MINUTES OF THE 85TH MEETING
OF THE MEDICINES ASSESSMENT ADVISORY COMMITTEE
HELD on 18th MARCH 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).

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

The Committee considered an application submitted by GW Pharma (UK) Ltd for Sativex. The proposed indications are

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

The discovery of the endogenous cannabinoid system and the pharmacological characterisation of the CB subtype-1 and CB subtype-2 receptors as distinct subtypes have provided a powerful stimulus to cannabinoid research. The distribution of these receptors appears to be remarkably consistent across a number of mammalian species. The distribution of CB_1 receptors within the CNS indicates likely functions for endogenous cannabinoids in motor control, reward mechanisms and cognitive functions. CB_1 and CB_2 receptors are found in certain peripheral tissues. Many of the CNS effects of the cannabinoids are mediated by the CB_1 receptor.

The Committee noted that the initial evaluation of the data relating to the composition, manufacture, quality control, stability and bioavailability of this product had not been completed.

There is evidence in animal models of multiple sclerosis (MS) that endogenous cannabinoids are involved in spasticity.

No studies have examined the effects of cannabidiol alone in animal models of MS but there is evidence that cannabidiol has activity that may be useful in treating spasticity. Cannabidiol decreased the amplitude of excitatory postsynaptic potentials in cat spinal motor neurons.

The anti-nociceptive activity of Δ^9-tetrahydrocannabinol (THC) had been demonstrated in mice, rats, rabbits and dogs using a variety of test systems.

In most studies cannabis and THC caused reversible suppression of immune function.

Animal studies showed that THC had analgesic activity, but there was a less marked analgesic effect from cannabidiol. Animal data suggested THC could relieve spasticity. Both compounds have psychotropic effects that might be beneficial in MS.

Animal pharmacokinetic studies with Sativex were not conducted, but the pharmacokinetics and metabolism of THC and cannabidiol were evaluated. None of the studies involved the oromucosal route proposed for Sativex, because of the difficulty of administering drugs by this route in animals.

Repeat doses of both THC and cannabidiol were associated with reduced uterine and testicular weight, increased oestrous cycle length and inhibition of spermatogenesis.

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In pregnancy, cannabinoids had a dose-related adverse effect on the number and weight of offspring and their survival. THC was also associated with increase embryo-foetal mortality in several species

GLP-compliant studies using a 1:1 mixture of THC and cannabidiol confirmed that cannabinoids have adverse reproductive effects. The results suggest Sativex should not be used during pregnancy and breast feeding.
Clinical pharmacokinetic studies showed cannabinoids have a low oral bioavailability, because of first-pass hepatic metabolism.

Most of the pharmacokinetic data were obtained from single dose studies in healthy volunteers. Sativex appeared in plasma within 15 to 30 minutes, T_{max} 90 minutes, C_{max} and exposure to THC were greater than for cannabidiol. Individual values for C_{max} and exposure showed a high degree of patient variability. Excretion of metabolites of THC was mainly faecal and renal. There were little data on the excretion of cannabidiol. Both THC and cannabidiol are highly lipophilic, leading to rapid uptake into tissues and a high volume of distribution.

In vitro studies suggested Sativex has a limited ability to inhibit CYP450 at concentrations in excess of those reached by the therapeutic administration of Sativex. Therefore important drug interactions with Sativex seem to be unlikely.

Study GWMS0001 was a double-blind, randomised, six week, parallel group, placebo controlled trial of THC + cannabidiol in patients with multiple sclerosis. Five symptoms were assessed: pain, spasticity, spasms, bladder problems and tremor. A 0-100 mm Visual Analogue Scale (VAS) was used. The VAS showed a non-significant decrease of 25.29 mm for the treatment group and a decrease of 19.35 mm for the placebo group. The estimated treatment difference for spasticity was 7.10 mm in favour of Sativex which was non-significant. In a subgroup of 39 patients in whom spasticity was the primary symptom, the results were significantly significant in favour of Sativex.

Study GWMS0107 was a single centre, double blind, randomised, placebo-controlled, parallel group study in 66 patients with multiple sclerosis and neuropathic pain (Box Scale 11 (BS-11) ≥4) and stable analgesic medication for the previous two weeks. After a 7 – 10 day baseline period, patients were randomised to a four week parallel group comparison of Sativex with placebo. The dose was self-titrated up to symptom resolution or the maximum tolerated dose. The primary efficacy measure was the severity of pain measured by the BS-11 after four weeks. The change from baseline of the mean BS-11 pain score showed a significant treatment difference of 1.25 boxes in favour of Sativex. The main secondary efficacy measure, the neuropathic pain scale also favoured Sativex. The actual level of pain relief achieved with Sativex, using the BS-11 score, represented a 41% improvement over baseline and an almost 20% improvement over placebo.

Study GWPS0105 was a multicentre, double-blind, placebo-controlled parallel group comparison of Sativex over three weeks in patients with chronic refractory pain (BS-11>4). 70 patients were randomised of whom 43 had MS. The primary efficacy endpoint was the change from baseline in the BS-11 score. Escape medication was permitted. The mean BS-11 score at 3 weeks decrease by 1.3 boxes in the Sativex group and 0.9 boxes in the placebo group. The difference in the use of escape medication between the two groups confounded the primary endpoint. The results for the MS subgroup were similar to the overall results.
Study GWMS0106 was a pivotal phase III study in patients with MS complicated by spasticity (Ashworth Score ≥2 in two or more muscle groups unrelieved by existing treatment). Sativex was used as add-on treatment for six weeks. The primary outcome was change from the baseline Numerical Rating Scale (NRS). In the intention to treat (ITT) population, the change in NRS was -1.11 for the Sativex groups and -0.52 for the placebo group (p= 0.048). When the "per protocol population" was analysed, the change in NRS was -1.23 for Sativex and -0.50 for placebo (p=0.01).

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Responders (patients achieving ≥30% improvement) were seen in 40% of the Sativex group and 22% of the placebo group (p=0.014).

Study GWCL0403 was a pivotal Phase III study in patients with MS who had not responded to existing anti-spasticity medications. Sativex was compared with placebo as add-on therapy. The duration of the placebo controlled period was 14 weeks. There was no statistically significant difference between Sativex and placebo in the ITT population. For the "per protocol population" the change in the NRS was -1.30 for Sativex and -0.84 for placebo (p=0.035).

When the results of the three pivotal studies for use in MS with spasticity are pooled there was a significant benefit for Sativex over placebo.

There was one randomised controlled study in patients with cancer pain. Study GWCA0101 was a two week, multicentre, double blind, randomised, placebo-controlled, parallel group studying patients with advanced cancer in a hospice setting. All patients had daily pain of at least moderate intensity despite treatment with opioids. Patients were randomised to one of three groups: Sativex, THC alone or placebo. Medication was self-titrated with a maximum of 48 actuations in 24 hours. The pain NRS was the primary efficacy variable (0 = no pain and 10 = very bad pain). The use of escape medication was also included as a primary endpoint. There were 177 patients in the ITT population. The mean changes in the NRS pain score in this population were Sativex -1.37, THC -1.01 and placebo -0.69. There was an estimated treatment difference of 0.32 points in favour of THC over placebo, but this was not statistically significant. There was no difference between groups in the reduction of the mean number of days that escape medication was used over the duration of the study, or the mean dose of escape medication. 43% of the Sativex patients achieved a 'clinically relevant' 30% improvement in pain vs. 21% of patients on placebo.

In the MS studies the most frequent adverse events in the Sativex group compared to the placebo group were

- gastrointestinal mainly nausea, dry mouth, vomiting, and constipation
- general mainly fatigue, asthenia, 'feeling abnormal' and feeling drunk
- nervous system mainly dizziness, somnolence, dysgeusia, disturbance in attention and dysarthria.
- Psychiatric mainly depression and confusion
- Ear and labyrinth mainly vertigo.

The frequency with which these mild and moderate adverse events occurred does suggest that the development of these symptoms may have unblended the patients receiving Sativex and may have implications for the interpretation of the results of these studies.

In all placebo-controlled studies in patients with MS, 10.7% on Sativex withdrew from study medication compared to 3.5% on placebo. The two most common adverse events which led to discontinuation of study medication were dizziness and nausea.

The most common adverse events reported in patients with cancer were somnolence, dizziness, nausea and confusion.

In the studies for the relief of neuropathic pain in multiple sclerosis there was a statistically significant benefit in short term pain relief compared to placebo in one study, GWMS0107, but in the other two studies there was only a non-significant trend towards benefit from Sativex. However the results of GWMS0107 were 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.

In the studies for the relief of spasticity in multiple sclerosis, study GWMS001 showed a non-significant trend towards benefit from Sativex. Sativex had a statistically significant beneficial effect in a subgroup of patients in whom spasticity was the

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primary symptom. When the results of the three pivotal studies were pooled, there was a significant benefit for Sativex over placebo.

The results of the one study for the relief of pain with cancer demonstrated a statistically significant benefit of Sativex over placebo for pain relief. However further evidence of efficacy is required for this indication.

Committee recommendations:

The Committee found there were insufficient data to recommend approval at this time for the application for Sativex (cannabis extracts Δ^9-THC and cannabidiol) for the following indications:

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

The Committee requested the following information:

- **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.**

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