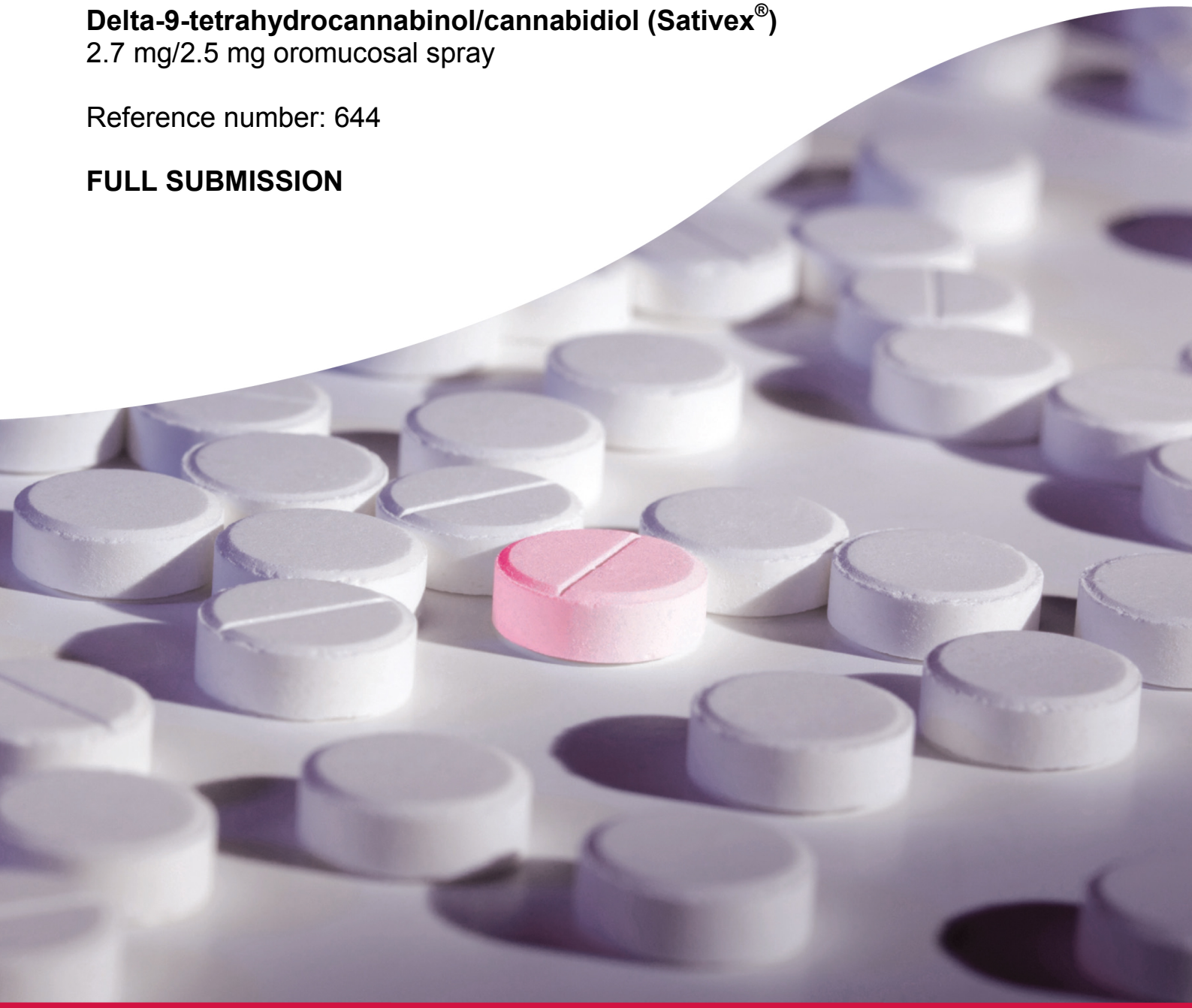
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®)
2.7 mg/2.5 mg oromucosal spray

Reference number: 644

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) 2.7 mg/2.5 mg oromucosal spray. Reference number: 644. July 2014.

AWMSG Secretariat Assessment Report
Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®)
2.7 mg/2.5 mg oromucosal spray

This assessment report is based on evidence submitted by Bayer Healthcare Pharmaceuticals on 11 April 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) is indicated 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[2].
Dosing	Each 100 microlitre spray of Sativex® contains 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol. A titration period is required to reach the optimal dose, where the patient may continue to gradually increase the dose by one spray per day, following the pattern specified in the Summary of Product Characteristics (SPC), up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays. Doses of greater than twelve sprays per day are not recommended. Following the titration period, patients are advised to maintain the optimum dose achieved; 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. The patient's response to Sativex® should be reviewed after four 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. Refer to the SPC for further information[2].
Marketing authorisation date	16 June 2010[2].

2.0 DECISION CONTEXT

2.1 Background

Multiple sclerosis (MS) is a chronic condition that affects the central nervous system (CNS), characterised by demyelination and axonal degeneration[3,4]. The course of MS is potentially highly disabling but decidedly variable, with patients typically developing multiple neurological dysfunctions, such as visual and sensory disturbances, limb weakness, gait problems, and bladder and bowel symptoms[3,4]. Estimates of MS prevalence and incidence tend to vary, with higher rates observed in more northern regions of the British Isles[5]. One study based in south east Wales demonstrated an increase in prevalence from 101 to 146 patients per 100,000 population between 1985

and 2005, while incidence increased from 4.25 to 9.65 per 100,000 population between 1985 and 2007[6,7].

Spasticity is a common symptom in patients with MS, affecting between 49% and 84% of patients[8,9], and impairing quality-of-life[10]. MS-related spasticity is characterised by increased stiffness and slowness in limb movement, development of certain postures, an association with weakness of voluntary muscle power, and with involuntary and sometimes painful spasms of limbs[11]. National Institute for Health and Care Excellence (NICE) guidance recommends that initial pharmacological treatment for spasticity or spasms should be baclofen or gabapentin (unlicensed use); tizanidine, diazepam, clonazepam and dantrolene should only be given when treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable. The next pharmacological options for patients with MS-related spasticity unresponsive to simpler treatments are intrathecal baclofen or phenol injections (to motor points or intrathecally) or, in specific cases, intramuscular botulinum toxin[11].

Sativex® is a cannabis-based medicine, containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as an oromucosal spray[2]. THC acts as a partial agonist at the cannabinoid receptor types 1 (CB_1) and 2 (CB_2), activation of which have been found to ameliorate limb stiffness and improve motor function in animal models of MS and spasticity[2,12]. CBD has been suggested to modulate the unwanted side effects of THC[12]. Sativex® is licensed for use to improve symptoms of moderate to severe MS-related spasticity, in patients who have not responded adequately to other anti-spasticity medication, in addition to the patient's current anti-spasticity medication[2].

2.2 Comparators

The comparator included in the company submission was standard of care (SoC).

2.3 Guidance and related advice

- NICE. Neurological conditions overview (2014)[13].
- The MS Trust. Multiple sclerosis information for health and social care professionals (2011)[4].
- Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, and the Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines (2009)[14].
- NICE. CG8. Multiple sclerosis: management of multiple sclerosis in primary and secondary care (2003)[11]. Expected review publication date: October 2014[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Evidence of clinical efficacy

The company submission includes the 16-week study GWSP0604 as the primary source of evidence of clinical effectiveness, along with data on longer-term efficacy from study GWMS0702[1]. In addition, a systematic review of published literature was conducted to identify studies investigating the effectiveness of Sativex® for the treatment of MS-related spasticity; however, no additional data or conclusions were presented in the company submission. Additionally, non-comparative data from registry, observational and questionnaire-based studies of patients receiving Sativex® were included in order to provide reassurance of efficacy and safety, but did not provide evidence on the comparative effectiveness of Sativex® used in line with the licensed indication and will not be discussed further[1].

3.1.1 Study GWSP0604

GWSP0604 was a randomised, double-blind, placebo-controlled, multicentre, parallel-group, phase III study evaluating the efficacy and safety of Sativex® in adult patients with MS experiencing spasticity of at least moderate severity (defined as a spasticity numeric rating scale [NRS] score of at least 4; see Glossary) not responsive to existing therapies[16]. All patients (n = 572) entered phase A of the study, and received Sativex® for four weeks in order to identify patients who responded sufficiently to treatment (≥ 20% improvement from baseline spasticity NRS score). Patients with sufficient response during phase A were eligible to progress to phase B, wherein patients (n = 241) were randomised to receive Sativex® (dose self-titrated through predefined escalation scheme up to a maximum dose of 12 sprays in a 24-hour period; n = 124) or placebo (n = 117) over 12 weeks. Patients continued to receive their pre-existing MS disease-modifying and/or anti-spasticity medications[16].

The primary endpoint was the change in mean spasticity NRS score from the point of randomisation (entry of phase B) to the last week of treatment, while secondary and tertiary endpoints included improvements in the modified Ashworth scale (MAS); sleep disruption NRS scores; Subject, Physician and Carer Global Impression of Change (SGIC, PGIC and CGIC, respectively); and assessments of quality-of-life, including the EuroQol-5 Dimension (EQ-5D) and the Short Form-36 (SF-36) assessments[1,16]. An overview of results is presented in Table 1. The mean baseline spasticity NRS score in the 572 patients entering phase A was 6.91[16]; of these 272 patients (47.6%) were identified as responders[17].

In the group of 241 patients entered into phase B, the mean spasticity NRS score at randomisation was 3.90 (3.87 in the Sativex® group and 3.92 in the placebo group). During phase B, this improved by 0.04 in patients receiving Sativex® and worsened by 0.81 in the placebo group; this treatment difference (0.84) was statistically significant (95% confidence interval [CI]: −1.29 to −0.40; p = 0.0002). Similar data was observed during analysis of secondary and tertiary endpoints, with patients who continued to receive Sativex® maintaining responses observed during phase A and patients from the placebo group demonstrating worsened scores; however, the differences in MAS, EQ-5D and SF-36 scores did not achieve statistically significance[1,16].

Table 1. Overview of results from clinical studies[16–18].

Endpoint	Sativex®	Placebo	Treatment difference	95% CI (P-value)
Study GWSP0604 (Phase B)	**n = 124**	**n = 117**		
Mean change in spasticity NRS score from randomisation to end of treatment	−0.04	+0.81	−0.84	−1.29 to −0.40 (p = 0.0002)
Change in MAS score from randomisation to end of treatment	+0.08	+1.83	−1.75	−3.80 to 0.30 (p = 0.094)
Patients achieving ≥ 30% reduction in spasticity NRS score	92 (74.2%)	60 (51.3%)	Odds ratio: 2.73	1.59 to 4.69 (p = 0.0003)
Mean change in sleep disruption NRS from randomisation to end of treatment	−0.13	+0.75	−0.88	−1.25 to −0.51 (p < 0.0001)
Study GWSP0702	**n = 18**	**n = 18**		
Median time to treatment failure	> 28.0 days	1.5 days	Hazard ratio: 0.335	90% CI: 0.162 to 0.691 (p = 0.013)
Patients with treatment failure	8 (44.4%)	17 (94.4%)	9 patients	Not reported
Adjusted mean change in spasticity NRS score from baseline to end of treatment	+1.00	+1.21	−0.21	90% CI: −1.22 to 0.79 (p = 0.720)
Adjusted mean change in MAS score	+1.11	+1.64	−0.53	90% CI: −4.68 to 5.74 (p = 0.862)
Mean change in sleep disruption NRS from baseline to end of treatment	+0.60	+1.24	−0.64	90% CI: −1.60 to 0.33 (p = 0.271)
CI: confidence interval; MAS: modified Ashworth scale; NRS: numeric rating scale.				

3.1.2 Study GWSP0702

Study GWSP0702 was a placebo-controlled, multicentre, parallel-group, randomised, phase III, withdrawal trial that evaluated the maintenance of efficacy of Sativex® in patients with MS who had gained long-term symptomatic relief from spasticity, and assessed the impact of sudden Sativex® withdrawal in these patients[18]. Eligible patients were those experiencing ongoing benefit from Sativex® for at least 12 weeks prior to study entry (mean duration of Sativex® use: 3.6 years). Patients continued to receive Sativex® at their current effective dose during the seven-day baseline period, and then were randomised to either continue receiving Sativex® or switch to receiving placebo for four weeks. Patients continued to receive their pre-existing MS disease-modifying and/or anti-spasticity medications[18].

Treatment failure occurred in 8/18 (44.4%) patients in the Sativex® group versus 17/18 (94.4%) in the placebo group, and the primary endpoint of time to treatment failure (see Glossary) was significantly in favour of Sativex® (median time: > 28.0 days in the Sativex® group versus 1.5 days in the placebo group; hazard ratio: 0.335; 90% CI: 0.162 to 0.691; p = 0.013). Most secondary endpoints demonstrated a similar trend, but several, including change in spasticity NRS scores, MAS scores and sleep disruption NRS scores failed to achieve statistical significance[18].

3.2 Comparative safety

The applicant company provided several safety studies[1], considered at the time of licensing by the Medicines and Healthcare Products Regulatory Agency (MHRA), who concluded that the profile of adverse events (AEs) and serious AEs (SAEs) for Sativex® is broadly in line with that expected from the pharmacology of cannabis, and noted that the main tolerability issues are related to CNS events[17].

Evidence of comparative safety comes from phase B of study GWSP0604, where similar proportions of patients reported at least one AE during the double-blind randomised phase (66/124 [53.2%] Sativex®-treated patients versus 57/117 [48.7%] in the placebo group)[16]. [Commercial in confidence data removed] There were two treatment-related SAEs (system organ class and preferred term unknown); both were

reported in patients receiving Sativex® and resolved upon cessation of treatment. [Commercial in confidence data removed] Psychiatric disorders were reported by 13 [10.5%] patients in the Sativex® group versus 7 [6.0%] patients in the placebo group[16]. [Commercial in confidence data removed]

During the placebo-controlled, randomised, withdrawal period of study GWSP0702, 15/18 (83.3%) patients receiving Sativex® and 14/18 patients (77.8%) receiving placebo reported at least one AE[18]. The most common AEs considered treatment-related were pain (2 [11.1%] in Sativex® group versus 5 [27.8%] in placebo group), muscle spasticity (2 [11.1%] versus 3 [16.7%] respectively), muscle spasms (2 [11.1%] in both groups) and fatigue (2 [11.1%] versus 0 respectively). One patient reported an SAE (pain in hip and thigh and lumbar spinal stenosis; considered unrelated to study medication), and two patients in each treatment group experienced a severe AE. Additionally, nine patients discontinued treatment due to an AE (one patient from the Sativex® group versus eight in the placebo group). No deaths were reported during the study[18]. The applicant company concluded that the study showed no evidence of a withdrawal syndrome in patients who stopped Sativex® suddenly, despite a prolonged period on the medicine[1].

3.3 AWTTC critique

- Spasticity is associated with higher levels of disability in patients with MS[19], and affects a large proportion of these patients, with 30% of patients reporting symptoms rated as moderate to severe[8]. Currently available treatments for spasticity are limited, and there is an unmet clinical need in those patients for whom spasticity continues to be troublesome despite receiving treatment[17].
- Sativex® provided a statistically significant improvement in patients with MS-related spasticity when compared with placebo over 12 weeks, in terms of the outcomes: NRS scores for spasticity and sleep disruption; and SGIC, CGIC and PGIC scores[16]. During a four-week study in patients judged to be benefiting from long-term Sativex® therapy, withdrawal of Sativex® caused significantly more patients to report treatment failure than those continuing to receive Sativex®[18].
- MS is a chronic disease[4] and long-term, comparative evidence of clinical effectiveness of Sativex® is limited. The applicant company has noted that non-comparative registry, observational and questionnaire-based studies provide reassurance of efficacy and safety in this patient population[1]. In patients judged to be benefiting from long-term Sativex® therapy, withdrawal of Sativex® caused significantly more patients to report treatment failure; however, of those patients continuing to receive Sativex® during the four-week study period, almost half (44.4%) of patients reported treatment failure[18]; the applicant company notes that this reflects the nocebo effect, where there is a tendency for outcomes to be worse in patients expecting that this might happen[1]. Additionally, the company submission included a 50-week study where assessments of spasticity tended to be better for Sativex®-treated patients than those receiving placebo, but this was not statistically significant and the study did not include the SPC-specified initial therapeutic trial period to identify responders[20]. The long-term comparative clinical effectiveness of Sativex® is thus subject to uncertainty.
- The company submission provides evidence of the clinical effectiveness of Sativex® in patients with MS-related spasticity in terms of improvement of a patient-reported spasticity NRS score[1]. A key issue considered by MHRA is whether the NRS is a valid measure of spasticity as opposed to a measurement of other symptoms. An objective spasticity measure, the MAS[17], was recorded as a secondary endpoint in several studies and tended to be higher in Sativex®-treated patients than those in the placebo group. This improvement has yet to achieve statistical significance[16–18], but MHRA has noted that the ability of MAS to measure change can be limited[17]. At the time of licensing,

MHRA considered that the validity of the NRS has been reasonably demonstrated as a measure of symptoms related to spasticity for the purpose of supporting an indication for the symptomatic treatment of spasticity in patients with MS[17].

- At the time of licensing, MHRA concluded that the profile of AEs and SAEs for Sativex® is broadly in line with that expected from the pharmacology of cannabis, and noted that the main tolerability issues are related to CNS events[17]. MHRA highlighted concerns regarding the potential for psychological and psychiatric morbidity. However, such events are common in the MS population and MHRA concluded that there are insufficient data to establish whether there might be a causal association with Sativex®[17]; this was reflected in the risk management plan and SPC[2,17].
- Following failure to respond to available oral therapies, it is recommended that the next pharmacological options for patients with MS-related spasticity are intrathecal baclofen or phenol injections (to motor points or intrathecally) or, in specific cases, intramuscular botulinum toxin[11]. Sativex® would be a noninvasive therapeutic option for this patient group[2].
- Sativex® should be directed at different sites on the oromucosal surface, changing the application site each time the product is used, in order to dimish risk of developing application site reactions. There should be at least a 15 minute gap between sprays, so for patients receiving the maximum dose of 12 sprays, administration as per the SPC dosing pattern would take a minimum of 90 minutes for the seven evening doses and 60 minutes for the five morning doses. However, once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of Sativex® as an add-on to SoC in its licensed indication, versus SoC, where SoC is defined as a combination of anti-spasticity medication and physical therapies[1]. A Markov model has been developed, which defines five spasticity-related health states based on categorised spasticity scores measured on the spasticity NRS used in the key trials. The base case model uses a 28-day cycle length and a time horizon of 30 years. Patient-level data from the GWSP0604 trial is used to define the initial proportion of a cohort of patients in each of the health states. For patients treated with SoC, the transition between the health states in the first 4 cycles is based on the placebo arm of the GWSP0604 trial. Deterioration in spasticity over time is estimated from a retrospective analysis of case records of patients in Spain with spasticity resistant to more than one previous treatment[21] (company data on file; not verified). This rate of deterioration is assumed to be constant. For patients treated with Sativex®, the transition between the health states for the first four 28-day cycles is reported to be derived from patient-level data from the GWSP0604 trial (referenced to company data on file; not verified). It is assumed that Sativex®-treated patients experience deterioration at the same rate as SoC-treated patients. Sativex® discontinuation is reported to be modelled from the GWSP0604 trial data for the first four cycles, and from a long-term UK/German registry study for the remainder of the modelled period (referenced to company data on file; not verified). The deterioration in spasticity in patients who discontinue Sativex® is reported to be based on the effects observed in placebo recipients in the randomised phase of the GWSP0604 trial[1].

Sativex®-treated patients are assumed to use a mean of [commercial in confidence data removed] sprays per day, reportedly based on use observed in the long-term UK/German registry study (reference to company data on file; not verified). Other anti-spasticity drug costs are excluded from the analysis on the assumption that there are no differences in other drug costs between Sativex®-treated and SoC-treated patients. Resource use associated with each of the spasticity-defined health states are based on a company-conducted UK questionnaire survey of 221 health and social care specialists experienced in the management of MS, with published unit costs applied[1].

Utility weights associated with each of the spasticity-defined health states are based on patient-level EQ-5D data collected at visits 2, 3 and 6 of the GWSP0604 trial and are assumed to be independent of treatment received. AEs are not considered in the analyses. Costs and outcomes accrued beyond one year are discounted at 3.5% per annum. A range of sensitivity and scenario analyses have been conducted, including: assuming no worsening of spasticity over time; widening the costing perspective to include carer costs; exclusion of equipment costs; and sensitivity analyses around discount rates.

4.1.2 Results

The results of the base case analysis are presented in Table 2. Sativex® treatment is estimated to deliver an additional 0.35 quality-adjusted life-years (QALYs) at an additional overall cost of around £4,000 over the 30-year time horizon.

Table 2. Base case CUA results.

	SoC	SoC plus Sativex®	Difference	ICER	Key plausibility considerations
Total cost (per patient)	£98,501	£102,337	£3,836	£10,891	The model does not address the decision problem of Sativex® plus SoC versus SoC alone, as the costs and benefits of Sativex® over the first cycle is included in the SoC alone arm. Short-term data are modelled to 30 years, which is subject to uncertainty. The assumed dose of Sativex® in the model is lower than observed in the key trials.
Total QALY (per patient)	10.65	11.00	0.35		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SoC: standard of care.

Probabilistic sensitivity analysis based on 5,000 simulations of the base case scenario (assuming a 25% standard deviation around resource use rates and costs) suggested a 100% probability for the incremental cost-effectiveness ratio (ICER) being less than £20,000 per QALY gained. Of the one-way sensitivity analyses presented, the company reports the base case ICER estimate is most sensitive to the costs of hospital admissions, occupational therapy, district nurse, physiotherapy and neuro-rehabilitation specialists for patients with the most severe categories of spasticity (scoring 8–10 on the spasticity NRS). None of the sensitivity analyses presented by the company explored the assumed efficacy of Sativex® and SoC (i.e. the proportion of patients in each health state based on treatment received) or the assumed daily dose of Sativex®.

Results of initial scenario analyses presented by the company are provided in Table 3. The key plausibility considerations of the base case analysis remain applicable to all of those scenario analyses.

As the base case model includes four weeks of Sativex® benefits and costs for the SoC alone arm, and assumes a lower number of Sativex® dose sprays per day than observed in the GWSP0604 trial, the company has subsequently provided supplementary analyses to explore the impact of removal of Sativex® use from the SoC alone arm, and alternative Sativex® dosing assumptions. In these analyses, Sativex® plus SoC dominates SoC alone (i.e. is less costly and more effective) at daily doses observed in the GWSP0604 trial using a 30-year time horizon of analysis.

The company has also provided supplementary analyses to explore the combined impact of a shorter time horizon of analysis of five years together with the inclusion of home care visits in the model, and a range of alternative Sativex® dose assumptions that span the doses observed in the GWSP0604 trial (but retaining the assumption of Sativex® costs and benefits for the first four weeks in the SoC alone arm). In each of these analyses, the inclusion of home care costs outweigh the additional costs of Sativex® to the extent that Sativex® plus SoC dominates SoC alone(i.e. Sativex® plus SoC is less costly and more effective than SoC alone).

Table 3. Initial scenario analyses (over 30-year time horizon).

Scenario Description	Scenario details	Incremental cost per QALY	Plausibility considerations
Inclusion of carer costs	As base case but with inclusion of home carer costs; estimates based on expert survey	Sativex® dominant over SoC (cost saving of £33,609 and gain of 0.35 QALYs)	Incorporation of home carer costs may be relevant if these are considered to fall into the category of NHS and Personal Social Services costs. This result is driven by the extrapolation of 16-week data over 30 years, which leads to a higher proportion of patients on SoC modelled to require home care visits over time.
Exclusion of equipment costs	As base case but with exclusion of equipment costs	£11,929 (Additional cost of £4,202 and gain of 0.35 QALYs)	Demonstrates that equipment cost offsets are not a major driver of the base case analysis.
Exclusion of spasticity worsening	As base case but with removal of assumption spasticity worsens in all patients over time	£6,829 (Additional cost of £3,336 and gain of 0.49 QALYs)	Seems plausible that patients would deteriorate over time, although MS can relapse and remit over time. It is unclear whether this or the base case analysis approach is most plausible, because the base case analysis would mean that at 30 years, 30% of the cohort has died and 86% of the remaining patients have the most severe levels of spasticity possible, which seems unlikely
Discontinuation of Sativex® to same health state	As base case but assumes that when patients discontinue Sativex® they maintain the treatment benefit they had received	£4,364 (Additional cost of £2,019 and gain of 0.46 QALYs)	This scenario would appear to bias the analyses in favour of Sativex®. Trial data demonstrate that patients who responded to Sativex® deteriorated when it was discontinued. Assumption of base case analysis would seem more plausible in this regard.
Discount rates sensitivity	As base case but with discount rate on costs and benefits varied together in range 0%–6% per annum	£10,665–£11,051	Model is not sensitive to assumed discount rate.

MS: multiple sclerosis; QALY: quality-adjusted life-year; SoC: standard of care.

4.1.3 AWTTC critique

The base case model compares Sativex® plus SoC against Sativex® plus SoC for four weeks followed by SoC alone, and therefore does not reflect the decision problem. Supplementary analyses that exclude the benefits and costs of four weeks of Sativex® from the SoC alone arm estimate that the addition of Sativex® to SoC is both more effective and less costly than SoC alone over a 30-year time horizon at the doses observed in the key phase III trial. However, these analyses rely on unadjusted indirect comparison of the Sativex® data from the GWSP0604 trial and observational registry data.

The base case analysis extrapolates short-term data over a 30-year time horizon. It also excludes the costs of home care visits, which may be relevant to include from the perspective of NHS and Personal Social Services. In scenario analyses incorporating home care visit costs, the addition of Sativex® to SoC is estimated to be more effective than SoC alone and to reduce overall costs over 5- and 30-year time horizons of analysis.

Key limitations and uncertainties of the economic evidence include:

- The data used in the base case model to derive the proportion of SoC-treated patients in each of the spasticity-related health states was based on the placebo arm data from the GWSP0604 trial. This would not reflect patients' experience with SoC alone. There are no trial data to directly compare the addition of Sativex® to SoC with SoC alone. The supplementary analyses provided by the company explore removal of the impact of Sativex® from the SoC alone arm, but rely on simple, unadjusted, indirect comparison of the Sativex® data from the GWSP0604 trial and Spanish observational data. The applicant company has noted the limitations of this approach.
- Categorisation of patients into spasticity-defined health states has been conducted via post hoc analyses (data on file; not verified), which may result in numeric differences by chance. The impact of small differences in actual spasticity NRS scores may become magnified by such categorisations, particularly when there are assumed large differences in outcomes and costs associated with neighbouring health state categories. [Commercial in confidence data removed] No sensitivity or scenario analyses have been conducted around the trial-derived proportion of patients assumed to be in each health state on Sativex® or the observational data providing longer-term transition probabilities for both the Sativex® plus SoC and the SoC alone arms of the model.
- There are limited data on the longer-term efficacy of Sativex®; however, the modelled treatment effect of Sativex® observed from 16-week trial data is extrapolated across a 30-year time horizon. As there are no differential mortality effects between Sativex® and SoC, and data with ᵂhich to robustly model long-term outcomes are lacking, a short-time horizon of analysis may be justified. Reducing the time horizon of analysis to five years (as used in previous cost-effectiveness analyses of Sativex®[22–24]) increased the base case ICER to £22,500 per QALY gained. However, this excluded the costs of home care visits. When home care visits are incorporated, Sativex® dominates SoC alone over a five-year year time horizon.
- The base case model assumed that patients would use a mean of [commercial in confidence data removed] sprays of Sativex® per day throughout treatment, reportedly based on that observed in a UK/German registry study (not verified). However, the GWSP0604 trial on which the Sativex® data in the model are based used a dose escalation guide to titrate doses until optimum symptom relief (with total daily doses as per the schedule in the SPC[2]), and the mean number of doses in the first four-week enrichment phase was 6.9 sprays per day, and in the randomised phase was 8.3 sprays per day[16]. At seemingly plausible daily doses in the range 6.9–8.3 sprays, all else being equal to the

base case scenario, the ICER over a 30-year time horizon ranges from £19,000 to £26,000 per QALY gained. At those doses, over a shorter time horizon of five years the ICERs ranged from £35,600 to £45,500 per QALY gained. However, when home care visits are incorporated, Sativex® is estimated to dominate SoC alone over 5- and 30-year time horizons at the trial-observed doses of Sativex®.

- The company has not provided any analyses over a five-year time horizon that exclude the impact of Sativex® from the SoC alone arm; however, AWTTC analyses using the company's model estimate the ICER to remain below £10,000 per QALY gained at trial-observed Sativex® doses, excluding the costs of home care visits. This is subject to uncertainty due to the lack of direct comparative data for Sativex® and SoC alone.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified one fully published CUA of Sativex® conducted from the perspective of the UK NHS[22]. Two other published analyses were also identified, conducted from the perspective of German and Spanish health care systems.

4.2.1 UK Study

The study conducted from the UK NHS perspective adopts a simpler modelling approach than the other published analyses and that utilised by the applicant company[22]. A Markov model is used, based on three health states: response to treatment (defined as at least a 20% reduction in spasticity NRS scores); non-response; and death. A 28-day model cycle was adopted. Transition probabilities for Sativex®-treated patients were based on withdrawals over the first 16 weeks observed in the key GWSP0604 trial. For SoC, no patients were modelled to experience improvements in response. To extrapolate treatment effects beyond the 16-week period, it was assumed that no further withdrawals occurred over time. No worsening of spasticity states over time was included[22].

Utility values were based on the EQ-5D data observed in the GWSP0604 trial for those responding to treatment and those who were unresponsive. Costs included in the model were those associated with drug acquisition and administration, and patient monitoring. As there were no published data available on the subsequent frequency of clinic visits over time for patients using Sativex® or SoC, and no predictable difference in the long-term pattern of clinic visits for patients receiving either treatment, it was assumed both would require the same six-monthly clinic visits. No other resource use associated with other health care professional contacts, equipment or personal social services was considered. Sativex® was assumed to be dosed at 6.9 sprays per day in cycle 1 and 8.3 sprays per day in all other cycles, as observed in the GWSP0604 trial. A five-year time horizon of analysis was adopted, as this was felt sufficiently long to capture the differences between the two patient cohorts given that no mortality advantage is suggested for Sativex® and follow-up data are limited[22].

In the base case model, the ICER for Sativex® plus SoC versus SoC alone was estimated to be £49,257 per QALY gained, based on (discounted) additional costs of £7,627 and a gain of 0.15 QALYs over five years. A wide range of sensitivity and scenario analyses were conducted to explore key source of uncertainty, including alternative response rates, withdrawal rates and assumed number of daily Sativex® doses. Probabilistic sensitivity analysis estimated the probability of the ICER being less than £30,000 per QALY to be 10.2%[22].

4.2.2 German and Spanish Studies

The German and Spanish studies were commissioned by the applicant company[24]. The model employed a similar approach to that in the company's submission, by categorising the trial-based spasticity NRS scores into distinct spasticity-related health

states. However, only three health states were defined (mild, moderate, and severe spasticity). Transition probabilities for Sativex® treatment were based on the same GWSP0604 trial data as in the company's model for cycles 1 to 4. Sativex® patients were assumed to stay at the same severity level they reached by cycle 4 unless they discontinued Sativex® treatment, in which case deterioration of their condition was based on data from a Spanish observational study. Transition probabilities for SoC were based on the Spanish observational study throughout. Utility values were based on the GWSP0604 trial EQ-5D data and resource use associated with each health state was based on the expert opinion of eight neurologists from each country, and included drugs, monitoring, home care costs and a range health professional visits. Sativex® dosing was assumed to be 6.9 sprays per day in cycle 1 and 8.3 sprays per day in cycles 2-4, as observed in the GWSP0604 trial. However, beyond this a linear decline in dosing over 1.2 years, to 4.2 sprays per day was assumed, reportedly based on company data on file. A five-year time horizon of analysis was adopted[24].

In the German analysis, the base case ICER Sativex® plus SoC versus SoC alone was estimated to be €11,214 per QALY gained, and in the Spanish analysis, Sativex® plus SoC was more effective and resulted in lower overall costs than SOC alone. A wide range of sensitivity and scenario analyses were conducted, but no probabilistic sensitivity analyses were reported[24].

4.2.3 Summary of published evidence on cost-effectiveness

Of the published studies, the UK-based study would seem most relevant, although it is also the most simplistic. It does not consider the wider costs associated with different levels of spasticity severity, which would appear to be a limitation. However, the pragmatic approach adopted also reduces some of the uncertainty that is associated with the company's approach to modelling, such as the use of potentially disparate sources of efficacy estimates from observational studies conducted in different health settings, and extrapolations of short-term data over a very long-time period. All published studies consistently adopted a five-year time horizon, in contrast to the 30-year time horizon adopted in the company's model.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a recent General Practice Research Database study, the prevalence of MS in the UK was 203.4 per 100,000 and incidence 9.64 per 100,000/year between 1990 and 2010[25]. Based on a registry of over 20,000 MS patients in the USA, it is estimated that 17.2% have moderate spasticity and 16.8% have severe spasticity, and that 34.6% and 45.9% of these, respectively, use two or more oral drugs to treat spasticity[8]. The company assumes that 50% of these patients are inadequately controlled with their current combination treatment and so would be eligible for a four-week trial of Sativex®.

The company anticipates uptake rates of 15% in year 1, 18% in year 2, 25% in year 3, 35% in year 4 and 50% in year 5. The company uses its economic model to determine the discontinuation and death rates, and hence the number of patients treated, in each of years 1 to 5. Resource use and costs for these patients in each year, as modelled for the base case cost-effectiveness analysis, are also derived from the economic model.

5.1.2 Results

Table 4 presents the base case net uptake and cost estimates provided by the company. Sativex® is estimated to increase costs by around £84,000 in year 1, rising

to £1 million in year 5 (based on discounted costs, excluding home care visit cost estimates).

Table 4. Company base case budget impact estimates.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	452	473	493	514	535
Uptake (%)	15%	18%	25%	35%	50%
Number of patients treated at start of year	68	85	123	180	268
Net costs					
Sativex acquisition cost	£104,523	£261,374	£496,528	£843,336	£1,358,937
Primary care community based visits plus outpatient clinic visits)	−£16,817	−£47,943	−£94,935	−£162,793	−£260,402
Secondary & tertiary care	−£3,842	−£11,101	−£22,263	−£38,580	−£62,221
Personal social services	not included in base case				
Overall net cost	**£83,865**	**£202,330**	**£379,330**	**£641,963**	**£1,036,314**

The base case estimates exclude consideration of home care visit costs. Table 5 presents the results of an alternative scenario including home care visit costs, as modelled in the alternative cost-effectiveness scenario analysis. In this scenario analysis, Sativex® acquisition costs are more than offset by the large modelled savings in home care visits.

Table 5. Company budget impact estimates including home carer visit costs.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	452	473	493	514	535
Uptake (%)	15%	18%	25%	35%	50%
Number of patients treated at start of year	68	85	123	180	268
Net costs					
Sativex acquisition cost	£104,523	£261,374	£496,528	£843,336	£1,358,937
Primary care (community based visits plus outpatient clinic visits)	−£16,817	−£47,943	−£94,935	−£162,793	−£260,402
Secondary & tertiary care	−£3,842	−£11,101	−£22,263	−£38,580	−£62,221
Personal social services	−£124,336	−£357,423	−£713,736	−£1,232,610	−£1,982,632
Overall net cost	**−£40,471**	**−£155,093**	**−£334,405**	**−£590,647**	**−£946,318**

5.1.3 AWTTC critique

- Estimates of the inclidence and prevalence of MS vary. The company has provided analyses based on recent estimates from the UK up to 2010.
- The number of eligible patients and all cost estimates used in the budget impact analysis are derived from the economic model. The limitations and uncertainties of the economic analysis outlined in Section 4 therefore feed through to the budget impact estimates that have been provided.

5.2 Comparative unit costs

Sativex® is used as an add-on to SoC. There are no comparators. The current list price is £375 for three bottles[26], each of which contains 90 sprays. The number of daily sprays required per patient varies on an individual basis. The company reports the median dose in clinical trials to be 8 per day, which would cost around £4,056 per year.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, delta-9-tetrahydrocannabinol/ cannabidiol (Sativex®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 24 February 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Modified Ashworth scale (MAS)

MAS is an assessor-reported rating of the resistance to passive movements of a joint using a scale of one to five[4,27]. During study GWSP0604, all 20 muscle groups were assessed for spasticity using the scale, wherein one was equivalent to no increase in muscle tone and five is equivalent to passive movement is difficult and affected part is rigid in flexion or extension. The score for all 20 muscle groups were added to give a total score out of 100; minimum score was 20. A decrease in score indicates an improvement in condition[27].

Sleep disruption numeric rating scale (NRS)

The sleep disruption NRS is a self-reported 11-point assessment of sleep disruption, where patients evaluate, on a scale of zero to ten, the level of sleep disruption due to spasticity in the previous night, where zero is equivalent to no sleep disruption and ten is equivalent to completely disruption[27].

Spasticity numeric rating scale (NRS)

The spasticity NRS is a self-reported 11-point assessment of perceived spasticity, where patients evaluate, on a scale of zero to ten, the average level of their spasticity over the last 24 hours, where zero is equivalent to no spasticity and ten is equivalent to worst possible spasticity[28]. One published validation of the spasticity NRS, established that a reduction of approximately 30% constituted a clinically important difference (the level of change in an outcome scale that corresponds to the patient's determination of being much improved), while a decrease of 18% represented a minimally improved change or better.

Time to treatment failure

Treatment failure was defined in Study GWSP0702 as: the cessation of randomised treatment before end of study; a worsening of spasticity (i.e. an increase in mean spasticity NRS score of at least 20% over the last seven days of the treatment period and at least one unit from the treatment baseline); or a clinically relevant increase in or addition to anti-spasticity medicines or disease-modifying medications after randomisation. The time to treatment failure was calculated as the number of days from the first day of randomised treatment to the first day of treatment failure[18].

REFERENCES

1 Bayer Healthcare Pharmaceuticals. Form B: Detailed appraisal submission. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®). Apr 2014.

2 GW Pharma Ltd. Sativex®. Summary of Product Characteristics. Mar 2014. Available at: http://www.medicines.org.uk/emc/medicine/23262/SPC/Sativex+Oromucosal+Spray/. Accessed Mar 2014.

3 National Institute for Health and Clinical Excellence. Clinical Guideline in development. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Final scope. Aug 2012. Available at: http://www.nice.org.uk/nicemedia/live/13595/60372/60372.pdf. Accessed Mar 2014.

4 The MS Trust. Multiple sclerosis information for health and social care professionals. Nov 2011. Available at: http://www.mstrust.org.uk/downloads/ms-info-health-professionals.pdf. Accessed Apr 2014.

5 Kingwell E, Marriott JJ, Jette N et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol* 2013; 13: 128.

6 Hirst C, Ingram G, Pickersgill T et al. Increasing prevalence and incidence of multiple sclerosis in South East Wales. *J Neurol Neurosurg Psychiatry* 2009; 80 (4): 386-91.

7 Swingler RJ, Compston DA. The prevalence of multiple sclerosis in south east Wales. *J Neurol Neurosurg Psychiatry* 1988; 51 (12): 1520-4.

8 Rizzo MA, Hadjimichael OC, Preiningerova J et al. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult Scler* 2004; 10 (5): 589-95.

9 National Collaborating Centre for Chronic Conditions. CG8 Multiple sclerosis: full guideline. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Nov 2003. Available at: http://www.nice.org.uk/nicemedia/live/10930/46699/46699.pdf. Accessed Mar 2014.

10 Flachenecker P, Henze T, Zettl UK. Spasticity in patients with multiple sclerosis - clinical characteristics, treatment and quality of life. *Acta Neurol Scand* 2014; 129 (3): 154-62.

11 National Institute for Health and Care Excellence. Clinical Guideline 8. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Nov 2003. Available at: http://guidance.nice.org.uk/CG8. Accessed Mar 2014.

12 Leussink VI, Husseini L, Warnke C et al. Symptomatic therapy in multiple sclerosis: the role of cannabinoids in treating spasticity. *Ther Adv Neurol Disord* 2012; 5 (5): 255-66.

13 National Institute for Health and Care Excellence. Neurological conditions overview. Mar 2014. Available at: http://pathways.nice.org.uk/pathways/neurological-conditions. Accessed Mar 2014.

14 Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy et al. Spasticity in adults: management using botulinum toxin. National guidelines. Jan 2009. Available at: http://www.rcplondon.ac.uk/sites/default/files/documents/spasticity-in-adults-management-botulinum-toxin.pdf. Accessed Mar 2014.

15 National Institute for Health and Care Excellence. Clinical Guideline in development. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Apr 2014. Available at: http://guidance.nice.org.uk/CG/WaveR/115. Accessed May 2014.

16 Novotna A, Mares J, Ratcliffe S et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as

add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011; 18 (9): 1122-31.
17 Medicines and Healthcare Products Regulatory Agency. Public Assessment Report. Decentralised Procedure. Sativex® oromucosal spray. UK/H/2462/001/DC. May 2010. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf. Accessed Mar 2014.
18 Notcutt W, Langford R, Davies P et al. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). *Mult Scler* 2012; 18 (2): 219-28.
19 Barnes MP, Kent RM, Semlyen JK et al. Spasticity in multiple sclerosis. *Neurorehabil Neural Repair* 2003; 17 (1): 66-70.
20 Wright S, Vachova MM, Novakova I. The effect of long-term treatment with a prescription cannabis-based THC:CBD oromucosal spray on cognitive function and mood: a 12 month double blind placebo-controlled study in people with spasticity due to multiple sclerosis. Presented at 29th Congress of the European Committee for Research and Treatment in Multiple Sclerosis (ECTRIMS) and the 18th Annual Conference of Rehabilitation in MS (RIMS). 4 Oct 2013.
21 Arroyo R, Vila C, Clissold S. Retrospective observational study of the management of multiple sclerosis patients with resistant spasticity in Spain: the '5E' study. *Expert Rev Pharmacoecon Outcomes Res* 2011; 11 (2): 205-13.
22 Lu L, Pearce H, Roome C et al. Cost effectiveness of oromucosal cannabis-based medicine (Sativex®) for spasticity in multiple sclerosis. *Pharmacoeconomics* 2012; 30 (12): 1157-71.
23 Flachenecker P. A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany. *Expert Rev Neurother* 2013; 13 (3 Suppl 1): 15-9.
24 Slof J, Gras A. Sativex® in multiple sclerosis spasticity: a cost-effectiveness model. *Expert Rev Pharmacoecon Outcomes Res* 2012; 12 (4): 525-38.
25 Mackenzie IS, Morant SV, Bloomfield GA et al. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry* 2014; 85 (1): 76-84.
26 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed Apr 2014.
27 GW Pharma Ltd. NCT00681538. A study of the safety and effectiveness of Sativex®, for the relief of symptoms of spasticity in subjects, from phase B, with multiple sclerosis (MS). Jun 2013. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00681538. Accessed May 2014.
28 Farrar JT, Troxel AB, Stott C et al. Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2008; 30 (5): 974-85.