REPORT ON THE EVALUATION OF THE PRECLINICAL AND CLINICAL DATA OF A NEW MEDICINE APPLICATION UNDER SECTION 21

ASSESSOR:	[redacted]
COMPOUND:	Cannabis extracts (delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
PRODUCT:	Sativex
MEDSAFE FILE No:	TT50-8053
DOSE FORM:	Buccal spray
STRENGTH:	27 mg/ml delta-9-tetrahydrocannabinol 25 mg/ml cannabidiol
INDICATION:	Relief of neuropathic pain in multiple sclerosis Relief of spasticity in multiple sclerosis (MS) Relief of pain in cancer

A New Medicine Application was considered on 18th March 2008, but the Committee found there were insufficient data to recommend approval. The application was reconsidered on 29th July 2008, but again the Committee did not recommend approval due to insufficient data. A new submission was made to Medsafe in June 2009 and the current report is an evaluation of new data contained in this submission.

I. New data in support of the indication of relief of spasticity in multiple sclerosis.

Background.

The original submission included the results of three randomised, placebo-controlled trials in support of this indication. In GWMS0001 there was a non-significant trend towards benefit from Sativex ($p = 0.062$), but in the 39 patients in whom spasticity was the primary symptom, the results were highly statistically significantly in favour of Sativex ($p = 0.001$). There were two pivotal Phase III placebo-controlled trials. In one (GWMS0106) there was a marginally significant benefit for Sativex over placebo ($p = 0.048$), but there was no statistically significant difference between Sativex and placebo in the second pivotal trial. When the results for the intention-to-treat populations of the three Phase III trials (GWMS0001, GWMS0106 and GWCL0403) were pooled (666 patients), the difference between Sativex and placebo in the Numeric Rating Scale (NRS) at the study end was –0.32, 95% CI –0.61, -0.04, $p = 0.027$. The proportion of 30% responders at the study end was 37% for Sativex and 26% for placebo; OR 1.62; 95% CI 1.15, 2.28, $p = 0.0073$.

The study reports of two recently completed studies are provided in the current submission.

GWSP0604.

This was a two-phase, Phase 3 study of the safety and efficacy of Sativex in the relief of spasticity in subjects with MS and moderate or severe spasticity (NRS ≥ 4) not adequately relieved by current treatment. The maximal dose was 12 actuations per 24 hours. The study was designed to identify those subjects who responded to Sativex and then randomise these subjects to active drug or placebo in a parallel group design. The first phase (Phase A) was a single-blind, 4-week treatment period. Subjects who had a ≥ 20% reduction in the mean 0-10 point NRS spasticity score between screening and the 4-week endpoint were eligible for Phase B. Subjects did not know that this transition was happening, or that there might be a change in treatment at this point. Phase B was a 12-week double blind, randomised, placebo-controlled, parallel group study. The primary efficacy endpoint was the change in the mean NRS score from baseline to the end of treatment. Secondary endpoints in Phase B included the percentage of ≥ 30% and ≥ 50% responders.

572 subjects entered Phase A. Of these, 241 were randomised into Phase B, 124 in the Sativex group and 117 in the placebo group. The other 331 (58%) subjects were not eligible to enter Phase B. Of these, 300 subjects did not achieve the 20% level of improvement in spasticity and were classed as non-responders. One-half of the non-responders achieved < 5% level of improvement in spasticity. Other reasons for not entering Phase B were an adverse event (5%), withdrawal of consent (2%) and lack of efficacy (1%).

In Phase B, the adjusted mean reduction in the NRS score for Sativex was 0.04 points, compared with an increase of 0.81 points for placebo; adjusted mean difference -0.84 points (95% CI: -1.29 to -0.40) in favour of Sativex, p = 0.0002. 92 subjects (74%) in Phase B who received Sativex were 30% responders compared with 60 subjects (51%) on placebo; odds ratio 2.73 (95% CI: 1.59, 4.69; p = 0.0003). 56 subjects (45%) who received Sativex were 50% responders compared with 39 subjects (33%) on placebo; odds ratio 1.65 (95% CI: 0.98, 2.78; p = 0.061). Several other secondary endpoints showed a significant difference in favour of Sativex, but the treatment differences for the Modified Ashworth Scale (p = 0.094), the timed 10-metre walk (p = 0.069) and the Carer Global Impression of Change (CGIC) for ease of transfer (p = 0.061) showed non-significant trends in favour of Sativex. The adjusted mean change from baseline in the 10 metre walk test showed a decrease of 0.13s from a mean baseline of 24.5s in the Sativex group compared to an increase of 3.22s from a baseline of 25.3s for placebo. The estimated treatment difference of an improvement in the 10 metre walk was 3.34s (95% CI: -6.95, 0.26) in favour of Sativex (p = 0.069).

The most prevalent treatment-emergent adverse events (AEs) in Phase A were dizziness (14%), fatigue (5.9%), somnolence (5.1%), dry mouth, (4.2%), nausea (4.0%) and vertigo (3.7%). 20 subjects (3.5%) experiencing severe adverse events (SAEs). One subject experienced a treatment-related SAE (muscular weakness, lethargy, mood altered and somnolence). The most prevalent treatment-emergent AEs for Sativex in Phase B were vertigo (6%), dry mouth (3%), somnolence (3%) and euphoric mood (3%). Most of the AEs were mild to moderate in severity, but there were twice as many SAEs in the Sativex group (5.6%) compared with the placebo group (2.6%). One subject, in the Sativex group, experienced a treatment-related SAE (suicidal ideation). There were two deaths, both in the Sativex group (urosepsis and bronchopneumonia), but neither event was considered to be treatment-related. Nine subjects (7%), all in the Sativex group, stopped study medication due to AEs. There were no differences in changes in mood between the groups, as assessed by the Beck Depression Inventory-II. No differences in suicidal ideation were seen between Sativex and placebo.

Comment on GWSP0604. This study was designed so that only patients who showed >20% improvement with Sativex were entered into the randomised, controlled phase. The majority of the subjects enrolled in Phase A did not show a response to Sativex. The trial was designed this way to make it similar to clinical practice, where treatment is continued only in responders. The randomised phase of the trial showed a statistically significant deterioration in various measures of spasticity in the group randomised to treatment withdrawal. This difference between the Sativex and the placebo groups might be explained by unintentional unblinding of the subjects, but the company has refuted this argument in a previous submission.

GWSP0702

This was a 5-week (1-week baseline, 4-week randomised treatment period), placebo-controlled, parallel group, randomised withdrawal study to evaluate the maintenance of effect of Sativex in patients who had been receiving long term benefit from Sativex. At the end of the baseline period, subjects stopped open label treatment with Sativex and were randomised to receive either Sativex or placebo. The primary endpoint was the time to treatment failure in the randomised withdrawal period. Treatment failure was defined as cessation of treatment, worsening spasticity (≥ 20% increase in NRS), or an increase in anti-spasticity medication or disease modifying treatment. Originally it was planned to recruit 60 subjects, but because of difficulty recruiting this number, the study was closed after 36 subjects had been recruited.

36 subjects entered the randomised withdrawal phase with 18 in each treatment group. At the end of the 4-week randomised withdrawal phase, 17 subjects (94%) from the placebo group failed treatment (worsening of NRS in 11 and cessation of study medication in 6) compared with 8 subjects (44%) in the Sativex group (all due to worsening of NRS). The difference in time to treatment failure between the two groups was statistically significant in favour of Sativex (OR = 0.335, 90% CI: 0.162, 0.691; p = 0.013). For the Sativex group, the adjusted mean spasticity NRS increased (deteriorated) 1.00 point from a baseline of 3.60 points, compared with an increase of 1.21 points from a baseline of 4.13

points for placebo; treatment difference -0.21 points (90% CI: -1.22, 0.79 points) in favour of Sativex (p = 0.720). For the Sativex group, the adjusted mean change in the Modified Ashworth Scale was 1.11 points (baseline 23.2 points) compared with a change of 1.64 points for the placebo group (mean baseline score 23.0 points). The estimated treatment difference of 0.53 points (90% CI: -4.68, 5.74 points) in favour of the placebo group was not statistically significant (p = 0.862). (Note that this analysis included only 8 subjects in the placebo arm compared with 17 in the Sativex arm, because a number of the subjects who withdrew early from the study restarted their own Sativex before the assessment was done). The difference between Sativex and placebo was significant for the SGIC (p = 0.017) and the CGIC (functional ability) (p = 0.001). Subjects, who were receiving Sativex, experienced a deterioration in the adjusted mean walk time of 3.46 seconds (baseline 40.1 seconds) compared with a deterioration of 5.24 seconds (baseline 24.1 seconds) for subjects receiving placebo; estimated treatment difference 1.78 seconds (90% CI: -14.52, 10.96 seconds) in favour of Sativex (p = 0.808).

No new significant safety issues were raised. There was no evidence of a withdrawal syndrome in subjects randomised to receive placebo.

Comment on GWSP0702: There was a statistically significant benefit in favour of Sativex for the primary endpoint. Several secondary endpoints did not show a significant difference between the groups, but the interpretation was complicated by the premature termination of the trial and the small numbers of subjects for some of the endpoints.

Clinical Overview. A clinical overview written by [redacted] from the Walkergate Park International Centre for NeuroRehabilitation, Newcastle upon Tyne, is provided.

Overall comment on Sativex for this indication. The results of the two new studies provide some further support of efficacy for this indication. However, although these two studies were randomised, they both were randomised withdrawal studies in subjects who already had shown a beneficial response to Sativex.

II. New data in support of the indication of relief of neuropathic pain in MS

Background.
Originally the results of 3 randomised, placebo-controlled trials were presented in support of this indication. In one of these studies (GWMS0107) there was a statistically significant benefit in short-term pain relief compared with placebo, but in the other two trials (GWMS0001 and GWMS0105) there was only a non-significant trend towards benefit from Sativex. A summary of the results of a new study GWMS0501 was provided with an earlier submission. The full study report has been provided with this submission.

GWMS0501
This was a double-blind, randomised, placebo-controlled, parallel group study of Sativex when added to existing treatment, in the relief of central neuropathic pain in subjects with MS. Subjects were randomised to receive Sativex or placebo for 14 weeks. Subjects were

instructed to titrate the dose according to efficacy and tolerability up to a maximum of 24 does per day. After the study had been started it was decided this dosing schedule might discriminate against Sativex, because the placebo patients were using about twice as many doses. The primary efficacy measure was the proportion of subjects showing an improvement of ≥ 30% in their mean pain NRS score from baseline to the primary endpoint. 167 subjects were randomised to Sativex and 172 to placebo. The proportion of 30% responders was 50% in the Sativex group vs. 45% in the placebo group ($p = 0.24$). The adjusted mean change in the NRS pain score was 1.93 in the Sativex group vs. 1.76 in the placebo group ($p = 0.47$). When patient responses were compared at similar doses, the results were significantly in favour of Sativex except at doses > 12 per day. A disproportionate number of placebo patients responded at high doses.

Treatment-emergent (all-causality) AEs were reported by 120 subjects (72%) receiving Sativex and 106 subjects (62%) receiving placebo. Treatment-related AEs were reported in 99 subjects (59%) in the Sativex group and in 68 (40%) of subjects in the placebo group. In the double-blind phase, the most commonly reported treatment-related AEs were dizziness (34 subjects [20%] in the Sativex arm vs. 7 subjects [4%] in the placebo arm), somnolence (16 subjects [10%] Sativex vs. 3 [2%] placebo), headache (7 subjects [4%] Sativex vs. 6 [3%] placebo), nausea (13 subjects [8%] Sativex vs.7 [4%] placebo), dry mouth (12 subjects [7%] Sativex vs. 10 [6%] placebo), diarrhoea (7 subjects [4%] Sativex vs. 5 [3%] placebo), fatigue (16 [10%] Sativex vs. 9 [5%] placebo) and vertigo (15 [9%] Sativex vs. 6 [3%] placebo). In the psychiatric disorders, the most commonly reported treatment-related AEs amongst subjects on Sativex were anxiety and disorientation, each occurring in 3 subjects. In the double-blind phase 16 subjects experienced SAEs, eight (5%) in each arm of the study.

Upon completion of the first part of this study, French and Czech subjects could choose to enter a 14 week open-label treatment period, followed by a 4-week randomised-withdrawal-phase. Eligible subjects were randomised to receive either Sativex or placebo in a double-blind manner for up to 28 days. 53 subjects took part in the open label treatment and 42 were randomised to the withdrawal phase: 21 to Sativex and 21 to placebo. There was deterioration in the pain score in the placebo group (baseline 3.75, end of study 4.51) and a slight improvement in the Sativex group (baseline 3.83 vs. end of study 3.72) ($p = 0.028$).

Comment on GWMS0501. This new study does not provide much support for this indication, because there was no significant difference between Sativex and placebo for the primary efficacy endpoint and the secondary endpoints.

Overall Summary.

Overall, there is some evidence that Sativex improves spasticity in a subset of patients with MS, but of the two pivotal Phase III placebo-controlled trials, one showed a marginally significant benefit for Sativex over placebo ($p = 0.048$) and in the other there was no statistically significant difference between Sativex and placebo. When the results for the intention-to-treat populations of the three Phase III trials (GWMS0001, GWMS0106 and GWCL0403) were pooled, the difference between Sativex and placebo

in the NRS at the study end was -0.32, 95% CI -0.61, -0.04, p = 0.027. The proportion of 30% responders at the study end was 37% for Sativex and 26% for placebo; OR 1.62; 95% CI 1.15, 2.28, p = 0.0073. The two new studies are randomised withdrawal studies in subjects who had already shown a beneficial response to Sativex provide some further support for this indication, but there is insufficient evidence to recommend approval. GW Pharma is seeking approval under Section 23, but it is not clear if there is sufficient unmet need for approval under Section 23.

The new study presented in support of the indication of neuropathic pain in MS does not provide much support for this indication. There is insufficient evidence to recommend approval for this indication.

No new data has been presented to support the third requested indication of relief of pain in cancer.