MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC) REPORT
29 July 2008

Assessor:	[redacted]
Compound:	Delta-9-THC and Cannabidiol
Product:	Sativex
Dose form:	Buccal spray
Proposed indication:	1. Relief of neuropathic pain in MS 2. Relief of spasticity in MS 3. Relief of pain in cancer
MOH file number:	TT50-8053

Background

We considered this application at the March 2008 meeting and the application was deferred for some further Part 2 data along with a request for further and more robust evidence of efficacy in spasticity and cancer pain. Further information was also requested on the neuropsychiatric profile and cognitive function effects. The company has replied very promptly with answers to these concerns.

The committee will be well aware of the interesting discussion we had and the fact that I did support this application!

In response, the company has indicated that there are three further studies in progress which are beginning recruitment and are expected to yield headline results in the beginning of 2009. GWSP0702 is a placebo-controlled parallel group randomised withdrawal study of subjects with symptoms of spasticity due to MS who are receiving long-term Sativex. Study GWCA0701 is a similarly designed study assessing the relief of pain in patients with advanced cancer who experience inadequate analgesia during optimised chronic opioid therapy. The study is actively recruiting in a number of countries and results are hoped to be available in the beginning of 2009. Study GWSP0604 is a further study assessing the safety and efficacy in symptomatic relief of spasticity in patients with spasticity due to multiple sclerosis. There are two phases to this; one being a single-blind and the other being a double-blind parallel group study. This has been designed in consultation with the MHRA and it has been designed to address the main issue identified by the MHRA. Recruitment has taken place in a number of European countries and again results are hoped to be available in the beginning of 2009.

The company has responded to the concern regarding blinding when using an agent where there is a high frequency of dizziness. [redacted] was asked to provide an objective assessment and he concluded with regard to relationship with the three most common adverse events, dizziness, somnolence and headache, that there is no evidence of a relationship between overall treatment effect and experience of one or more of these three adverse effects. The general consensus is that if blinding has been compromised, there is no evidence of any bias in the assessment of the treatment difference between Sativex and placebo. They are unable to absolutely refute the possibility of bias, but at least there is no evidence of a major problem.

In regard to the validity of the numerical rating scale (NRS), they make the point that there may be some influence of other symptoms in the score report by patients but that should not be an issue in supporting the validity of the NRS. The clinical relevance of the treatment effect of MS spasticity is such that the pooled data in which there is a meaningful response of 30% of more occurs in 37% of Sativex patients compared with 26% of placebo patients (p=0.0073). Sativex consistently achieved more responders. Note is also made of the consistent long-term benefit through to 52 weeks.

Additional data from independent reports was obtained from work done through the health department of the regional government of Catalan, Spain. This report demonstrated that half the patients who received Sativex responded well by reporting improvement of pain and spasticity symptoms in MS. Patients with neuropathic pain from other causes also experienced improvement of their pain. In those patients undergoing chemotherapy there was a reported improvement in nausea and vomiting.

In regard to the neuropsychiatric profile and cognitive function, further information has been prepared by [redacted], Psychiatrist from Oxford University. Most of the psychiatric symptoms have appeared to be related to the THC content of cannabis. They are said to be self-limiting and there is no convincing evidence that they have any implications for long-term mental health. He does state, however, that there are non-definitive epidemiological studies that show that cannabis smoking in childhood or adolescence may be associated with an increased risk of functional psychotic outcome in later life. He does note that all these studies have methodological shortcomings. "At worst the risk to an individual of developing schizophrenia as a result of using cannabis is very small."

In regard to Sativex, the evidence over one year or longer is such that there are very low levels of intoxication and there is no evidence of tolerance.

The pharmacokinetics of the oromucosal cannabinoids is markedly different from the profile following inhalation as smoke or vapour. The co-administration of THC and CBD has advantages beyond the therapeutic benefits that both drugs bring individually. The possibility of a positive effect of CBD on cognition has been supported.

Psychiatric adverse effects do occur more frequently following Sativex than placebo (18% vs. 5.5%); however, a large majority of these (85%) were either mild or moderate in intensity and of the 921 patients who received Sativex only 29 withdrew as a result of psychiatric adverse effects.

In a double-blind cross-over trial of 17 patients with MS over eight weeks' treatment, a publication in 2008 compared the neuropsychiatric and cognitive effects of Sativex with placebo. The PASAT, a measure of auditory information processing speed, revealed no significant difference between Sativex and placebo. The cognitive deficits and psychiatric adverse effects are thought to be due to the THC content of Sativex. The presence of CBD is likely to exert a protective effect since it is known to inhibit hydroxylation of THC to the psychoactive metabolite. Moreover, there is accumulating evidence that CBD has anxiolytic and antipsychotic effects in its own right.

Certainly in the short term (<1 year) there is no compelling evidence to demonstrate major psychiatric and cognitive deficits in the use of Sativex.

Conclusion

As the committee know only too well, I have previously supported this application. We have not been provided with any further efficacy data and we do await the three studies' results at the beginning of 2009. I am reassured about the cognitive and psychiatric adverse effect profile.