MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC) 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

This application was considered at the last meeting of the MAAC. The application was deferred pending a satisfactory response to the following:

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

Further data and more robust evidence of efficacy in spasticity and cancer pain
The response addresses various issues raised by assessors:

Maintenance of blinding. The high frequency of mild and moderate adverse events (AEs) may unblind patients receiving Sativex. Unblinding of the subjects in the pivotal trials may have distorted the results, because the primary efficacy endpoints were patient-reported. The company's response is that:

1. The frequency of dizziness is similar to that seen with other agents used for similar indications e.g. gabapentin, pregabalin.

2. There is no published evidence that subjects with a more marked AE profile report greater efficacy than those without.

3. An "independent statistician", [redacted], assessed whether the occurrence of AEs predicted efficacy in the three Phase 3 studies of Sativex in people with MS and spasticity[redacted] concluded there was no evidence of a relationship between treatment effect and the occurrence of one or more of the 3 most common AEs: dizziness, somnolence and headache. [redacted] found no evidence that blinding was seriously compromised. [redacted] report was not included in the submission.

4. The pharmacokinetics of THC administered as Sativex are different to those of THC administered as smoked cannabis.

Comment: Despite [redacted] *report, it is still possible AEs unblinded subjects in the pivotal trials. It would have been helpful if* [redacted] *full report had been included in the submission.*

The validity of the Numeric Rating Scale (NRS) in the assessment of spasticity.
The NRS is a subjective, patient-reported measure of spasticity. The company presents evidence that that the traditionally used Ashworth Scale is not an appropriate tool for assessing change in spasticity. The argument is made that the NRS for spasticity is similar to the numeric scales used to measure pain and quality of life. Several papers supporting the validity of the NRS were submitted. The NRS has been shown to correlate well with the Ashworth Scale, but the NRS had greater sensitivity to change. A letter from [redacted], Kings College, London advocates the use of the NRS for the assessment of spasticity in patients with MS.

Comment: The points made about the drawbacks of the Ashworth Scale are valid, but in a trial in which the subjects may be unintentionally unblinded by AEs, an endpoint that was not subjective may have helped circumvent the problem.

The clinical relevance of the treatment effect in spasticity.
The company argues that the patients recruited in these trials had advanced disease, they had not responded adequately to existing treatments and they were less likely to respond to a new treatment than most patients with MS and spasticity. Hence, any treatment effect is likely to be small. They emphasise the significant difference in the number of patients who showed a ≥30% response in the pooled analysis of the 3 pivotal trials (37% on Sativex vs. 26% on placebo). A 30% improvement is considered to be a clinically meaningful response. The U.K. assessor concluded "Sativex consistently achieved more responders than placebo regardless of the definition of responder."

Comment: Currently available treatments for spasticity in MS are not very effective and it is unrealistic to expect Sativex will have a large effect. However, the argument that the patients recruited in the pivotal trials had very treatment resistant spasticity is more difficult to sustain, as there is no treatment that is particularly effective i.e.: most patients with MS and spasticity could be considered treatment resistant. It does not necessarily follow that severe spasticity is less likely to show a response that mild spasticity. It seems more likely that there would be a better chance of an improvement in patients with severe spasticity. The 30% responder analysis of the pooled results is emphasised, but there was only a marginally significant benefit for Sativex compared with placebo for the primary endpoint in the pooled results and the results for the 30% responder analysis in the individual trials were inconsistent.

Maintenance of benefit in long-term use of Sativex.
In Study GWMS0106, subjects who elected to maintain treatment with Sativex over prolonged periods showed efficacy was maintained without an increase in dose.
Comment: Reasonable response.

The company also presented independent data supporting the requested indications for Sativex.

1. *Catalan compassionate use programme.* Patients were included in the programme if they had neuropathic pain or spasticity due to MS, neuropathic pain due to other reasons, anorexia or cachexia due to cancer or HIV infection, or nausea or vomiting due to cancer chemotherapy. The results were released at a press conference. Overall there was a prolonged benefit in about 50% of the patients. The results have not been published.
2. An investigator-initiated neurophysiological study in people with MS. The flexion reflex was studied in a double blind, randomised, cross-over study of Sativex vs. placebo in 18 patients with MS. The results showed a significant effect of Sativex on the RIII flexion reflex. The paper is in press.

Comment: This data is unhelpful in making a decision. The Catalan programme was not a randomised trial and the only information available is in the form of a press release.

Two new Phase 3 studies using Sativex in patients with MS and spasticity are currently recruiting. No results are available:

GWSP0604. This is 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 unrelieved by current treatment. The first phase (Phase A) is a single blind, response assessment and Phase B is a double blind, randomised, placebo-controlled, parallel group study. The study is recruiting patients in several European countries. The recruitment target is 244 patients in Phase B. The primary endpoint is the mean spasticity NRS score.

GWSP0702. This is a placebo-controlled, parallel group, randomised withdrawal study in subjects with spasticity due to MS who are receiving long-term Sativex. The study is designed to assess the maintenance of the effect of Sativex compared with placebo in relieving symptoms of spasticity due to MS, in subjects who have already been receiving long-term benefit from Sativex. The primary endpoint is the time to treatment failure. The study is recruiting in the UK. Results are expected early in 2009. The recruitment target is 60 patients, equally randomised between Sativex and placebo.

GWCA0701 is a Phase 2 double blind, randomised, placebo-controlled, parallel group dose-range exploration study in relief of pain in patients with advanced cancer, who experience inadequate analgesia with optimised opioid therapy. The primary endpoint is a ≥30% reduction in the Interactive Voice Response System 11-point NRS pain score during the last 3 days of Week 5 compared with the 3-day baseline period. The study is recruiting in the US and other countries will be participating. The recruitment target is 336 patients in 3 dose groups (randomization to Sativex or placebo in a 3:1 ratio).

Further information on the neuropsychiatric profile and cognitive function
A response prepared by [redacted], Medical Director of the Cannabinoid Research Institute, GW Pharma, was presented. The main conclusions are summarised below:

Cannabis and cognition. There is no reliable evidence that even heavy, prolonged cannabis smoking produces structural brain damage. It is uncertain whether there is residual impairment in cognitive function after abstinence in heavy, long-term users. If such deficits occur, they are likely to be subtle.

Cannabis and neuropsychiatric effects. There is some evidence from epidemiological studies that cannabis smoking in childhood and adolescence is associated with an increased risk of psychosis in later life. One of these studies (Moore et al. Cannabis and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370: 319-328) found an increased risk of psychosis in individuals who had ever used cannabis (adjusted odds ratio 1.41; 95% CI 1.20-1.65). The report argues that these studies had methodological shortcomings. There is an association between recreational cannabis smoking and anxiety and depression.

Effects of Sativex on cognition. Using treatment-related AEs in the latest (September 1, 2007) safety analysis, cognitive impairment occurred more frequently following Sativex than placebo: disturbance of attention (4% vs. 0.2%), memory impairment (1.5% vs. 0.5%), amnesia (1% vs.0.1%), abnormal coordination (0.5% vs. 0), cognitive disorder (0.2% vs. 0), depressed consciousness (0.2% vs. 0). However, out of 921 patients who received Sativex, only 5 were withdrawn from treatment as a result of cognitive AEs.

The effects of oromucosal THC 15 mg, Sativex (5 mg and 15 mg) and placebo on nocturnal sleep, early morning performance and sleepiness were studied in a double-blind, crossover study in 8 healthy subjects. THC was associated with impaired immediate and delayed word recall, whereas there was no significant difference from placebo in either memory test with Sativex 15 mg.

The report argues that co-administration of THC and CBD has advantages beyond the therapeutic benefits that both drugs bring individually in terms of increased alertness, but the evidence supporting this hypothesis has been derived from an EEG study and another study using auditory-evoked potentials in healthy subjects. A neurophysiological response does not necessarily imply increased alertness.

Sativex was compared with placebo using a battery of neuropsychological effects in a trial comparing Sativex with placebo in 64 patients with MS and neuropathic pain. There was no difference between Sativex and placebo in 4/5 components of the neuropsychological battery. In a selective reminding test, there was a significant difference in favour of the placebo group, which was attributed to an improvement in the placebo group ($p = 0.009$). In another trial in which Sativex was used in 125 patients with neuropathic pain, there was no difference between Sativex and placebo in any component of the neuropsychological tests. In a double-blind crossover trial in 17 patients with MS comparing Sativex with placebo, there was no significant difference between Sativex and placebo on the PASAT, a test of auditory information processing speed.

Neuropsychiatric effects of Sativex. Psychiatric AEs occurred more frequently following Sativex (18%) compared with placebo (5.5%) in the latest safety analysis. 85% of these AEs were either mild or moderate in intensity and only 29/921 (3.1%) patients who received Sativex withdrew as a result of psychiatric AEs.

The data from 496 patients with MS who received Sativex and 434 who received placebo was pooled. Psychiatric AEs were more common in the group treated with Sativex, but the frequency of individual AEs was low. The overall rates of psychiatric AEs were not provided. 87% of the MS patients who experienced a psychiatric AE did so in the first 28 days vs. 57% for placebo. 14% of the MS patients with a psychiatric AE occurring with Sativex discontinued study treatment.

Importance of Cannabidiol. The cognitive deficits and psychiatric AEs associated with cannabis and Sativex are thought to be due to THC, but CBD may exert a protective effect. CBD inhibits the hydroxylation of THC to the psychoactive metabolite 11-hydroxy-THC. CBD may have anxiolytic and anti-psychotic effects of its own.

Comment. There is a detailed response to this question. It seems that Sativex is associated with an increased risk of neuropsychiatric and cognitive AEs, but these events are usually mild.

SUMMARY AND CONCLUSION

The potential unblinding of subjects treated with Sativex and the magnitude of the response to Sativex are still issues. No new clinical trial data is available, but the results of two trials currently recruiting patients with MS and spasticity should provide further evidence about the efficacy of Sativex for this indication. The response contains very little information in support of the other two proposed indications. Sativex is associated with an increased risk of neuropsychiatric and cognitive side effects, but these events are usually mild. Further deferral is recommended.