TRANSPARENCY COMMITTEE OPINION SUMMARY

TCAPS (levothyroxine sodium), thyroid hormone

High clinical benefit in the treatment of hypothyroidism and in circumstances, whether associated with hypothyroidism or not, where TSH needs to be limited, but no demonstrated clinical advantage in the therapeutic strategy.

Main points

- TCAPS has been granted a marketing authorisation in the treatment of hypothyroidism and in circumstances, whether related to hypothyroidism or not, when TSH needs to be limited.
- The low level of evidence of the studies conducted with TCAPS does not allow any additional clinical effect of TCAPS (levothyroxine in soft gel capsule) over available levothyroxine-based alternatives to be ascertained.

Therapeutic strategy

- **Hypothyroidism**

  Levothyroxine hormone replacement therapy is the first-line treatment for hypothyroidism. Its half-life (6-7 days) allows it to be taken daily. As, in most cases, hypothyroidism is a chronic disease, treatment must be continued indefinitely.
- **Special case of frustrated hypothyroidism**
  - The expected benefit of thyroxine treatment will depend on the initial TSH value, the clinical, biological and therapeutic context and of the risk of conversion to proven hypothyroidism. Due to broadly moderate impact of the treatment, three situations should be distinguished: high risk of conversion (TSH > 10 mIU/L and/or presence of anti-TPO), for which treatment is recommended; low risk of conversion (TSH < 10 mIU/L and lack of anti-TPO antibodies), for which TSH should be monitored at 6 months, then every year; intermediate situation (TSH between 4 and 10 mIU/L), for which initiation of treatment may be considered in light of the presence of anti-TPO antibodies or of clinical signs highly suggestive of hypothyroidism (intermediate risk of conversion) and hypercholesterolaemia.
  - Treatment relies on levothyroxine. This latter should be initiated at progressive doses, aimed at normalising TSH levels. Dosage progression and therapeutic target should be reconsidered in the event of risk of coronary disease. Levothyroxine treatment may be justified once TSH levels exceed 4 mIU/L, with a therapeutic target of TSH < 2.5 mIU/L.
- **Circumstances, whether related to hypothyroidism or not, in which TSH needs to be limited**
  - The main circumstances under which TSH should be limited are TSH-dependent thyroid cancer, along with the presence of goitre or thyroid nodules. The first-line treatment of differentiated follicular thyroid cancer is total thyroidectomy. Next, hormone replacement or limiting therapy (depending on the risk level) should be initiated. For this latter, only levothyroxine is recommended.
  - At the simple goitre stage, inhibition of thyroid growth is achieved by TSH-limiting treatment (levothyroxine), potassium iodide, or a combination of the two products.
  - Treatment of thyroid nodules is determined by the risk of complications. In cases of benign nodule(s), TSH limitation can stop the growth of existing nodules and prevent the appearance of new nodules. In all cases, the prescription of levothyroxine-based limiting treatment should be preceded by assessment of the individual benefit to risk ratio. Treatment safety, along with its efficacy on the nodule and on perinodular dystrophy, should be considered during monitoring, in order to ascertain the need to prolong or discontinue the treatment.

- **Recommendations for the substitution of levothyroxine sodium-based proprietary medicinal products**

Levothyroxine sodium is indicated in the treatment of hypothyroidism and in circumstances, whether related to hypothyroidism or not, when TSH needs to be limited. Levothyroxine sodium is a synthetic thyroid hormone with a narrow therapeutic window (so-called “critical dose” substance). The dosage of this long-term treatment is adjusted on an individual basis and requires close clinical and biological control as the patient’s thyroid balance may be sensitive to minute dose variations.
In some patients, dose adjustment requires adaptation steps of 12.5 µg. Considering the exposure variations that may arise when changing levothyroxine-based proprietary medicinal product in some high-risk patients within the following categories: particularly in patients treated for thyroid cancer, but also those suffering from cardiovascular disorders (heart failure or coronary heart disease, rhythm disorders), pregnant women, children, elderly subjects, along with in some situations in which therapeutic balance was particularly difficult to achieve. In these high-risk patients, maintenance of clinical balance must be confirmed by a clinical or even biological assessment (TSH assay performed between 6 and 8 weeks after substitution, except in pregnant women for whom surveillance should be adapted to the progression of thyroid disease and according to the pregnancy term).

- **Role of the medicinal product in the therapeutic strategy**
  TCAPS is a first-line replacement therapy for hypothyroidism and a first- or second-line treatment, in circumstances, whether associated with hypothyroidism or not, where TSH must be limited.

Clinical data

- Two pharmacokinetic studies compared the bioavailability of levothyroxine after administration of TIROSINT (TCAPS) soft gel capsules and after administration of a tablet presentation, not currently available in France, to patients with normal gastric pH and increased gastric pH. They suggest improved bioavailability of levothyroxine with TCAPS compared to the proprietary medicinal product in tablet form in cases of increased gastric pH, though no conclusions can be drawn concerning its benefit over one of the other proprietary medicinal products currently available in France.
- One American retrospective chart review studied the effect of changing treatment from a “tablet” form (no additional details) to a “soft gel capsule” form on TSH levels, the percentage of patients with thyroxine dose modification and on symptoms. This study did not allow any conclusions to be drawn concerning the benefits of “soft gel capsules” over one of the proprietary medicinal products currently available in France.
- Two studies with a low level of evidence analysed the effect of changing treatment from a tablet form to a soft gel capsule form (TIROSINT/TCAPS) in cases of disease causing an increase in gastric pH and after drinking coffee. They suggested better absorption of levothyroxine in soft gel capsule form (TIROSINT/TCAPS). These studies did not provide any data concerning the possible clinical effect of this change of proprietary medicinal product on the patients.

Benefit of the medicinal product

- The actual clinical benefit* of TCAPS is high
- TCAPS does not provide any clinical added value ** (CAV V) in the therapeutic strategy
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".