Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2473

delta-9-tetrahydrocannabinol 2.7mg and cannabidiol 2.5mg per 100 microlitre spray (Sativex® Oromucosal Spray)

GW Pharma Ltd

05 August 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

delta-9-tetrahydrocannabinol and cannabidiol (Sativex®) is accepted for use within NHSScotland.

Indication under review: As treatment for 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 demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

In four phase III/IV studies, Sativex® was associated with greater improvements in patient reported spasticity symptom numerical rating score (NRS) and response rate compared with placebo.

Chairman
Scottish Medicines Consortium

Indication

As treatment for 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 demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. [1]

Dosing Information

A titration period of up to 2 weeks is required to reach optimal dose of Sativex®. The number of sprays should be increased each day following the pattern detailed in the Summary of Product Characteristics (SPC). The patient may continue to gradually increase the dose by 1 spray per day until they achieve optimum symptom relief, up to a maximum of 12 sprays per day. There should be at least a 15 minute gap between sprays.

Following the titration period, patients are advised to maintain the optimum dose achieved. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses of greater than 12 sprays per day are not recommended.

The patient's response to Sativex® should be reviewed after 4 weeks of treatment. If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then treatment should be stopped. In the clinical trials this was defined as at least a 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale. The value of long-term treatment should be re-evaluated periodically.

Sativex® is intended to be used in addition to the patient's current anti-spasticity medication. Starting or stopping some concomitant medicinal products may require a new dose titration.

Sativex® is for oromucosal use only and the spray should be directed at different sites on the oromucosal surface changing each time the product is used.

Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population. [1]

Product availability date

16 June 2010

Summary of evidence on comparative efficacy

Sativex® is a solution for oromucosal use containing a combination of two extracts from *Cannabis sativa L.*, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts as a partial agonist of cannabinoid (CB) receptors, CB1 and CB2 receptors, which are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. It may modulate

the effects of neurotransmitters. In animal models of MS and spasticity, CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. [1]

Four short-term, double-blind, randomised studies compared Sativex® with placebo in patients with MS related spasticity. Three were phase III studies (GWMS0106, GWCL0403, GWSP0604) and one was a phase IV study (SAVANT).

These studies recruited adults with significant (defined in GWMS0106 study by an Ashworth score of ≥2 in at least two muscle groups) or moderate to severe treatment-resistant spasticity (defined in the three other studies by spasticity score ≥4 on a 0 to 10 numerical rating scale [NRS]) due to MS. Patients had a diagnosis of MS for ≥6 months (in GWCL0403 and GWSP0604) or ≥12 months (in SAVANT) or stable MS for ≥3 months (in GWMS0106). They had MS related spasticity for ≥3 months (in GWCL0403 and GWSP0604) or ≥12 months (in SAVANT). Patients had been receiving stable antispasticity treatment for ≥30 days (in GWSP0604, GWCL0403 and GWMS0106) or ≥3 months (in SAVANT). In SAVANT, previous treatment had to be with at least two different optimised oral MS spasticity therapies that included at least one of oral baclofen or oral tizanidine and patients were currently receiving optimised treatment with one or more oral antispasticity drugs (with baclofen and/or tizanidine and/or dantrolene).[2-9]

In GWMS0106, patients were randomised in a 2:1 ratio to receive Sativex® or placebo for 6 weeks (with 2-week self-titration; maximum daily dose: 48 sprays per day). In GWCL0403, patients were randomised equally to receive Sativex® or placebo for 14 weeks (with self-titration; maximum daily dose: 24 sprays per day). Two studies, GWSP0604 and SAVANT, used an enriched design with only patients who responded to Sativex®, randomised to study treatment. In GWSP0604 (with 10-day self-titration; maximum of 12 sprays per day), all patients received 4-week treatment with Sativex® (phase A) and only those with an initial response (≥20% reduction in NRS spasticity score) were randomised equally to receive Sativex® or placebo for 12 weeks (phase B). In SAVANT (with self-titration per the SPC; maximum of 12 sprays per day), all patients received Sativex® for 4 weeks (Phase A) after which initial responders (≥20% reduction in NRS spasticity score) entered a 1 to 4 week washout phase before initial responders whose improvement reduced by ≥80% during the washout period were randomised equally to receive Sativex® or placebo for 12 weeks in Phase B. In GWSP0604, GWCL0403 and GWMS0106, anti-spasticity medication dose were to remain stable. In SAVANT, optimisation of underlying antispasticity medications (oral baclofen and/or tizanidine and/or dantrolene) was permitted.[2-9]

In GWMS0106, GWCL0403 and GWSP0604, the primary outcome was the change from baseline to the end of randomised treatment in mean NRS spasticity score (patient-reported outcome ranging from 0 to 10, with 0 = no spasticity and 10 = worst possible spasticity).[2, 3, 5-7, 9] In SAVANT, the primary outcome was the proportion of responders after 12 weeks of randomised treatment (Phase B), with response defined as ≥30% improvement in the MS spasticity NRS score from Phase B baseline.[4, 8]

In GWSP0604 and in GWMS0106, Sativex® was associated with a statistically significant reduction in spasticity NRS score over the randomised treatment periods versus placebo. In GWCL0403, the

difference in mean change in spasticity NRS score over the randomised treatment period numerically favoured Sativex® but did not reach statistical significance compared with placebo. In SAVANT, Sativex® was associated with a statistically significant higher proportion of responders achieving ≥30% improvement in the spasticity NRS score over the randomised treatment period.[6-9]

NRS responder rate (defined as ≥30% improvement in spasticity NRS score) was a secondary outcome in GWSP0604 and GWCL0403 and was also analysed in GWMS0106. In these studies, Sativex® was associated with a higher proportion of responders; however, the difference versus placebo only reached statistical significance in GWSP0604. [10] Mean change from baseline in spasticity NRS score at end of treatment was a secondary outcome in SAVANT; Sativex® was associated with a statistically significant reduction in mean change in spasticity NRS score over the randomised treatment period versus placebo. [6-9] Results are detailed in Table 1.

Table 1: Spasticity NRS outcomes in SAVANT, GWSP0604, GWCL0403 and GWMS0106 [6-11]

Study	**SAVANT[a]**		**GWSP0604[a]**		**GWCL0403**		**GWMS0106**	
Population	**Phase B ITT**		**Phase B ITT**		**ITT**		**ITT**	
Randomised treatment period	12 weeks		12 weeks		14 weeks		6 weeks	
Number of patients	**Sativex® (n=53)**	**Placebo (n=53)**	**Sativex® (n=124)**	**Placebo (n=117)**	**Sativex® (n=167)**	**Placebo (n=170)**	**Sativex® (n=120)**	**Placebo (n=64)**
Mean baseline (at randomisation) spasticity NRS score	-	-	3.87	3.92	6.48	6.77	5.49	5.39
Mean change from baseline in spasticity NRS score at end of treatment	-3.5	-1.6	-0.04	0.81	-1.05	-0.82	−1.18	−0.63
Treatment difference	-1.9 p<0.001 (secondary outcome)		-0.84 (95% CI: -1.29 to -0.40); p=0.0002 (primary outcome)		-0.23 (95% CI: -0.59, 0.14); p=NS (primary outcome)		−0.52 (95% CI: −1.029 to −0.004); p=0.048 (primary outcome)	
NRS responder (30% reduction in MS spasticity score from baseline) at end of treatment	77%	32%	74%	51%	31%	25%	40%	22%
Adjusted odd ratio	7.0 (95% CI: 2.95 to 16.74); p<0.001 (primary outcome)		2.73 (95% CI: 1.59 to 4.69); p=0.0003 (secondary outcome)		1.34 (95% CI: 0.83 to 2.17); p=NS (secondary outcome)		2.38 (95% CI: 1.19, 4.78); p value: NR (prospectively planned)	

[a] These studies were of enriched design with only patients who initially responded to Sativex® randomised to study treatment; see details above.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MS, multiple sclerosis; NRS, numerical rating scale; NR: not reported; NS: not significant.

Secondary outcomes also included change from baseline in mean spasticity score at the end of treatment based on the Ashworth scale (5 point scale) in GWMS0106 or modified Ashworth scale (6 point scale) in the other studies. These scales are measured by an observer stretching the selected muscle group passively and scoring the resistance to movement. A negative treatment difference is a difference in favour of Sativex®. The treatment difference (varying from -0.11 in

GWMS0106 to -1.75 in GWSP0604) was generally not statistically significant. Spasms frequency was also assessed in three studies; but statistically significant reduction was only seen in GWSP0604. [6-9, 12]

Three of these studies also assessed various general Health Related Quality of Life (HRQoL) outcomes and in one study an MS-specific HRQoL outcome. Overall, no significant differences were detected between the Sativex® and placebo groups.[7-9]

The submitting company summarised a meta-analysis of seven studies[6-9, 13-15], including the four studies described above, that was conducted to inform another HTA agency evidence review for spasticity on cannabis-based medicinal products.[12] This meta-analysis was performed using both fixed and random-effect models to evaluate the efficacy and safety of Sativex® compared with placebo in patients with MS related spasticity. Efficacy outcomes assessed were: NRS responder rate (>30% improvement in spasticity) using four main studies (n=404); change from baseline in spasticity (Modified Ashworth Scale) using four studies (n=417); change from baseline in spasticity (NRS) using seven studies (n=684). Patients treated with Sativex® were significantly more likely to show a greater than 30% improvement in NRS spasticity than patients who received placebo (placebo versus Sativex® risk ratio: 0.62 [95% confidence interval [CI]: 0.48, 0.81]; p=0.0004). For this response outcome, an odds ratio (OR) of 2.61 (95% CI: 1.40, 4.86), derived from this meta-analysis (derivation methods not described), was used in the economic analysis. The company reported an NRS responder rate of at least 20% improvement as an OR of 3.84 (95% CI: 2.29-6.42), indicating higher likelihood of response with Sativex®. Benefit in change from baseline in spasticity was seen with Sativex® compared placebo when spasticity was measured using the modified Ashworth Scale (Sativex® versus placebo mean difference: −0.23 [95% CI: (−0.36, −0.10]; p=0.0006) or using the NRS (mean difference: −0.75 [95% CI: −1.20, −0.29] p=0.001). [12]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The profile of adverse event (AEs) and serious AEs was considered broadly in line with that expected from the known pharmacology of cannabis. The main safety and tolerability issues were related to CNS events. It was noted that the side effects that are relatively common on initiation of treatment and during dose titration may limit tolerability of Sativex®. Overall, the safety profile was considered acceptable for the proposed patient population and indication.[10]

Any treatment-emergent AE was reported in the Sativex® group and in the placebo group: in GWMS0106, by 82% (102/124) of patients and 71% (46/65), respectively; in GWCL0403: by 93% (156/167) and 78% (132/170), respectively; In GWSP0604: by 53% (66/124) and 48% (57/117), respectively; In SAVANT: by 23% (12/53) and 13% (7/53), respectively. [6-9]

The treatment-related AEs reported for the Sativex® group compared to the placebo group, respectively were as follows: in GWCL0403, 87% and 56%; in SAVANT, 9.4% and 1.9%. [6-9, 16, 17]

Patients with a reported serious AE for the Sativex® group compared to the placebo group, respectively were as follows: in GWMS0106, 3.2% and 4.6%; in SAVANT, in 1.9% in both groups. [6-9, 17, 18]

Patients with an AE leading to treatment withdrawal for the Sativex® group compared to the placebo group, respectively were as follows: in GWMS0106, 4.8% and 3.1%; in GWCL0403, 5.4% and 2.9%. [6-9, 11, 17]

The most frequently reported treatment-emergent AEs of any grade which showed a higher incidence (with difference ≥10%) in the active treatment group compared with placebo were: in GWMS0106, dizziness (32% versus 11%); in GWCL0403, dizziness (32% versus 10%), somnolence (14% versus 4%), asthenia (16% versus 6%), nausea (32% versus 10%), and dry mouth (14% versus 4%); in GWSP0604 and in SAVANT, the between groups differences were <10% for all AEs. [6-9]

The meta-analysis of seven studies summarised by the submitting company also assessed safety outcomes. These outcomes were: total AEs (using three studies [N=646]); treatment-related AEs (using three studies [N=629]); total serious AEs (using two studies [N=290]) and withdrawal due to AEs (using six studies [N=1,331]). Patients receiving Sativex® were more likely to experience AEs, treatment-related AEs and to withdraw from treatment due to AEs compared with placebo. The chance of developing a serious AE was similar between the two groups. [12]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Spasticity is a common symptom experienced by patients with MS. It can range from a feeling of tightness/stiffness in a limb, especially the legs causing mild problems with walking, to a severe generalised muscle tightness preventing voluntary movement. If left untreated, it can lead to complications such as muscle shortening, permanent contractures and pain. Management of spasticity is usually multimodal, combining non-pharmacological and pharmacological interventions. Recommended oral pharmacological options include baclofen and/or gabapentin, tizanidine, dantrolene, or benzodiazepines. [19, 20] Clinical experts consulted by SMC considered that Sativex® will fill an unmet need, namely by providing an additional treatment option for patients who do not adequately respond to or cannot tolerate conventional therapies. Sativex® is first in class for this indication.

In four phase III/IV studies, Sativex® was associated with greater improvements in spasticity NRS score compared with placebo, although this improvement did not reach statistical significance in all studies (treatment difference not significant in GWCL0403). In GWCL0403 and GWMS0106, the treatment difference was modest (<-0.52 on an 11-point scale). In the two studies with an enriched design (GWSP0604 and SAVANT, where only initial responders during the initial 4-week phase were included in the second and randomised treatment phase), the treatment difference was higher (-0.84 and -1.9, respectively). This treatment effect was supported by higher odds of 30% improvements in NRS spasticity score with Sativex® compared with placebo (with OR >1 in all

studies); although this was significant only in the two enriched design studies. Although the enriched design improved the relative treatment effect due to only responding patients being randomised to study treatment, this reflects likely use in clinical practice following the SPC's recommendation for an initial 4-week trial of treatment. Of note, the treatment effect seems quite different even between these two enriched design studies and so the true magnitude of treatment effect remains uncertain; though this may be due to differences between these two studies (specifically, only in SAVANT, initial responders had to enter an up to 4 week washout phase and only those whose improvement reduced by ≥80% during the washout period were randomised to treatment). Overall, it appears that not all eligible patients will benefit from treatment with Sativex®, but for those who respond to the initial treatment trial it could result in clinically meaningful improvements in spasticity. Based on the three registration studies, GWMS0106, GWCL0403 and GWSP0604, the MHRA considered that Sativex® benefits were of clear clinical significance in this difficult to treat patient population. [10]

The maximum recommended dose of Sativex® is 12 sprays per day and when initiating treatment the number of sprays should be increased each day over a 2-week titration period following a detailed pattern. However, this differed to the maximum daily doses and self-titration schedules used across the studies.[6, 7] All studies comprised a self-titration period; however the phase IV study, SAVANT, was the only study with a titration schedule in line with that specified in the SPC. Of note, the MHRA noted that the lack of evidence of a dose-response relationship with Sativex® was a weakness; however it was agreed that showing dose-response in terms of clinical efficacy was difficult especially because of the high inter-individual variability in pharmacokinetics. There was also little indication of a clear dose relationship in terms of incidence of common AEs. A flexible individual patient dose titration regimen was considered well-justified.[10]

Efficacy outcomes were assessed only after short randomised treatment periods varying from 6 to 14 weeks across the main studies. These studies did not provide evidence to support Sativex® long-term benefits and long-term comparative data are limited. However, regulators noted that based on data from open-label extension and withdrawal studies the efficacy of long-term treatment with Sativex® has been satisfactorily demonstrated.[10]

Prior and concomitant anti-spasticity medications varied across studies (details of prior medications were not available for all studies), with baclofen being the most commonly used anti-spasticity therapy prior to and during the studies. It is uncertain whether prior and concomitant anti-spasticity medications used in the studies are generalisable to Scottish clinical practice. No subgroup analyses based on prior or concomitant anti-spasticity medications are available; the effectiveness of Sativex® based on prior or concomitant anti-spasticity medications is uncertain.

In all four studies, the primary outcomes assessed symptoms as patient-reported subjective outcomes based on spasticity NRS. The MHRA acknowledged that spasticity was difficult to measure. They noted that the objective and clinician-measured Ashworth Scale (assessed as secondary outcomes in the studies) had previously been considered the standard tool for measuring spasticity; however, it is associated with poor reproducibility and insensitivity to change.[10] The MHRA noted that extensive data were provided to validate the NRS measure; and

although there were weaknesses in these, demonstration of the validity of the NRS as a measure of symptoms related to spasticity in patients with MS was considered reasonable. [10]

Clinical experts consulted by SMC generally considered that Sativex® will be used as add-on treatment and will not displace any treatment. The submitting company rightly noted that as Sativex® is intended to be used in addition to standard of care, a placebo comparator as a proxy for standard of care is relevant.

The submitting company presented a meta-analysis that compared Sativex® with placebo and concluded that Sativex® improves spasticity-related outcomes in patients with MS related spasticity, while modestly increasing the likelihood of AEs. However, there were a number of limitations that affected the validity of these results. All studies, apart from one, were assessed to have a high risk of bias or some concerns bias due to the study design, short follow-up periods and variation in dosing regimen. There is significant clinical and methodological heterogeneity across included studies (such as in selection criteria, duration of follow-up, maximum daily dose of treatment and in particular study design [some had enriched enrolment design]). The robustness of the meta-analysis results are not tested by exploring the heterogeneity with pre-specified sub-group analysis or sensitivity analysis. The NRS response threshold of 30% improvement does not seem to reflect the 20% threshold that is, according to Scottish clinicians' feedback received by the submitting company, often considered in clinical practice to define clinically significant improvement in spasticity related symptoms during an initial trial of therapy. Due to these limitations, the meta-analysis' conclusions are highly uncertain.

Sativex® will provide an additional treatment option for the management of patients with spasticity due to MS. Clinical experts consulted by SMC felt that the degree to which there would be service implications due to the introduction of this medicine will depend on who is responsible for the prescribing and management of treatment (management by specialists in this area would require increased capacity/resource).

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing Sativex® plus standard of care (SoC) with SoC alone in adults with moderate to severe spasticity due to MS who have not responded adequately to other anti-spasticity medication. SoC consists of continuing with current medicines. The comparator seems appropriate as SMC clinical expert feedback was generally that Sativex® would be in addition to current oral anti-spasticity treatments.

The economic model was based on a model developed for the NICE clinical guideline NG144[12], and consisted of a Markov structure with three health states of response, no response and death. Cycle length was 4 weeks and a 5 year time horizon was adopted. Patients were defined as responders if they demonstrated a clinically significant improvement in spasticity related symptoms during an initial 4 week trial of therapy, measured as a ≥30% reduction on the NRS

spasticity scale. Patients who did not respond were assumed to discontinue Sativex® and receive SoC alone.

Data on the relative effectiveness of Sativex® versus SoC is from a meta-analysis of four key randomised controlled trials of Sativex® versus placebo, with placebo representing SoC alone outcomes.[12] The baseline characteristics of MS patients (mean age 51 years, female proportion of 53%, and baseline spasticity NRS of 7.5) were derived from an Italian observational study.[21] Treatment effect (patients achieving response) was defined as an odds ratio of 2.61 for Sativex® versus placebo derived from the meta-analysis, with the reciprocal of the OR combined with Sativex® response data to estimate the SoC response (response rates at 4 weeks estimated at 0.364 for Sativex and 0.18 for SoC). Patients discontinue Sativex® after the initial 4 week trial if they do not respond or at any time point beyond due to loss of efficacy or adverse events, with response discontinuation rates based on 2 year data on Sativex® use from the Italian observational study. [21] Estimates for discontinuations due to adverse events were from a published study on incidence of serious adverse events and selected non-serious adverse events for medical cannabinoids versus placebo[22], with the estimates stated to be validated by three clinical experts in Scotland. In the base case an estimate of natural annual progression in population NRS of 0.227 was included. The same excess mortality risk for MS patients was assumed for Sativex® and comparator.

Utility estimates were based on a published regression analysis of EQ-5D data with spasticity NRS and expanded disability status scale (EDSS) score in patients with MSS.[23] Utility values per spasticity NRS score were estimated based on a simulation of 10,000 hypothetical patients with mean baseline NRS of 7.5 and EDSS of 6.4 derived from the Italian observational study. The proportion of patients achieving response level categories above 30% was derived from this source in order to estimate weighted average utilities used in the economic analysis for response and non-response of 0.538 and 0.355 respectively. These were age adjusted. Estimates of adverse event duration and disutilities were derived from NICE NG144, utilising published sources and applying these in a multiplicative manner with the health state utilities.

Medicine acquisition costs were estimated for Sativex® at £1.11 per dose administered in three phases of treatment, the first and second 12 week phases consisting of an average of 8.55 and 6.5 sprays per day respectively, based on that seen in the SAVANT clinical study.[8] The third phase was treatment continuation until discontinuation with an average daily dose of 6.3 sprays assumed. Disease management resource use was estimated per spasticity NRS category (1-2, 3-4, 5-6, 7-8, 9-10) derived from a published study[24], with an assumption that 50% of resource utilisation could be attributed to MS spasticity[12]. Using the published source resource use per spasticity category was estimated for five types of health care resource, covering district nurse visits, outpatient visits, A & E visits, hospital admissions, and home care visits, with greatest costs associated with home care and outpatient visits. Unit costs were from Scottish sources or assumption. Disease management costs varied from £87.81 for NRS 1-2 to £1,677.17 for NRS 9-10, with weighted responder versus non-responder costs of £749 and £1,216 estimated respectively. Adverse event costs per cycle were also estimated.

The base case results are presented in Table 2. The incremental cost is primarily driven by additional medicine costs, but also additional adverse event management costs, and mostly offset by lower disease management costs associated with Sativex® plus SoC.

Table 2: Base case results

	Sativex® +SoC versus SoC
Incremental costs	£779
Incremental QALYs	0.095
ICER: Incremental Cost/ QALY gained	£8,191

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality Adjusted Life Year; SoC, standard of care

In one-way deterministic sensitivity analysis, the results were most sensitive to varying the odds ratio for response treatment effect, serious adverse event rates (impact on costs), proportion of costs that are spasticity related, and SoC response (Table 3). Probabilistic sensitivity analysis was performed but there was a lack of deterministic scenario analyses in the submission to adequately explore uncertainty around the base case incremental cost-effectiveness ratio (ICER), so a set of scenario analyses were requested (Table 3).

Table 3 Selected sensitivity and scenario analyses

	Sensitivity Analysis	**ICER Range (£/QALY)**
1.	OR for treatment effect varied 4.86 to 1.40 (base case: 2.61)	"Dominant" to £166,837
2.	Sativex® + SoC serious AE event rates varied 0.185 to 0.740 (base case: 0.37)	"Dominant" to £44,268
3.	Non-responder costs varied by ±20%	"Dominant" to £29,790
4.	SoC treatment response varied 0.147 to 0.217 (base case: 0.180)	"Dominant" to £26,080
5.	% costs spasticity related 69.4% to 30.6% (base case: 50%)	"Dominant" to £24,982
6.	Sativex® + SoC serious AE event rates varied 0.185 to 0.740 (base case: 0.37)	"Dominant" to £20,333
7.	Responder utility varied by ±20%	£5,300 to £17,800
8.	Number of daily doses varied simultaneously across treatment phases ±20%	£581 to £15,800
	Scenario Analysis	**ICER**
1.	Time Horizon of 2 years	£16,118
2.	≥20% NRS spasticity score improvement for response	£18,446
3.	Assuming 10% or 20% of non-responders continue Sativex®	£16,682 and £25,212
4.	No treatment discontinuation for SoC	£17,215
5.	No NRS progression over time	£16,663
6.	Health state utility values from Lu et al. 2012[25] (0.57, 0.48 for responder and non-responder respectively)	£35,167
7.	OR estimated from 2 Sativex enriched RCTs only	"Dominant"
8.	Combined scenario (10% of non-responders continue treatment, mean NRS progression of 0.114, and ≥20% NRS spasticity score improvement for response)	£27,286

Abbreviations: OR, Odds Ratio; ICER, incremental cost-effectiveness ratio; AE, adverse events; QALY, quality-adjusted life-year; NRS, numerical rating scale; SoC, standard of care. TBC, to be confirmed

The economic analysis was associated with a number of weaknesses and uncertainties:

- Limitations and uncertainties with the robustness of the meta-analysis of four studies used in the economic analysis for estimating treatment effect (including uncertainties over the use of odds ratios rather than a risk ratio), as described in the summary of clinical effectiveness issues above. These limitations mean there is high uncertainty in the cost-effectiveness results, and sensitivity analysis demonstrates an upper ICER of £166,837/QALY gained applying the lower 95% OR bound (Table 3). When only the two enriched design studies for Sativex® are used, which are more in line with the product label as the only studies where responders at 4 weeks continue treatment, the cost-effectiveness results improve, although results in this scenario are now only based on two of seven available Sativex® studies (see scenario analysis 7 in Table 3). The small difference in incremental costs and QALYs means the ICER is likely to be sensitive to varying key parameters.
- The choice of response threshold (≥30% NRS improvement) applied in the economic analysis does not match that used in some clinical studies for determining initial treatment response after a 4-week treatment trial (i.e. a ≥20% NRS improvement).[1] Adjustments were not made in the company's base case analysis to account for the use of a higher threshold, although this has been done in scenario analysis. SMC clinical experts consulted largely thought other measures would be used in clinical practice to determine response, such as the modified Ashworth Scale and physical features presented, which adds to the uncertainty over response rates and impact on Sativex® cost-effectiveness.
- In addition, there is the potential that in clinical practice some non-responders at 4 weeks would continue treatment with Sativex® (in line with feedback from SMC clinical experts), hence allowing for this increases the ICER – scenario 3 in Table 3.
- There is a general lack of transparency in the submission: it is unclear in the NPAF what specific modelling methods have been used and, other than citing precedence (NICE), there is little justification for their selection. For example, the methods for modelling NRS progression, NRS improvement in responders and treatment waning were either not documented and/or not explained by the company. In addition, given the utility and resource use data were available by NRS categories, defining model health states after the initial 4 week response cycle based on NRS states might have been more appropriate than using response at a 30% threshold, but has not been considered (the company has stated due to lack of data and for simplicity).
- NRS distribution: there is uncertainty about the NRS distribution over time, particularly for the responders. It has been assumed that the percentage NRS response is independent of baseline NRS and is unaffected by the diminishing treatment effect over time.
- Treatment waning: From examination of the model it appears as though only adverse event related discontinuations were included for the SoC arm in the company's model, in contrast to the clinical guideline model, in which only non-adverse event related discontinuations were included.
- There is ICER sensitivity to varying parameters such as non-responder disease management costs, number of daily Sativex® sprays, and applying an alternative published source of

utilities (Table 3). Due to the multiple areas of uncertainty, the company were requested to provide a combined parameter scenario analysis which is reported in table 3, scenario 8.

Despite the above uncertainties, the economic case for Sativex® has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The MS Trust, The MS Society and Revive MS Support. All three organisations are registered charities.

- The MS Trust has received 15.5% pharmaceutical company funding in the past two years, including from the submitting company. The MS Society has received less than 1% pharmaceutical company funding in the past two years, with none from the submitting company. Revive MS Support has received 1.6% pharmaceutical company funding in the past two years, with none from the submitting company.

- MS-related spasticity is one of the most common symptoms of multiple sclerosis, with 1 in 8 describing their symptoms as severe. Spasticity has a major impact on the ability to carry out tasks of daily living and on quality of life, both for the person with MS and carers. Depending on what part of the body is affected by spasticity, it can impair mobility, toileting, sexual function, dressing, feeding and increase the risk of falls. It is also a very painful condition. The effects of coping with spasms and spasticity can aggravate other MS symptoms, such as fatigue and depression. All of these aspects can have a detrimental effect on employment or education and impact on fulfilment of life roles such as those of a partner or parent.

- There are a variety of medications to support patients with spasticity in MS and response varies from person to person. Some have side effects of dizziness and fatigue, exacerbating symptoms many already experience due to their MS. Generally many patients on these medications find they work well but there is a percentage who feel it is not enough and wish to add or try other medication to manage it better.

- In a survey conducted by one of the patient groups, 66% felt Sativex had improved their symptoms and impacted positively on their quality of life. One of the patient groups described how people taking Sativex reported gaining benefit in small advances, such as remaining mobile enough to self-toilet or being able to transfer with less pain from wheelchair to bed and vice versa. They said these subtle but important gains improve quality of life and reduce the burden of care. Patient groups also said the proposed prescribing protocol of a four week trial period provides people with the opportunity to assess whether Sativex will be effective for them and decide if the side effects were prohibitive for them.

Additional information: guidelines and protocols

National Institute for Health and Care Excellence (NICE) published in 2014 a clinical guideline on the management of multiple sclerosis in adults. This guidance was last updated in November 2019. The first-line medicine interventions for spasticity to consider are baclofen or gabapentin; a combination of both can be considered if adequate symptom relief is not achieved on an individual medicine or side effects from the individual medicine prevent dose increase. For second line treatments tizanidine or dantrolene, and for third line treatment benzodiazepines are considered. [19] An updated version is expected to be published in June 2022.

NICE published NICE Guideline 144: cannabis-based medicinal products in 2019; last updated in March 2021. This recommends a 4-week trial of Sativex® spray treatment (provided by company with a pay-for-responders scheme) in patients with moderate to severe MS related spasticity if other pharmacological treatments are ineffective. It recommends that Sativex® spray should be continued after the 4-week trial, only if the person has had at least a 20% reduction in spasticity related symptoms on a 0 to 10 patient-reported numeric rating scale. [12]

The Royal College of Physicians published in 2018 national guidelines on "Spasticity in adults: management using botulinum toxin. This includes a section on pharmaceutical interventions for generalised spasticity. The guideline notes that oral anti-spasmodics such as baclofen and tizanidine may be considered for generalised or segmented spasticity but frequently cause unwanted side effects of drowsiness and muscle weakness. This guideline also notes that it is not uncommon to have a mixed pattern of spasticity with both focal and generalised element; and so interventions for generalised spasticity and for focal spasticity are often combined. Intramuscular botulinum toxin type A injections or (less commonly) nerve blockade with phenol in aqueous solution were cited as the pharmacological treatments of choice for focal spasticity. [26]

The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) endorsed a systematic review and consensus paper on pharmacological management of spasticity in multiple sclerosis, which was published in 2016. It recommends for generalised spasticity that is only mild, physical therapy, and if not only mild the use of baclofen, tizanidine and gabapentin in monotherapy as first-line options. Diazepam or dantrolene could be considered if no clinical improvement is seen with the previous medicines. If no clinical improvement is seen with the previous options, it recommends oral medicines in combination therapy or Sativex® can be added to monotherapy. It notes that Sativex® has a positive effect when used as add-on therapy in patients with poor response and/or tolerance to first-line oral treatments. Despite limited evidence, it notes that intrathecal baclofen and intrathecal phenol show a positive effect in severe spasticity and suboptimal response to oral medicines. In addition, for spasticity that is not generalised and with lower limb involvement, it recommends botulinum toxin (repeated if improvements are seen) and physical therapy; and phenol injection if no improvements are seen with botulinum toxin.[20]

Additional information: comparators

Sativex® will be used in addition to standard of care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
delta-9-tetrahydrocannabinol and cannabidiol (Sativex®)	**One to maximum 12 sprays per day by oromucosal route**	**404 to 4,853**

Costs from BNF online on 06/06/22.

Additional information: budget impact

The submitting company estimated there would be 552 patients eligible for treatment in year 1 rising to 557 patients in year 5 with an estimated uptake rate of 35% in year 1 (195) rising to 42% in year 5 (235).

The gross impact on the medicines budget for all patients was estimated to be £477,394 in year 1 rising to £591,549 in year 5 based on the number of patients estimated to be eligible. As no other medicines were assumed to be displaced, the net medicines budget impact was estimated to be the same as the gross impact.

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This assessment is based on data submitted by the applicant company up to and including 14 July 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.