Pharmacotherapeutic report, summary

Delta-9-tetrahydrocannabinol and cannabidiol (Sativex®) is indicated as treatment to improve symptoms in patients with moderate to severe spasticity due to multiple sclerosis (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.

Recommendation by the National Health Care Institute [*Zorginstituut Nederland*] dated 24 February 2014, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has approved a pharmacotherapeutic report for the medicine delta-9-tetrahydrocannabinol and cannabidiol (Sativex®) spray for oromucosal use as adjuvant to existing treatment. In determining its therapeutic value as adjuvant to existing treatment, whereby comparison took place with placebo, they reached the following conclusion.
- the therapeutic value of Sativex® as treatment to improve symptoms in patients with moderate to severe spasticity due to multiple sclerosis (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, has a lower therapeutic value in comparison with placebo.

Medicine. delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) spray for oromucosal use

Registered indication. "Treatment to improve symptoms in patients with moderate to spasticity due to multiple sclerosis (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."
Posology. 2.7 mg THC and 2.5 mg CBD (1 spray) up to a maximum of 32.4 mg THC and 30.0 mg CBD (12 sprays) a day, once or twice daily. A titration period is required to reach optimal dose. Based on clinical research, the average maintenance dose is 8 sprays a day (21.6 mg THC and 20.00 mg CBD).
Mechanism of action. THC is a partial agonist of both the CB_1 and the CB_2-receptors which are part of the endocannabinoid system. These receptors play a role in the retrograde regulation of the synaptic function.
Specific details. Sativex® is intended for use in addition to current anti-spasticity medication.

Summary of the therapeutic value

Intended effects. A statistically significant difference was found between Sativex® and placebo during the randomised phase of the pivotal clinical study, amounting to 0.84 points on the 11-point NRS spasticity scale. This difference was demonstrated after the selection of 'responders' during a 4-week one-arm "roll-in" phase carried out in a single-blind study. A statistically significant difference between Sativex® and placebo was also found on a scale for activities of daily living (ADL). There was no statistically significant difference between Sativex® and placebo for quality of life. Uncertainty about concurrent anti-spasticity medication in the study and differences in comparison with the medicines commonly used in the Netherlands sheds doubt on the external validity of the study. Furthermore, the 16-week follow-up is too short – in relation to the chronic treatment of spasticity – to be able to determine the favourable effects of Sativex® in the long term, in particular when considering the progressive course of MS. Furthermore, the blinded nature of the study may have been compromised during the randomisation phase of patients in the placebo arm. All this means that the clinical relevance of the differences of Sativex® in comparison with placebo has not been demonstrated.
Unintended effects. Sativex® leads to an increased incidence of unintended effects in comparison with placebo, the most frequent of which are dizziness and fatigue. However, the unintended effects are generally not serious, transitory in nature and rarely lead to terminating treatment.

As few patients have been treated longer than a year with Sativex®, it is possible that insufficient light has been shed on unintended effects that occur after long-term use.
Experience. Experience with Sativex® is limited.
Applicability. The applicability of Sativex® may be limited due to interactions with existing medication and the increased risk of, or a history of, mental disorders.
Ease of use. The addition of Sativex® to existing treatment leads to a reduction, albeit a small one, in the ease of use of anti-spasticity treatment in general.
Final conclusion on therapeutic value.
The clinical relevance of the difference found with Sativex®, in comparison with placebo in the treatment of spasticity due to MS when added to existing anti-spasticity treatment for patients who demonstrated an improvement during a trial treatment, has not been demonstrated. The reason is that the external validity of the pivotal study is insufficient and the follow-up of this study is too short, in particular considering the progressive course of the underlying disease. The risk of deblinding also carries weight. The unintended effects of the study treatment are generally not serious and rarely lead to terminating the study. Insufficient light may have been shed on the uncertainty regarding unintended effects in the long term. However, this was not a decisive factor in forming the final conclusion.

Treatment with Sativex® to improve symptoms in patients with moderate to severe spasticity due to multiple sclerosis (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' has a lower therapeutic value in comparison with placebo.

*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.*
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.