladder and mammary cancer have also been reported.

In all, for each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit.

[1] In the context of the coordinated European procedure for the validation of radiopharmaceutical drugs, pharmacotoxicological and clinical documentation have been created based on bibliographical data

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

THERACAP is indicated to treat hyperthyroidism associated with Basedow's disease, with toxic multinodular goitre or autonomous nodules, and to treat papillary and/or follicular thyroid carcinoma, with or without metastases and residual thyroid tissue. These conditions are life-threatening.

Public Health Benefit

The public health burden caused by thyroid conditions such as hyperthyroidism and differentiated thyroid carcinoma can be considered moderate. The burden for the subpopulation of patients concerned by the aforementioned THERACAP indications is low. The improvement in the management of cancer patients and their quality of life constitutes a priority in term of public health need (Public Health Act 2004, Cancer plan, Plan on improvement in quality of life of patients with chronic diseases). In the absence of clinical data and in light of existing sodium iodide (131I)-based alternatives, THERACAP is not expected to have an additional impact on morbidity and mortality.

THERACAP has no effect on the healthcare system's organisation.

Consequently, THERACAP is not expected to have an impact on public health.

The efficacy/adverse effects ratio of THERACAP (iodine-131) is high. This product is generally prescribed as second-line treatment (particularly for Basedow's disease) and is often combined with surgery or synthetic anti-thyroid drugs. There are alternative medicinal products available.

The actual benefit of THERACAP is substantial.

4.2. Improvement in actual benefit

THERACAP capsules do not provide any improvement in actual benefit (IAB V) compared to other therapeutic iodine (^{131}I)-based radiopharmaceuticals.

4.3. Therapeutic use

One essential prerequisite for considering iodine-131 treatment is the identification of the precise type of hyperthyroidism. The following classification may be proposed:

- autoimmune hyperthyroidism: Basedow's disease, Hashimoto thyroiditis, mixed form;
- autonomous hyperthyroidism on diffuse goitre or on multinodular or simple goitre.

4.3.1. Hyperthyroidism

Iodine-131 was introduced in 1941 in the treatment of hyperthyroidism. The efficacy of internal radiotherapy by radioiodine is connected to the high-level dose absorbed (D) in Gray (Gy) able to be delivered to the thyroid tissue and to the relative tissue specificity of the irradiation.

According to the clinical conditions, the patient is prescribed synthetic anti-thyroid drugs (SAT), internal radiotherapy with iodine-131 or surgery.

- In Basedow's disease, in France, the patient is usually offered medical treatment using SAT (induction treatment then maintenance treatment with or without levothyroxine). In the event of a recurrence, of a very large goitre, a contraindication to SAT and in uncooperative or elderly patients, surgery or iodine-131 is considered.

- In the event of toxic adenoma and toxic multinodular goitre, iodine-131 or surgery is used (particularly in the event of a large goitre).

4.3.2. Differentiated follicular and/or papillary thyroid cancer[2][3]

Iodine-131 is prescribed after surgery (vectorized internal metabolic radiotherapy with iodine-131, completion radiation therapy, completion isotopic therapy or isotopic ablation) with the aim of:

- destroying the normal remaining thyroid tissue (thyroid remnants) to facilitate subsequent monitoring (through serum thyroglobulin assays, an ultrasound of the brain and if necessary total body scan (TBS) diagnosed with iodine-131);
- treating any postoperative macro-or microscopic tumour focuses;
- completing the extent assessment by way of the post-treatment scintigraphy with iodine-131, a high sensitivity examination when the thyroid remnants are small;
- increasing the survival rate of high-risk patients.

4.3.3. Iodine-131 treatment methods in France

These are found in a procedure guide[4] for nuclear medicine specialists (published in 2006 by the SFMN and inspired by a European guideline from 2003). This guide took into account the French legislation on radiation protection (including the European directives). Authorisation to conduct vectorized internal metabolic radiotherapy with iodine-131 is granted by the Authority for Nuclear Safety (ASN).

In addition:
- In accordance with the SPC, “in theory, synthetic anti-thyroid drugs are not suited to the treatment of hyperthyroidisms linked to subacute or post-partum thyroiditis, functional cancer metastases, thyrotropic adenomas and resistance to thyroid hormones. They are contraindicated in cases of TSH-dependent thyroid cancer”.
- “To avoid the onset of sialitis, the patient is advised to eat something sweet or drink a beverage containing citric acid to stimulate saliva”.
- The administration of elevated iodine-131 activities carries environmental risks: suitable collection and storage regulations for contaminated waste must be observed, particularly in cases of urinary or faecal incontinence. Depending on the activity administered, appropriate measures should be taken to avoid contamination (particularly for children under the age of 10 and pregnant women).

4.4. Target population

The target population corresponds to patients with hyperthyroidism or thyroid cancer concerned by treatment with iodine-131. The number of iodine-131 treatments is at least 20,000 in France each year (expert opinion).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicinal products approved for use by hospitals and various public services in the MA indication and dosage.

[2] Consensus conference: management of differentiated follicular thyroid cancer. Guidelines. Annales d’Endocrinologie 2007;68:S57–S72

[3] Furio Pacini et al. Consensus conference: European consensus for the management of patients with differentiated follicular thyroid cancer. European Journal of Endocrinology 2005;153:651-659

[4] Guide for drafting iodium-131 treatment protocols and for monitoring papillary and follicular thyroid cancers. Workgroup on Endocrine surgery Nuclear Medicine Endocrinology (CEMEN), Société Française de Médecine Nucléaire (SFBMN), FRANCE 2006, Médecine Nucléaire-Imagerie fonctionnelle et métabolique, Vol. 30, no10, p. 679-690