Cost effectiveness of Sativex® for symptom improvement in adults, 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 Sativex®.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Sativex® (delta-9-tetrahyrocannabinol and canabidiol). Following assessment of the Applicant's submission, the NCPE recommends that Sativex® not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Almirall) Health Technology Assessment dossier on 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 examines 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.

National Centre for Pharmacoeconomics **July 2021**

Summary

In August 2019 (following the publication of the SAVANT trial (2018)), Almirall submitted a revised Health Technology Assessment dossier on Sativex®. Given Review Group concerns regarding the cost-effectiveness modelling approach taken, the Applicant submitted a new cost-effectiveness model in December 2020. Reimbursement is sought under the High Tech Drug Arrangement.

Sativex® modulates excitatory neurotransmitter activity through its effect on the human cannabinoid system. The neurotransmitter activity is thought to contribute to multiple sclerosis (MS)-related spasticity. 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 Sativex®.

Sativex® is an oromucosal spray. Each single 100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol. Sativex® is supplied in 10 ml vials with a pump. There are up to 90 measured sprays in each vial. Vials are presented in boxes of three units. A titration period is required to reach optimal dose. The starting dose is one spray on day 1. The patient may continue to gradually increase the dose by one spray per day, up to a maximum of 12 sprays per day, until optimum symptom relief is achieved. Patients are advised to maintain the optimum dose achieved.

1. Comparative effectiveness of Sativex

Sativex® is indicated as add-on treatment to existing anti-spasmodic therapy. Such anti-spasmodic therapy (standard of care (SoC)) commonly consists of single or combination therapy with baclofen, tizanidine, benzodiazepines, anticonvulsants and other agents used to control pain associated with spasticity. The comparator in this assessment is SoC.

Evidence from two pivotal trials (GWSP0604 and SAVANT) was included in this submission. Both trials incorporated a four-week, single arm, single-blinded, response-determination phase (Phase A), followed by a 12-week, randomised, double-blind, placebo-controlled phase (Phase B). Patients in both trials received concurrent SoC; thus patients in Phase B received Sativex® + SoC or placebo + SoC. In both trials, patients were required to have at

least a 20% reduction in spasticity on the Numerical Rating Scale (NRS) in Phase A (i.e. initial responders) to be eligible for Phase B. Unlike GWSP0604, SAVANT included a Sativex® washout period between Phase A and Phase B. Patients were required to revert to at least 80% of their baseline NRS score, during this washout, to be eligible for Phase B.

The NRS is a validated, measure of spasticity; patients self-report their level of spasticity (over the previous 24 hours) from 0 to 10 (0 is no spasticity; 10 is the worst possible spasticity). The primary endpoint in GWSP0604 was the change in the degree of severity of spasticity (assessed by the NRS) from Phase B randomisation to the end of treatment. The primary endpoint in SAVANT was the proportion of patients who responded (response defined as at least a 30% improvement in NRS score) from Phase B randomisation to the end of treatment. A number of key secondary endpoints were examined in both trials including the Modified Ashworth scale of spasticity, spasm frequency, sleep disruption and adverse events.

In GWSP0604, of the 572 subjects enrolled in Phase A, 272 achieved at least a 20% reduction in NRS score and 241 were randomized to Phase B. After 12-weeks of treatment in Phase B, the estimated treatment difference between the two arms (Sativex® + SoC vs. placebo + SoC) in mean spasticity NRS was -0.84 points, 95% CI -1.29 to -0.40; p=0.0002. Also, a higher proportion of patients on Sativex® + SoC achieved at least a 30% improvement from baseline NRS score (74% vs. 51%, odds ratio=2.73, 95% CI 1.59 to 4.69; p = 0.0003). In SAVANT, of 191 patients who entered Phase A, 106 were randomised in Phase B. After 12 weeks of treatment in Phase B, a higher proportion of patients on Sativex® + SoC achieved at least a 30% improvement from baseline NRS score (77.4% vs. 32.1%, adjusted odds ratio = 7.0, 95% CI 2.95 to 16.74; p<0.0001.

Thus, in both trials, a greater proportion of patients treated with Sativex® +SoC had an improvement in spasticity compared to those treated with SoC. However, the magnitude of improvement is uncertain given that the trials had a risk of bias (mainly due to enriched enrolment design and a potential for un-blinding in Phase B (given that all patients had received Sativex® in Phase A)).

There was no significant difference in health-related quality of life in patients treated with Sativex® +SoC compared to those treated with SoC in Phase B of GWS0604 (as measured by

the EQ-5D-3L and the SF-36). Also, there was no significant difference observed between arms in Phase B of SAVANT (as measured by the SF-36).

2. Safety of Sativex®

The Sativex® clinical program has involved over 1,500 patients with MS in placebo controlled trials and long-term open label studies. In the placebo controlled trials, most adverse events were mild-to-moderate and the rate of withdrawal from trials due to adverse events was low. The most common adverse events seen with Sativex® were dizziness (14 to 32%) and fatigue (11 to 25%), which tended to occur during the first four weeks of exposure.

Data from observational studies have shown that the incidence of adverse events varied between 10% and 17% and decreased with prolonged use. The most common adverse events affected the nervous system and comprised dizziness (4%), drowsiness (1.9%), and fatigue (2.5%). Nausea was seen in approximately 2% of patients. Most of the adverse events were mild to moderate and occurred during the titration phase.

3. Cost effectiveness of Sativex®

The Applicant examined the cost effectiveness of Sativex® using a Markov state-transition model comprising three health states: “On Treatment”, “Off Treatment” and “Death”. The time horizon is lifetime; the cycle length is 28.1 days. The distribution of NRS scores among patients in each health state is modelled as an assumed beta distribution. In line with the definition used in the GWSP0604 and SAVANT trials, the Applicant defined an initial treatment response as at least a 20% reduction in the NRS score.

All patients on SoC enter the model in the “Off Treatment” health state; they remain here until death. All patients on Sativex® + SoC enter the model in the “On Treatment” health state. After the first cycle, patients who do not attain an initial treatment response do not continue Sativex® + SoC in Cycle 2 onwards (i.e. Phase B). They move to “Off Treatment”. Some patients on Sativex® discontinue treatment over time and move to “Off Treatment”. Patients in “Off Treatment” are assumed to have a higher NRS score compared to those in “On Treatment”. Also, the NRS Score of patients in “Off Treatment” will not decrease with time. Patients in “On Treatment” are modelled to have increased utility and incur less health care costs compared to those in “Off Treatment”.

Health-care resource use associated with spasticity was estimated from Applicant-led interviews with health care professionals working in the Irish healthcare setting. In the Applicant base case, utilities (stratified by NRS levels) were derived from an analysis of the health-related quality of life data from SAVANT and GWSP0604. EQ-5D-3L data was collected in GWSP0604. Also, SF-36 data collected in SAVANT was translated into the SF-12 and then mapped to UK EQ-5D-3L scores.

The Review Group had a number of concerns regarding the cost-effectiveness analysis. In the model, the mean NRS score of patients in the "Off Treatment "state cannot decrease with time. However, in GWSP0604 and SAVANT, some patients on placebo + SoC had a decrease in NRS score with time. The approach taken may bias the cost-effectiveness results in favour of Sativex® + SoC. Other concerns relate to the derivation and application of treatment effects and the assumption of benefit on health-related quality of life associated with Sativex® + SoC (given limited evidence to support this).

The three most influential parameters (as identified by the Review Group) were the treatment effect (Sativex® +SoC vs SoC) during Phase B of SAVANT and GWSP0604, the utility value at NRS score 10 and the mean number of sprays of Sativex® required per day. The Review Group made a number of adjustments to these parameters in the Applicant base case. Results of the incremental analysis under the NCPE adjusted base case and the Applicant base case are presented in Table 1 and Table 2 respectively.

Table 1: NCPE Adjusted Base Case Analysis

	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
SoC	190,928	2.889			
Sativex® + SoC	223,797	3.268	32,869	0.379	86,704

ICER: Incremental Cost Effectiveness Ratio; QALY: Quality Adjusted Life Year; SoC: Standard of Care.

Figures in the table are rounded, and so calculations may not be directly replicable.

Table 2: Applicant Base Case Analysis

	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
SoC	190,928	2.889			
Sativex® + SoC	207,012	3.628	16,084	0.738	21,783

ICER: Incremental Cost Effectiveness Ratio; QALY: Quality Adjusted Life Year; SoC: Standard of Care.
Figures in the table are rounded, and so calculations may not be directly replicable.

Under the NCPE adjusted base case, the probability of cost effectiveness was 1% and 14% at cost-effectiveness thresholds of €20,000 and €45,000 per QALY respectively.
Given concerns regarding the generalisability of the SAVANT trial (due to the inclusion of a washout period), the Review Group applied treatment-effectiveness estimates from GWSP0604 alone in a scenario analysis. All other Review Group assumptions are maintained. This resulted in an incremental cost effectiveness ratio (ICER) of €169,528 per QALY.

4. Budget impact of Sativex

The price to wholesaler of Sativex® is €395 per pack (three x 10 ml vials). The total cost per pack, inclusive of wholesale-mark up and rebate, is €404.88 (excluding pharmacy fees). No VAT is payable as Sativex® is an oral product. The total cost, per patient, per year will vary depending on the number of sprays required per day. Assuming that 8.1 sprays are required per day (dose assumption derived from the Summary of Product Characteristics), the total cost, per patient, per year is €5,181 (including mark-up, rebate and pharmacy fees).
The Applicant applied MS prevalence and incidence data to CSO population figures. The expected eligible population was then derived by applying estimates derived from a survey of clinicians in Ireland. These estimates included the proportion of patients with moderate or severe spasticity, the proportion receiving SoC, and the proportion uncontrolled on SoC. The Review Group consider that these estimates may not be independent of each other. Thus, the number of patients eligible for Sativex® might be underestimated. Market share estimates were based on German sales data provided by the Applicant. It is estimated that the number of patients who will receive long-term treatment with Sativex® (i.e. after accounting for non-response and discontinuations) will increase from 60 in Year 1 to 442 in Year 5.
Under the assumption that 8.1 sprays are required per day (while maintaining all other Applicant base case assumptions), the five-year cumulative gross drug budget impact is about €6.2 million. The net budget impact is expected to be equivalent (as Sativex® is an

add-on treatment). The five-year cumulative health budget impact is estimated to be €5.4 million. The Review Group are concerned that this is an underestimate; assumed savings (accrued from homecare worker hours) may not be realised in practice. Indeed, the Review Group are concerned that all budget impacts may be underestimated (given the uncertainty in the size of the eligible population).

5. Patient submission.

A patient organisation submission from MS Ireland has been received and will form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that Sativex® not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.