



Cost-effectiveness of Delta-9-tetrahydrocannabinol/cannabidiol (Sativex[®]) 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.

The NCPE has issued a recommendation regarding the use of Sativex[®] for this indication. The NCPE does not recommend reimbursement of Sativex[®] at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the company's (Almirall) economic dossier on the cost effectiveness of Sativex[®]. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) was licensed to be used in Ireland on July 11th 2014. Almirall submitted a dossier on the clinical and cost-effectiveness of Sativex® to the NCPE. Sativex® is indicated 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. Sativex® contains 38-44 mg and 35-42 mg of two extracts (as soft extracts) from *Cannabis sativa L.*, folium cum flore (Cannabis leaf and flower) corresponding to 27mg 9-delta-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD) per millilitre. Through its effect on the human cannabinoid system, Sativex® modulates excitatory neurotransmitters activity which is thought to contribute to MS-related spasticity.

1. Comparative-effectiveness

- Sativex® is indicated as add-on therapy to patients' current anti-spasmodic regimen, which most commonly consists of single or combination therapy with baclofen, tizanidine, benzodiazepines and other agents. The comparator is current standard of care (SoC).
- The evidence submitted to support efficacy was derived from the GWSP0604 study. The phase III GWSP0604 study incorporated a four week, single-arm, single-blind response determination phase, followed by a 12 week double-blind, placebo-controlled comparative phase. 572 patients with MS and refractory spasticity received single-blind Sativex® for four weeks. After four weeks on active treatment 241 (42%) met the entry criterion of a reduction of at least 20% on the spasticity symptom numerical rating scale (NRS, self-reported scale rating spasticity from 0-10). These patients were then randomised to either continue to receive Sativex® or switch to placebo for the 12 week double-blind phase, for a total of 16 weeks treatment overall. The primary endpoint was the change in spasticity NRS from the point of randomisation to the end of treatment. The mean baseline NRS score at randomisation was 3.90 ± 1.51 (range 0-7.1). This score improved (-0.04) in patients receiving Sativex® and disimproved (+0.81) in patients receiving

placebo representing a statistically significant adjusted mean difference of 0.84 (95% CI -1.29, -0.40 p=0.0002). Of those patients who achieved at least a 20% reduction from screening in NRS score during the initial single-blind phase 74% of patients in the Sativex® group achieved a 30% reduction at the end of the double-blind phase, compared with 51% of patients in the placebo group. Similar trends were observed in the secondary endpoints Modified Ashworth Score and health-related quality of life outcomes, with maintained improvement in the Sativex® group and worsening in the placebo group, however differences between treatment groups were not statistically significant.

- Comparative efficacy in the model relates to differences in the movement of patients between mild, moderate and severe spasticity while receiving Sativex® or SoC. The NCPE had concerns regarding the validity of stratifying the NRS scale into 0-3.3, 3.3-6.6 and 6.6-10, to represent mild, moderate and severe spasticity.
- In the economic model, the company compared Sativex® treatment in Sativex® responders with SoC. The comparative efficacy data underpinning the model was derived from the Sativex® arm of the GWSP0604 study and a Spanish retrospective study (Arroyo *et al*) of case records from patients with MS and spasticity that was resistant to at least one previous course of therapy. The Arroyo *et al* study was chosen by the company to model the natural history of spasticity progression among patients treated with SoC. The NCPE review team identified a number of limitations with the Arroyo *et al* study including selection bias in the analysis set used by the company and the lack of information on the population characteristics and the nature of the SoC treatment received by patients in the analysis set.
- The NCPE review team had a number of concerns with the company's comparison of a "natural history" cohort with the responder-enriched cohort of the GWSP0604 study. This approach was considered by the NCPE review team to yield an upwardly biased estimate of treatment efficacy, due to selection bias in the GWSP0604 cohort. A comparison between Sativex® and SoC among the Sativex® eligible population, i.e. not just among Sativex® responders, is of greatest interest to the healthcare payer. This comparison

was not presented by the company. The NCPE review team considered that the placebo data of GWSP0604 most accurately reflected the potential benefit of Sativex® in this setting, and that it represented the most homogeneous population for the purposes of comparison. Additional scenarios were submitted by the company where the SoC arm of the model was informed by data from a) the placebo arm of the GWSP0604 study and b) the placebo arm of the GWSP0604 study adjusted for a “hypothetical placebo effect”.

2. Safety

- In the MS population, the most commonly reported all-cause adverse events (in at least 5% of subjects) in both comparative and non-comparative studies were dizziness, fatigue, nausea, urinary tract infection, somnolence, vertigo, headache, dry mouth, asthenia and diarrhoea. The majority of these adverse events were rated mild to moderate.
- Use of Sativex® is not recommended in patients with serious cardiovascular disease. Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with Sativex®, generally mild to moderate in severity and well tolerated
- In comparative studies, the overall incidence of treatment-emergent serious adverse events was 4.6%. In the GWSP0604 study there was a statistically significant higher level of discontinuations in the Sativex® arm compared with the placebo arm (n=15 vs 2), with the majority of the discontinuations in the Sativex® arm driven by adverse effects (n=8).

3. Cost-effectiveness analysis

Methods

- A cost utility analysis comparing Sativex® with SoC was submitted by the company. Health benefits were measured in quality-adjusted life years (QALYs) and capture health state utilities associated with mild, moderate and severe spasticity. Costs included drug acquisition, neurologist consultation and health state costs. Additional social services costs were included in scenario analyses.

- A multi-state Markov model, comprising health states based on mild, moderate and severe spasticity, was used to predict costs and QALYs over a five year time horizon from the perspective of the Irish healthcare payer (the Health Services Executive (HSE)). Health state utility values were derived from data collected using the EQ-5D questionnaire in the GWSP0604 study randomized population. The model included mean utility values calculated for the mild, moderate and severe spasticity health states at the end of the GWSP0604 study. Irish neurologists were surveyed to estimate health state costs using a two stage Delphi approach.
- The NCPE review group had a number of concerns in relation to the economic model presented by the company:
 - The comparison of interest to the healthcare payer i.e. between Sativex® and SoC among the Sativex® eligible population, and not just among Sativex® responders, was not presented by the company.
 - The validity of constructing a disease model based on the stratified NRS scale has not been shown.
 - The model assumes that all patients who fail to achieve $\geq 20\%$ improvement in NRS (classified as “non-responders”) will discontinue Sativex®. Observational studies have shown that while 42% of patients receiving Sativex® could be classified as "responders", up to 79% of patients remained on treatment after four weeks and 55% remained on treatment after three months, indicating continued use in non-responders after the trial period.
 - The impact of treatment-related adverse events on quality of life was not included in the model. Pre-treatment health state utility values (health-related quality of life) from a homogeneous patient population with respect to Sativex® treatment were considered by the NCPE to more appropriately reflect health state utility in the target population than the post-treatment values used in the model.

Results

- Under base case assumptions made by the company, total five-year costs and QALYs per Sativex®-treated patient were estimated at €26,039 and 2.6 respectively, equating to an incremental increase of €4,232 and 0.24 QALYs

compared with SoC, and yielding an incremental cost-effectiveness ratio (ICER) of €17,826/QALY. Under these assumptions, the probability that Sativex® is cost-effective at a willingness to pay threshold of €45,000/QALY was 97%.

Sensitivity Analysis

- Parameters which influenced the ICER included the number of sprays per day (mean 6.7 sprays per day assumed by company), the initial distribution of patients between moderate and severe spasticity, the inclusion of social care costs, and the source of health state utility values.
- Additional analyses conducted by the NCPE review team applied alternative assumptions with significant effects on the ICER: using placebo data from the GWSP0604 study as a source of transition probabilities for the SoC arm (€49,208/QALY); using adjusted placebo data from the GWSP0604 (€24,926/QALY); assuming that 62% of “non-responders” continue treatment (€52,076/QALY). The cumulative effect of changing the source of SoC transition probabilities and assuming that 62% of non-responders continue Sativex® after the initial trial period was an increase in the ICER of up to €107,057/QALY. This is likely a conservative estimate as the model is not equipped to capture any alternative benefit which may be observed in “non-responders” on the spasticity NRS scale.

4. Budget Impact Analysis

The ex-factory price of Sativex® used for the submission was €471.29 per 3 x 10ml vial pack. Each 10ml delivers up to 90 actuations. The drug cost per annum is likely in the range €4,500 to €5,000 per person although there is a substantial degree of uncertainty associated with the variability of dosing. A gradual dose titration up to a maintenance dose of 6.7 sprays per day was applied in the budget impact model. The median dose in clinical trials for patients with MS was eight sprays per day, while the maximum dose is 12 sprays per day. Based on the company estimates of eligible population (approximately 830 patients), predicted market uptake and discontinuation rates, the gross drug budget impact of Sativex® is predicted to be €396,901 in year 1 rising to €797,014 in year 5. If continued use in “non-responders” is higher than predicted, as observed in post-launch observational studies, the budget impact could

rise to €1.3 million in year 5. The company's net budget impact model predicts a reduction in healthcare resource requirements following Sativex® treatment but there is little evidence to support this.

5. Conclusion

A number of treatments are currently available for spasticity however there is an unmet need in patients whose spasticity symptoms deteriorate and become less responsive to these therapies. A four week trial of Sativex® is required to identify patients who receive an initial response. A 12 week comparative study of Sativex® versus placebo in these patients found that response was maintained for those on Sativex® while those randomised to placebo disimproved. The clinical significance of the observed difference of 0.84 on the 0-10 point NRS spasticity scale is difficult to assess. An evaluation of the cost-effectiveness of Sativex® in addition to SoC among the Sativex® eligible population, and not just among Sativex® responders, was not presented by the company. Among the population of initial responders, the cost-effectiveness of continued treatment with Sativex® is likely to exceed the current willingness to pay threshold, particularly if treatment duration exceeds the four-week trial period in non-responders. Following NCPE assessment of the company submission, reimbursement of Sativex® is not recommended at the submitted price.