Considerations for Commissioners

Sativex® Oromucosal Spray

For the treatment of spasticity associated with multiple sclerosis

Commissioning guidance:

Commissioners may wish to consider the following points relating to the implementation of Sativex Oromucosal spray:

- A locally agreed position on the prioritisation of Sativex and inclusion in local formularies.
- The place of Sativex in locally agreed treatment pathways. The NICE guideline on the use of cannabis-based medicinal products (NG144)[1] recommends it as an alternative treatment option if other spasticity treatments are not effective and funding is agreed via a 'Pay for Responders' scheme (requires an ongoing commitment to fund further treatment if a four-week trial is successful).
- A draft ESCA is available on the MTRAC website for local adoption and adaptation. The NICE guideline (section 1.5.2) advises that "after the initial prescription, subsequent prescriptions of cannabis-based medicinal products may be issued by another prescriber as part of a shared care agreement under the direction of the initiating specialist prescriber, if:
  - shared care is appropriate and in the person's best interest
  - the person's clinical condition is stable
  - the other prescriber is confident to make a fully informed prescribing decision about cannabis-based medicinal products.
- According to the guideline, efficacy and safety of cannabis-based medicinal products should be monitored and evaluated, and doses should be adjusted by the initiating specialist prescriber as part of the shared care agreement.
- The Summary of Product Characteristics for Sativex[2] states that treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

Strength of the evidence for efficacy

The strength of the evidence for efficacy is considered to be relatively weak. Of seven RCTs comparing Sativex with placebo, five found a significantly greater improvement in spasticity, scored using a 0 to 10 numerical rating scale (NRS), but differences between groups were small. In three of the five trials that reported the proportions of patients showing a response to treatment (≥ 30% improvement on an NRS scale), a significantly greater proportion of Sativex-treated patients showed a response compared with placebo. Two of those trials had an enriched enrolment design, which may introduce an element of bias, but also reflects the intended use of the product in practice.

MTRAC considered the implementation of Sativex in the context of the NICE guidance on cannabis-containing medicines at the request of local commissioners.

Description of technology

Sativex is derived from extracts of the *Cannabis sativa L*. plant. The main active substances are delta-nine tetrahydrocannabinol (THC) and cannabidiol (CBD). It is administered as an oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per 100µl dose[2].

It is licensed for use as add-on treatment for symptom improvement in patients with moderate-to-severe spasticity due to MS who have not responded adequately to other anti-spasticity medication, and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy[2].

See the Summary of Product Characteristics (SPC) for full details[2].

Background

Multiple sclerosis is an autoimmune disease of the central nervous system in which inflammation destroys the protective sheath surrounding nerve cells[3]. Estimates of the percentage of patients with MS who experience symptoms of spasticity vary from 21% to 69%[4]. This loss of muscle control can lead to pain, spasms, reduced mobility, limited range of movement and contractures.[4]

According to the NICE clinical guideline on multiple sclerosis[5], baclofen and gabapentin *[unlicensed indication]* are first-line treatment options for spasms and spasticity dependent on contraindications and the persons comorbidities and preferences. Other options are tizanidine, diazepam, clonazepam or dantrolene. Use of Sativex is referred to in the NICE guidance on Cannabis based medicinal products[1], published in 2019. For the treatment of spasticity in people with MS, Sativex is recommended as an alternative treatment option if other pharmacological treatments for spasticity are not effective and the conditions of a pay-for-responders scheme are met. The manufacturer funds the first four weeks' treatment provided that there is agreement for continued funding for people with at least a 20% reduction in spasticity-related symptoms as measured on a 0 to 10 patient reported numeric rating scale[1].

Treatment with Sativex should be initiated and supervised by a physician with specialist expertise in treating spasticity due to multiple sclerosis[2].

Clinical evidence for efficacy and safety

The evidence review supporting the cannabis guidance[4] found seven RCTs that evaluated Sativex in patients with a diagnosis of MS who did not obtain adequate relief with current therapy[3,6-11]. The trials were of two to 15 weeks'

duration, six were of parallel design and one crossover study. Two of the trials had an enriched design that enabled screening of participants and inclusion of people showing a minimum level of response to treatment[8,10]. Participants in all trials generally reported a mean number of 7-9 doses of Sativex per day, although three of the trials allowed maximum doses higher than the licensed dose of up to 12 sprays per day[6,7,11].

For the main outcome measures relating to spasticity, four of the seven trials reported statistically significantly greater improvement with Sativex versus placebo[6,8,10,11] (estimated mean treatment differences 0.23 to 0.84[6-8]) using a 0 to 10 numerical rating scale (NRS) and the fifth using the Ashworth score[3]; although clinical significance is unclear[12]. Two trials found no significant difference[7,9].

Response to treatment (defined as at least a 30% improvement in NRS score) was also a clinically significant outcome, and was reported in five of the trials[6-10]. Three of the five found a significantly greater proportion of Sativex-treated participants showing a response to treatment than those receiving placebo[6,8,10]. Proportions were 74% and 77% of Sativex-treated participants *vs*. 32-51% of placebo-treated participants in the enriched-design trials[8,10] and 40% *vs*. 22% in a trial that did not screen participants for a response first[6].

No studies found any significant differences in health-related quality of life (HRQoL) measures whether using the EQ-5D, SF-36 or VAS 0- 100 instruments.

There were no trials that compared Sativex with other anti-spasticity medication.

Adverse events

About 1,500 patients have been exposed to Sativex during the clinical trials programme[2]; the trials in this review include 749 exposures. About 80% of Sativex-treated patients reported at least one adverse event; the most common adverse events occurring more frequently with Sativex than placebo were: dizziness, fatigue, somnolence, nausea and dry mouth.

Common application-site reactions listed in the SPC were: oral pain and discomfort, dysgeusia (taste distortion), mouth ulceration and glossodynia (burning sensation in tongue). Regular inspection of the oral mucosa is advised during long-term administration[2].

Considerations for cost impact

The estimated prevalence of patients with MS in the West Midlands is about 9,050 people (10% of national prevalence), or 190 per 100,000 head of population. We estimated (using the methodology in the NICE Impact report[13] that in the West Midlands there are about 358 potential recipients of Sativex for longer than four weeks.

Costs at current prices from MIMS and the Drug Tariff (May 2021) for a year's treatment with:

Baclofen, 60 mg/day	£	45
Gabapentin 2,400 mg/day	£	297
Sativex, approx 9 sprays/day	£	3,240
Dantrolene sodium, 225 mg/day	£	185
Diazepam 15 mg/day	£	39
Tizanidine 24 mg/day	£	731

Depending on assumptions made, the drug acquisition costs to a GP practice in the West Midlands for a year's treatment with Sativex would be £19,660 per 100,000 head of population.

References

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