BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

SATIVEX (delta-9-tetrahydrocannabinol/cannabidiol), analgesic

No clinical benefit demonstrated in the treatment of spasticity due to multiple sclerosis

Main points

- SATIVEX is a mixture of two cannabis extracts with Marketing Authorization in the treatment of symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who are responders to an initial treatment.
- This is a symptomatic adjuvant treatment in patients who are not sufficiently relieved by standard anti-spasticity treatments.
- Efficacy on a spasticity score was observed in approximately 10% of patients insufficiently relieved by an optimal anti-spastic treatment.

Therapeutic use

- Pharmacological or surgical treatments for spasticity should most often be considered as only one component of a therapeutic program combining physical therapy, occupational therapy, use of equipment and self-directed rehabilitation in various degrees.
- In the case of focal or multifocal manifestations of spasticity, initial treatment involves local medical treatments (botulinum toxin, alcohol or phenol nerve block). If spasticity is widespread, oral administration of anti-spastic products such as baclofen, dantrolene, tizanidine (temporary authorization for use) or benzodiazepines (off-label) can be proposed. These treatments used in monotherapy or in combination have inconsistent and often moderate efficacy.
- Intrathecal administration of baclofen or surgical procedures (neurotomy, tenotomy or other neuro-orthopedic techniques) are offered at an advanced stage of spasticity.
- **Place of the medicinal product in the therapeutic strategy**
  SATIVEX is an adjuvant treatment in patients who are not sufficiently relieved by an optimal anti-spasticity treatment. Treatment should not be continued beyond 4 weeks if the clinical response is deemed insufficient.

Clinical data

- Three double-blind studies evaluated SATIVEX versus placebo:
  - In one study, 189 patients with MS insufficiently relieved by an anti-spastic treatment were recruited. A difference in spasticity score measured with a self-assessment numerical rating scale from 0 to 10 (NRS-11) of -0.52 point (p = 0.048) between the SATIVEX group and the placebo group was observed at 6 weeks of treatment. This difference was less than the hypothesis defined in the protocol. A difference of 18% was observed between the two groups concerning the percentages of patients who were treatment responders (reduction of the NRS-11 ≥ 30%).
  - The second study was conducted on 337 patients. It did not show a difference between the SATIVEX group and the placebo group on the same primary endpoint after 14 weeks of treatment. The pooled analysis of the changes in spasticity scores of these two studies showed a difference between the product and the placebo of -0.34 point (95% CI [-0.64;-0.04], p = 0.027) at 6 weeks of treatment. The percentages of responders (reduction in NRS-11 score of 30%) was different between the two treatments: 35% on THC/CBD versus 24% on placebo: OR: 1.63 (95% CI 1.10; 2.41, p=0.015).
  - The third study randomized 241 of 572 patients in adequately relieved by their anti-spastic treatment, after a screening phase for responders (reduction of at least 20% of the NRS-11 spasticity score during an initial SATIVEX treatment period of 4 weeks). The mean initial NRS-11 score was at least 4 points and the mean
change in NRS-11 score was 3 points. During the randomized period, the difference between the mean changes in the spasticity scores observed between the two groups after 12 weeks of treatment was -0.84 point \( p = 0.0002 \). The placebo effect in this study was substantial. Adjunctive treatment with SATIVEX achieved a clinically relevant improvement in spasticity (NRS-11 score reduction ≥ 30%) in about 20% of patients randomized into the study. Prior optimization of treating or not treating spasticity pharmacologically before patients were included and started on treatment is not discussed in these studies.

In these studies, the percentage of treatment discontinuations for adverse events was 9.8% in the SATIVEX group and 4.7% in the placebo group. The most common adverse events in the SATIVEX group were neuropsychological (dizziness, drowsiness/fatigue) and gastrointestinal (nausea, dry mouth).

Special prescribing conditions

- Narcotic: prescription limited to 28 days; prescription subject to the specifications established by the decree of 31 March 1999 (or restricted prescription).
- Initial 6-month hospital prescription reserved for neurologists and physical medicine and rehabilitation specialists. Unrestricted renewal.

Benefit of the medicinal product

- The actual benefit* of SATIVEX is low.
- SATIVEX does not provide any clinical added value** (level V, none CAV) in the treatment of symptoms associated with moderate to severe spasticity due to multiple sclerosis.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

* The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement for the National Health Insurance.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V of CAV means “no clinical added value”.

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