MINUTES OF THE 86TH MEETING
OF THE MEDICINES ASSESSMENT ADVISORY COMMITTEE
HELD on 29TH & 30TH JULY 2008 at 9:30am

Associate Professor R Robson (Chair),
Dr R Acland,
Professor N Anderson,
Dr R DeBoyer,
Associate Professor R Ellis-Pegler,
Dr D Gray,
Dr M Harrison-Woolrych,
Professor R Laverty,
Dr A Macleod,
Dr D Pethica,
Mr G Spears, and
Mrs M Prescott (Secretary).
Ms Andrea Kerridge (Secretary)

5.2.2 Sativex (cannabis extracts □9-THC and cannabidiol) buccal spray. TT50-8053

The Committee reconsidered an application submitted by GW Pharma (UK) Ltd for Sativex (cannabis extracts □9-THC and cannabidiol) buccal spray for the indications of

- Relief of neuropathic pain in multiple sclerosis
- Relief of spasticity in multiple sclerosis
- Relief of pain in advanced cancer.

Sativex was first considered at the MAAC meeting of 18 March 2008. The Committee recommended deferral under Section 21 pending a satisfactory response to the following:

- The Part II data relating to the composition, manufacture, quality control, stability and bioavailability of this product are found to be adequate and acceptable, when the evaluation is completed.
- The Company is requested to provide further and more robust evidence of efficacy in spasticity and cancer pain.
- Further information is requested on the neuropsychiatric profile and cognitive function.

The Committee was shown the following SCRIP article:
Sativex disappoints in multiple sclerosis pain trial. April 16th 2008.

The Part II data relating to the composition, manufacture, quality control, stability and bioavailability of this product are found to be adequate and acceptable, when the evaluation is completed.
The Committee noted that the evaluation of the Part II data had been completed and with the exception of the product labelling all pharmaceutical chemistry issues had been resolved.

The Company is requested to provide further and more robust evidence of efficacy in spasticity and cancer pain.
The Company's response addressed various issues raised by the assessors.

The assessors had commented that the high frequency of mild and moderate adverse events 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 was the frequency of dizziness was similar to that seen with other agents, and there was no published evidence that subjects with a more marked adverse event profile report greater efficacy that those without. The company quoted the findings of an independent statistician [redacted] who assessed whether an occurrence of adverse events predicted efficacy in the three phase III studies of Sativex in people with multiple sclerosis and spasticity. [redacted]

concluded that there was no evidence of a relationship between treatment effect and the occurrence of one or more of the three most common adverse events of dizziness, somnolence and headache [redacted] found no evidence that blinding was seriously compromised. [redacted] report was not included in the submission. It would have been helpful if [redacted] full report had been included in the submission.

The Committee had questioned 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 presented evidence that the traditionally used Ashworth Scale was not an appropriate tool for assessing change in spasticity. The argument was made that the NRS for spasticity was similar to the numeric scales used to measure pain and quality of life.

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

In response to the Committee's query as to the clinical relevance of the treatment effect in spasticity the company argued that the patients recruited in these trials had advanced disease, had not responded adequately to existing treatments and were less likely to respond to a new treatment than most patients with multiple sclerosis and spasticity.

The Committee said currently available treatments for spasticity in multiple sclerosis are not very effective and it was 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 was more difficult to sustain, as there is no treatment that is particularly effective, i.e. most patients with multiple sclerosis and spasticity could be considered treatment resistant. It does not necessarily follow that severe spasticity would be less likely to show a response than 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 was 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.

In study GWMS0106 subjects who elected to maintain treatment with Sativex over prolonged periods showed efficacy was maintained without an increase in dose.

The company presented independent data supporting the requested indications for Sativex from the Catalan compassionate use programme. This data were unhelpful. The Catalan programme was not a randomised trial and the only information available is in the form of a press release.

Two new phase III studies using Sativex in patients with multiple sclerosis and spasticity are currently recruiting.

Study GWSP0604 is a two phase, phase III study of the safety and efficacy of Sativex in the relief of spasticity in subjects with multiple sclerosis 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 primary endpoint is the mean spasticity NRS score.

Study GWSP0702 is a placebo-controlled, parallel group, randomised withdrawal study in subjects with spasticity due to multiple sclerosis 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 multiple sclerosis, in subjects who have already been receiving long-term benefit from Sativex. The primary endpoint is the time to treatment failure. Results are expected in early 2009.

Study GWCA0701 is a phase II 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 pains 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.

Further information is requested on the neuropsychiatric profile and cognitive function. Further information was presented in a response from [redacted] Medical Director of the Cannabinoid Research Institute, GW Pharma. Most of the psychiatric symptoms have appeared to be related to the THC content of cannabis.

There was some evidence from epidemiological studies that cannabis smoking in childhood and adolescence was associated with an increased risk of psychosis in later life.

Using treatment related adverse events in the latest safety analysis, dated 1 September 2007, cognitive impairment occurred more frequently following Sativex than placebo. These events are usually mild. 5 of 921 patients who received Sativex were withdrawn from treatment as a result of cognitive adverse events.

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

The cognitive deficits and psychiatric adverse events associated with cannabis and Sativex were thought to be due to THC, but the cannabidiol may exert a protective effect. Cannabidiol inhibits the hydroxylation of THC to the psychoactive metabolite 11-hydroxy-HC. Cannabidiol may have anxiolytic and antipsychotic effects of its own.

There were no new clinical data available, but the results of the two trials currently recruiting patients with multiple sclerosis and spasticity should provide further evidence about the efficacy of Sativex for this indication.

The response contained very little information in support of the other two proposed indications.

Committee recommendations.
The Committee were unable to recommend approval at this time for the application for Sativex (cannabis extracts □9-THC and cannabidiol) due to insufficient data.

In order to further their deliberations for the application for Sativex (cannabis extracts □9-THC and cannabidiol) for the indications of
Relief of neuropathic pain in multiple sclerosis
Relief of spasticity in multiple sclerosis
Relief of pain in advanced cancer

The Committee requested the following information:
- The Company is requested to provide the data from the ongoing studies when available.
- The Company is requested to provide a full transcript of [redacted] report.