MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC)
REPORT ON THE EVALUATION OF THE PRECLINICAL AND CLINICAL DATA OF A NEW MEDICINE APPLICATION

ASSESSOR:	[redacted]
COMPOUND:	Cannabis extracts (Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
PRODUCT:	Sativex
MEDSAFE FILE No.:	TT50-8053
FORMULATION:	Buccal spray
STRENGTH:	27 mg/ml THC and 25 mg/ml CBD
PROPOSED INDICATIONS:	Relief of neuropathic pain in multiple sclerosis Relief of spasticity in multiple sclerosis Relief of pain in cancer
DOSAGE:	Self-titration

BACKGROUND:

The Committee first considered a new medicine application for Sativex on 18th March 2008. The company was seeking approval under Section 23. The Committee found there were insufficient data to recommend approval. The following information was requested:

1. Part I data
2. Further and more robust evidence of efficacy in spasticity and cancer pain
3. Further information on the neuropsychiatric profile and cognitive function

The application was reconsidered on 29th July 2008. In their response the company addressed the following issues

1. Maintenance of blinding. They cited an independent statistician's [redacted]) report, which found no evidence that blinding was seriously compromised. The statistician's report was not included with the resubmission.

2. Validity of the Numeric Rating Scale (NRS) in the assessment of spasticity. The company's response made valid points about the drawbacks of the "traditional" Ashworth Scale. However, in a trial in which the subjects may have been unintentionally unblinded by adverse events, a more objective endpoint may have been more helpful.

3. The clinical relevance of the treatment effect in spasticity

The Committee did not recommend approval due to insufficient data and requested the following information:

1. Data from the ongoing studies. The company have given an undertaking they will provide data from ongoing studies as it becomes available, but stress that they are seeking approval under Section 23 and they believe further data is not required for Section 23 approval.

2. A full transcript of [redacted] report

CURRENT SUBMISSION
The Director of Regulatory Affairs for GW Pharmaceuticals deals with several issues:

Section 23. GW Pharma is seeking approval under Section 23. The company feels that the standards being applied to the assessment of this application are those that would be applied to a full application in a condition where there is no unmet need for the medication. The submission states that the original application was made because GW Pharma had been made aware by Medsafe that there was a particular need for a product such as Sativex in New Zealand. It says that an initiative had been taken by Medsafe to facilitate the supply of Sativex under Section 29.

The company believes there is an unmet medical need for Sativex. The company provides a supporting letter from [redacted] Medical Director of the Hibiscus Coast Hospice, Whangaparaoa. [redacted] strongest support is for the indication of relief of pain in cancer. There is a second letter of support from [redacted]

Comments. (1) [redacted] submission:. It is true that adequate treatment of cancer pain is difficult, but there are many other methods of treatment that can be used. In the original application, there was only one controlled randomised trial of Sativex in patients with cancer pain. There was a statistically significant benefit of Sativex over placebo for the primary endpoint (NRS pain score). There was no difference between groups in the reduction of the mean number of days that escape medication was used or the mean dose of escape medication. 43% of the patients on Sativex achieved a clinically relevant (30% improvement in pain) vs. 21% of patients on placebo (odds ratio 2.81; 95% CI 1.22-6.5). (2) [redacted] submission:. [redacted] is a stroke epidemiologist. His comments endorsing Sativex would have been made from his review of the trial data, rather than from the perspective of clinical practice.

Error in my report. In the summary section of my initial assessment (p.9) I incorrectly stated that the "interpretation of trial GWMS0107 was complicated by a large difference in the frequency of use of rescue medication in the two groups and the inclusion of patients with other causes of central neuropathic pain". The letter from GW Pharma correctly points out that these comments related to another study (GWPS0105), not GWMS0107 (see p.6-7).

Comment. This error in my summary does not alter the overall conclusion that for neuropathic pain in MS, one of three randomised placebo-controlled trials showed a statistically significant benefit in short term pain relief compared with placebo and the other two trials showed a non-significant trend towards benefit from Sativex.

Unblinding. There was concern that the high frequency of adverse events amongst subjects randomised to Sativex could have unblinded patients in the randomised placebo-controlled trials. In response, GW Pharma states it would be an especially high hurdle if the applicant was required to prove that an event was not possible. GW Pharma points out that [redacted] report was supplied with the initial documentation. However, it was not re-sent with the resubmission and the reviewers did not see it on that occasion. The report has been resubmitted with this application. There were two authors: [redacted], Principal Statistician, GW Pharma Ltd. and [redacted], Professor of Statistics in Medicine. The report concluded there was no statistical evidence of a relationship between efficacy and experience of one or more of three selected adverse events (dizziness, headache and somnolence). This suggested that even if subjects who experienced one or more of these adverse events were able to determine which treatment they were on, it did not lead to bias in the assessment of efficacy. They found no evidence that the change from baseline in spasticity was affected by prior use of cannabis. Even if prior cannabis users were able to distinguish between the treatments, this did not lead to bias in the assessment of efficacy. There was no evidence that prior cannabis users were able to identify which treatment they were receiving from experiencing an adverse event. The dose of the study drug did not differ between prior cannabis users and cannabis naïve subjects, which suggests prior use of study medication did not affect study drug dosing patterns and thus there was no evidence of unblinding. [redacted] and [redacted] point out that in GWMS0001 subjects reported subjective assessments of five symptoms (pain, spasticity, spasm, tremor and bladder problems), but spasticity was the only symptom for which Sativex showed evidence of efficacy. If subjects were not blinded to study treatment, it is unclear why their knowledge of treatment should result in bias for only one of these symptoms. [*Comment*: it should be noted, however, that there was a trend in favour of Sativex for the other symptoms, but the differences with placebo were not significant.] [redacted] concluded that there was no evidence that blinding was seriously compromised in the three studies and that if any subjects were unblinded, there was no evidence of any bias in the assessment of the treatment difference between Sativex and placebo for efficacy, adverse events, or study drug dosing.

Validity of the Numeric Rating Scale (NRS) in the assessment of spasticity.
I discussed this with the first resubmission. The points made about the drawbacks of the traditional Ashworth Scale were valid, but in trials in which the subjects may be unintentionally unblinded by adverse events, an objective endpoint may have been more helpful. GW Pharma argue there was no evidence unblinding affected the outcome (see above), it is "no longer scientifically tenable position to argue that the NRS is unsuitable". In the current submission, GW Pharma submit a paper (which has been accepted for publication in *Neuro-rehabilitation*), which has validated the use of the NRS in patients with spasticity due to MS. Another paper on the reliability of Ashworth scales in children with spastic cerebral palsy concluded these scales were unreliable.

Clinical relevance of the treatment effect. GW Pharma argue that the results of the completed studies have demonstrated "highly promising efficacy" in patients without alternative treatments available and therefore, should be approved under Section 23. The results from further trials are not yet available.

Neuropathic Pain in Multiple Sclerosis. The results of three randomised, placebo-controlled trials were originally presented in support of this indication. In one study (GWMS0107) there was a statistically significant benefit in pain relief compared with placebo and in the other two trials there was a non-significant trend towards benefit from Sativex.

In the first resubmission GW Pharma submitted a neurophysiological study of the RIII flexion reflex in a double-blind randomised cross-over study of Sativex vs. placebo in 18 patients with MS. It has been postulated that this reflex is a surrogate measure of the efficacy of treatment. GW Pharma argue that the findings of this study strongly support approval of Sativex for the treatment of neuropathic pain in patients with MS. They cite the European Federation of Neurological Societies' Guidelines for the Assessment of Neuropathic Pain, which state the "nociceptive reflex that is most used and appears to be most reliable in assessing treatment efficacy is the RIII flexion reflex". [*Comment.* Improvement in a surrogate measure does not necessarily translate into clinical efficacy.]

GWMS0501. GW Pharma has submitted the results of a new study of Sativex in support of the indication of neuropathic pain in MS. The Clinical Study Report has not been written, but the results are provided.

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. Patients were instructed to titrate the dose according to efficacy and tolerability up to a maximum of 24 doses per day. After the study had started it was decided that the dosing schedule might discriminate against Sativex, because the placebo patients were using about twice as many doses. The protocol was amended to reduce the maximum dose to 12 doses per day. The primary efficacy measure was the NRS (0-10). 167 subjects were randomised to Sativex and 172 to placebo. The primary efficacy analysis showed that 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.

The main study was followed by a 12-week open label treatment phase in which patients were then randomised either to continue Sativex or placebo. 53 patients 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 4.91) and a slight improvement in the Sativex group (baseline 3.83 vs. end of study 3.72) (p = 0.028). The majority of the deterioration in the NRS pain score occurred in the first week after randomisation.

GW Pharma argue that the neurophysiological study and the significant result from the randomised withdrawal study are sufficient to satisfy the requirements for Section 23 approval.

GW Pharma also submitted a Cochrane review of anti-spasticity agents for MS and a systematic review of treatment for spasticity and pain in MS

SUMMARY

Neuropathic Pain in Multiple Sclerosis. The original submission included three randomised, placebo-controlled trials in support of this indication. In one study (GWMS0107) there was a statistically significant benefit in pain relief compared with placebo and in the other two trials

there was a non-significant trend towards benefit from Sativex. The current submission includes the results of a new randomised, placebo-controlled trial. There was no significant difference between Sativex and placebo in the primary efficacy variable. GW Pharma attributed the negative finding to a defect in the trial design and an unexpectedly high placebo response. A randomised withdrawal study showed a statistically significant benefit for Sativex.. In a previous submission the results of a study using a neurophysiological test as a surrogate measure of efficacy were presented. There was a significant benefit from Sativex in this study.

Relief of pain in cancer

No new data has been presented to support this indication. One controlled randomised trial of Sativex in patients with cancer pain showed a statistically significant benefit of Sativex over placebo for the primary endpoint (NRS pain score). Further evidence of efficacy is needed for full approval for this indication and I doubt if the unmet need is great enough to warrant Section 23 approval.

Relief of spasticity in multiple sclerosis

No new data is presented in support of this indication. In the original submission one trial (GWMS0001) showed a non-significant trend towards benefit from Sativex. There were two pivotal Phase III placebo-controlled trials. In one, there was a marginally-significant benefit for Sativex over placebo ($p = 0.048$) and there was no statistically significant difference between Sativex and placebo in the second pivotal trial. When the results of these three studies were pooled, there was a significant benefit for Sativex over placebo.

RECOMMENDATION

The only new data presented with this submission was a randomised placebo-controlled trial in patients with MS and neuropathic pain; but there was no significant difference between Sativex and placebo. To determine the efficacy of Sativex, the results of further on-going studies are required.

OUTSTANDING ISSUE

Is there sufficient unmet need for Section 23 approval?