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

ASSESSOR: [redacted]

COMPOUND: Tetrahydrocannabinol (THC) & Cannabidiol (CBD) 50:50 ratio

PRODUCT: Sativex

DOSE FORM: Solution of the cannabis extracts in a vehicle consisting of propylene glycol and ethanol flavoured with peppermint oil, presented as an oromucosal spray. The solution is presented in a type 1 amber glass vile with crimp on 100 µL pump spray. An 8ml vial size contains 5.5ml solution.

MOH FILE NUMBER: TT50-8053

STRENGTH: THC 27mg/ml, CBD 25mg/ml

PROPOSED INDICATION(S): For the relief of neuropathic pain and spasticity in Multiple Sclerosis where patients have been unable to gain adequate relief from existing medications, and for the relief of pain in advanced cancer where the patient has been unable to gain adequate relief from the use of strong opioids.

PROPOSED DOSAGE: Each millilitre of Sativex contains 27mg THC and 25mg CPD. In addition to the active substances, the mixture contains more than 60 cannabinoids and a variety of compounds commonly found in other plant extracts. To obtain the two compounds, two strains of the Cannabis sativa L plant, rich in THC and CBD respectively are cultivated under licence from the UK Home Office. The treated cannabis plants are extracted with liquid carbon dioxide, followed by dissolution of the extracts in ethanol. Sativex is a blend of the two principal extracts (THC/Tetranabinex and CBD/Nabidiolex). Both of these active substances have been well studied. THC is the main psychotropic component found in cannabis when smoked.

BACKGROUND

THC has been marketed in Canada under the trade name of Marinol as an antiemetic for the treatment of severe nausea and vomiting associated with cancer chemotherapy and the treatment AIDS related anorexia and associated weight loss. Nabilone a synthetic cannabinoid with similar pharmacological profile to THC has been marketed in Canada since 2000 for the management of severe nausea and vomiting associated with cancer chemotherapy. CBD is not marketed in Canada, or anywhere else presently. The Sativex metered spray pumps 100 µL per delivery. The nominal dosage of each spray action is 2.7mg THC and 2.5mg CBD.

Sativex was approved in Canada for the relief of neuropathic pain in Multiple Sclerosis in April 2005 and for the relief of pain in advanced cancer in August 2007. The proposed indication in the UK is as an add-on treatment for symptomatic relief of spasticity in patients with MS who have not responses adequately to current antispasticity medication,

having a score of at least 6 on a 0-10 Numerical Rating Scale (NRS) and who demonstrate improvement during a four week trial of therapy of at least 20% and who have also improved by at least one category on a clinical global impression scale and whom the physician determines the risk benefit to be in favour of continuing treatment.

[redacted], The Old Piggery, is a prominent British Neurologist and past President of the GMC, the Royal Society of Medicine, the World Federation of Neurologists', and previously Professor of Neurology at the University of Newcastle upon Tyne. He coauthored a consensus statement (with a group of independent experts) in July 2007. It states "The clinical assessment of Sativex by the Medicines and Healthcare Products Regulatory Authority has concluded that the improvement seen in patients with MS (re spasisticity) following treatment with Sativex may not be of sufficient magnitude to be deemed clinically relevant. This consensus statement will show that Sativex does indeed produce benefits, which are worthwhile in the eyes of the patient, the carer and the treating physician. It states that Sativex is used as an unlicensed medicine in the UK. It notes that the carefully constructed questionnaire reveals 94% of respondents report an improvement on general life benefits from the improvement they have experienced on Sativex. We conclude that Sativex meets a currently unmet medical need in patients where there is no other conservative treatment options. It is our view that Sativex should be licensed and become available on prescription for patients with spasticity due to Multiple Sclerosis, and we urge MHRA to do so."

The discovery of the endogenous cannabinoid system and the pharmacological characterisation of 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. In the peripheral tissues, CB-1 receptors are present in most internal organs and glands whereas CB-2 receptors are present mainly in immune system components, cells and organs and glands and are also localised in the adrenals, heart, lungs, prostate, uterus, ovary, testes and pancreas. Some of the effects of THC and CBD may not be through these two subtypes (possibly TRPV-1 receptors).

PART III - PHARMACOTOXICOLOGICAL (PRECLINICAL) DATA

A. Animal pharmacology

1. Pharmacodynamics

Cannabinoids have been demonstrated to possess significant anti-nociceptive properties in a variety of animal model systems. The analgesic potency of THC is said to be comparable to that of morphine. There are a variety of CNS effects such as antipsychotic and anxyiolytic properties. The effect of the combination of THC and CBD appears to be additive. In regard to cardiovascular action (in conscious animals), effects are generally inconsistent and there is evidence to suggest that the cardiovascular effects of THC may diminish with repeated dosage. The effects of CBD appear to be considerably weaker. There was no significant effect on blood pressure of spontaneously hypertensive rats in doses of CBD up to 30mg/kg IV. Potential cardiovascular interactions of Sativex with other drugs was not fully investigated.

In regard to other CNS effects, reductions and increases in aggressive behaviour have been reported following THC. In mice THC was anxyiogenic whereas CBD was anxyiolytic. Both THC and CBD have been shown to exert significant anticonvulsant activity.

A very important area of the preclinical research with cannabinoids has been that concerned with potential effects of the substances on the immune system. The effect is complex. THC has been shown to both up and down regulate lymphocyte proliferation. The same is seen with cytokine production. Most studies have reported inhibitory effects of THC on antibody production and normal immune response to infectious agents. It does appear that further studies are needed to clarify the biological and clinical significance of the cannabinoids on the immune system and that the two agents may modify each other.

The effect on the endocrine system again is also confusing. Generally there is a reduction in the levels of prolactin, testosterone and progesterone.

In view of the widespread recreational use of cannabis, the addiction potential of THC and CBD are of obvious interest and have been studied in a variety of animal test systems. The consensus is that the tolerance to the behavioural effects of cannabinoids is slow to develop and when manifest is apparently linked to changes in the availability of cannabis receptors rather than to altered metabolism of cannabinoids. A level of physical dependence to THC has been demonstrated by abrupt withdrawal of the compound in rodents and monkeys. It is generally thought that the withdrawal effect is much milder than that seen with opioids and more closely resembles that observed with benzodiazepines.

2. Animal pharmacokinetics

Most of the information for THC and CBD is from the published literature. In most studies the cannabinoids were administered either IV or PO. To date no published non-clinical studies exploring the bioavailability of THC, CBD or cannabis extract following sublingual or buccal administration have been identified.

THC is a highly lipophilic compound. It exhibits high protein binding and demonstrates a long terminal half life. It readily crosses the placenta and has been shown to have foeto-toxic effects. Metabolism of THC has been widely studied. A wide range of metabolites has been identified in animal models. Cytochrome P450 is involved. Both faeces and urine are routes for excretion of THC and its metabolites. CBD is also absorbed and distributed very rapidly. It is also extensively metabolised by similar mechanism. Possible pharmacokinetic interactions between CBD and THC have been reported. CBD has been reported to be a potent inhibitor of cytochrome P450. However when CBD is co-administered with THC, the disappearance rates of both from rat plasma was identical to those determined when they were administered separately. In regard to drug-drug interactions with THC, there was an increase in blood levels of various test substances. Substances affecting THC metabolism include ethanol, cocaine, aspirin and barbiturates.

B. Toxicology

A considerable number of toxicological studies have been performed using THC and CBD. Single dose oral studies suggest low acute toxicity. In general the oral toxicity of cannabis extract closely paralleled its THC content suggesting that this was the principle active component present. Signs of toxicity were anorexia, reduced weight gain, sedation,

dyspnoea and hypothermia. Female rats were generally more susceptible that males. Oral LD50's for THC were generally greater than 1000mg/kg in rats, 3000mg/kg in dogs and 9000mg/kg in monkeys. Single dose studies do not appear to have been performed with CBD. LD50 values suggest that CBD is significantly less toxic than THC. Repeat dose studies performed for durations of 3-14 days using the 1-1 mix in rats, mice, dogs and rabbits suggest that the test material is very well tolerated by the oral route and there was no mortality. There is a possible cumulative toxicity in the early part of treatment. The main clinical signs were a change in behaviour pattern after about a week of treatment from signs of CNS depression to signs of CNS stimulation such as increased aggression and convulsion. A consistent finding in most repeat dose THC studies was decreased weight of male and female reproductive organs and increased adrenal weight. In toxicity studies with CBD there was no mortality in doses up to 300mg/kg/day in rats and monkeys. Two recent oral dosing studies in rats and dogs using the 1-1 mix revealed dosage related reductions in both food consumption and body weight gain.

A number of tests have been performed with these cannabinoids to evaluate genotoxic potential. The results have been largely negative but there is some conflicting data. THC has been evaluated for carcinogenic potential in two well documented two year duration studies in mice and rats. The results of the rat study were clearly negative in terms of neoplasm whereas in mice there was an increased incidence of thyroid follicular cell tumours at a single low dose level. There was no dose response relationship and lack of evidence to suggest that hyperplasia of thyroid follicular cells progressed adenomas or carcinomas.

In terms of reproductive effects, both cannabinoids reduced reproductive organ weight. Administration of these agents during pregnancy results in adverse effects in terms of number and weight of offspring and of their survival. These are probably dose related effects.

C. Summary of the pharmacotoxicological data

This is complex and there is marked variation within species. Cannabinoids certainly have diverse CNS effects and specific effects on the immune system which are probably more depressant. There are interactions with other agents through an effect on cytochrome P450. Foetal toxicity occurs. Animal data indicates that THC is a relatively potent analgesic and antispastic agent, whilst CBD has similar but less marked activity. In addition THC has been demonstrated to have marked effects on ameliorating symptoms and increasing life span in animal models of MS. Both THC and CBD have anti-inflammatory and neuroprotective activities. It is thought that CBD may reduce some of the psychomotor stimulatory effects of THC.

Overall the available animal data suggests that Sativex should not be used during pregnancy or during the period of breastfeeding.

PART IV - CLINICAL DATA

A. Clinical Pharmacology

1. Pharmacodynamics

A substantial amount of information regarding the main pharmacological effects of the cannabinoids present in Sativex comes from the published literature. There has been information also from Phase I clinical studies of Sativex. Data on possible mechanism of action specifically in the relief of spasticity are generally not as well established as the known neuropsychiatric, cognitive and neuromotor aspects. There is no biomarker for spasticity. The lack of pharmacodynamic data showing an effect of Sativex in either normal subjects or in patients with spasticity on muscle tone or spasticity, which is the basis of the claimed indication, is the principle weakness of the pharmacodynamic data. However in the animal models of spasticity it appears that stimulation of the cannabinoid receptors might have a favourable effect on spasticity. The lack of data showing a pharmacodynamic dose response relationship is a disadvantage but is not considered to be a major deficiency given that patients will titrate their dose according to clinical response.

2. Pharmacokinetics

There is wide intersubject variability in the pharmacokinetics of Cannabinoids. The lack of easily applied surrogate markers of effect create this difficulty. In the PK studies subject self assessment of intoxication was recorded and explored as an indicator of activity. In these studies however there was little evidence of a direct relationship between plasma concentrations and timing or degree of intoxication.

While absorption of the cannabinoid seems to be good, both THC and CBD have poor bioavailability by the oral route, largely due to an extensive first pass effect, presumably in the liver. The first metabolites are hydroxylated derivatives, which then may undergo oxidation by a number of CYP450 isoforms. Invitro studies suggest that Sativex has limited ability to inhibit CYP450-3A4 and 2C19 at concentrations substantially in excess of those reached by the therapeutic administration. Subsequent excretion of conjugated phase II metabolites of THC is largely faecal and urinary. There is little data on the route of excretion of CBD. The available pharmacokinetic data on Sativex is predominantly in healthy volunteers and 11 studies have investigated the pharmacokinetic intolerability. Sativex is absorbed fairly rapidly, appearing in the plasma in around 15-30 minutes with a Tmax around 90 minutes. A consistent finding has been that the Cmax and exposure to THC has been greater than to CBD, suggesting that THC may have a slightly greater bioavailability. The individual values for Cmax and exposure show a high degree of between patient variability, providing a pharmacokinetic rationale for within patient dose titration regime. Results from single dose pharmacokinetic studies using the proposed formulation of Sativex show that the sublingual route of administration and the administration to other parts of the oral mucosa result in similar plasma levels, showing that administration can successfully be made in any part of the oral mucosa.

In the Phase III study, GWMS0001EXT, a cohort of patients had PK sampling at 2 time points during chronic exposure. This demonstrated that there is no evidence of accumulation of THC or CBD in plasma and that the range of Cmax after dosing in chronic use is similar to the range of Cmax seen after single dose and that there is between patient variability in plasma levels in chronic dosing. Vaporised THC extract administered by inhalation has shown significant increase in mean plasma Cmax occurring within minutes after administration with significant psychoactivity. This is in contrast to orally administered Sativex where the Cmax has reached 90-120 minutes and a much lower Cmax with no evidence of psycho activity.

Efficacy

Whilst spasticity and pain are both common features of MS, tremor, fatigue, ataxia and lower urinary tract symptoms also contribute to the high incidence of anxiety and depression seen in people with this condition. A number of studies have looked at the use of cannabis and cannabinoids in the treatment of neuropathic pain with MS. These were generally with the oral agents, Nabilone and Dronabilone. Efficacy has been demonstrated compared to placebo.

Overall 10 clinical trials are presented in this application in regard to MS.

In regard to neuropathic pain, Study GWN19901A was carried out in patients with chronic refractory pain of neurological origin. Approximately half had MS. This was seen as an exploratory trial and in the ITT population there was significant improvements in overall pain symptoms. With this Phase III studies were then conducted. GWMS0107 included 66 randomised patients. The study was conducted over four weeks against placebo. Dosing was self titrated up to symptom resolution or maximum tolerated dose. The number of actuations per day was stable at the end of Week 1. Primary efficacy measure was severity of pain as measured on the Numeric Rating Scale. Statistical significance was demonstrated over placebo (P=0.005). These improvements were seen in patients who were already maintained on stable regimes of existing analgesic medication. This study was published in Neurology in 2005.

Study GWPS0105 also looked at pain compared to placebo. In this study escape medication was allowed and was measured. Primary end point was in favour but not statistically significant. However patients on Sativex used escape medication a median of 4.8% of the study days whereas patient's randomised placebo took escape medication on a median of 45% of the study days. This study was conducted over three weeks. This may have confounded the primary end point. Another study, GWBP0101, compared Sativex in pain of brachial plexus injury and revealed statistically significant benefits vs placebo.

An open label extension study was carried out, GWMS0107. The mean duration of exposure was 463 days. Reduction in pain score was maintained over one year with no evidence of tolerance. The rate of withdrawal due to lack of efficacy was low even though these were refractory patients.

The effect of Sativex in the relief of spasticity was also conducted in Phase II and Phase III studies. Three Phase III studies were similar in design, being placebo controlled randomised parallel group studies. The demographics of patients were similar in terms of gender, age and duration of MS. All were required to have at least moderate spasticity despite treatment with existing anti-spasticity medication. Therefore patients could be regarded as refractory. Essentially spasticity was their primary symptom. The method of assessment of spasticity was the use of a visual analogue scale in one study and a numeric rating scale in the other (0-100mm vs 0-10mm). Study GWMS0001 was conducted over six weeks. There was no statistically significant difference between treatment for primary end point which was a composite score of target symptoms. However analyses of the individual symptom scores showed encouraging results for spasticity. In GWMS0106, Sativex was studied over a six week period. The primary end point was the change from baseline in the diary based Numerical Rating Scale. The secondary composite scores of Ashworth Scale, Motricity Index Scores and patient global impression of change were

carried out. The mean number of doses per day was 9.4 for Sativex compared to 14.7 for placebo. The median was 6.8 vs 12.6. Patients receiving Sativex showed a 1.1 reduction on NRS compared to 0.59 with placebo. There was no significant findings in any of the secondary end points, weakening the internal validity of the study.

In Study GWCL0403, Sativex was compared to placebo as add-on therapy in the treatment of spasticity for a period of 14 weeks. Early treatment discontinuations were excluded and such discontinuations were likely to be as a consequence of reactions to treatment such as lack of efficacy and adverse events. Hence there was a possibility of large bias when considering the treatment effects. The trends in general favoured Sativex but they were very modest and did not approach statistical significance. The cornerstone of the company's response to these marginal effects is that the total population includes a substantial proportion that will be non-responders so that the magnitude of the treatment affect in those that do turn out to be responders will be substantially greater. Hence the clinical relevance of efficacy should be assessed by examination of the benefits in the responder population. It is suggested that a therapeutic trial to identify responders could be a reasonable approach. Throughout these studies blinding has been an issue as a large number of patients on Sativex do experience dizziness and therefore there could be a potential for measurement bias especially as the primary efficacy end points of the pivotal clinical trials are patient reported and subjective. The Company does reiterate that it is important to note that the PK profile of Sativex is very different from that of smoked cannabis. In the pivotal placebo controlled studies the mean daily dose of Sativex was nine sprays so the dosing interval was similar to the Tmax of a single dose. Such a pattern of drug administration would produce relatively little peak trough fluctuations. Plasma levels during treatment are approximately 30 times lower than those obtained by smoked cannabis. The measurement of spasticity is difficult and in these studies the subjective measure using the NRS has been used and possibly its validity is open to question. (A recent paper in Spinal Cord does in fact support its validity).

Pain in Cancer:

One study GWCA0101 was conducted for longer term exposure in cancer pain. This study was a two week randomised placebo controlled study. Study medication was self titrated according to individual response and tolerability. All patients had advanced cancer and were judged to have a limited life expectancy. This study was conducted in the Hospice environment. All patients were taking strong opioids. The maximum permitted dose was 48 actuations in any 24 hour period. The primary end point was a numeric rating scale recorded three times a day by the subject in their diary book. The use of escape medication was also reported. Patients also recorded level of sleep, nausea, memory, concentration and appetite. The level of pain relief was significantly in favour of Sativex compared to placebo but not for THC rich extract which was also compared. There is essentially no difference in the use of escape medication. Mean improvement in sleep quality was in favour of Sativex. At the end of the study, the investigator was asked whether the patient was at a level of optimum pain control. For the Sativex group this was judged optimal in 51% of cases compared to 40% on placebo. An extension open label study was carried out. The median duration was 25 days with a minimum of two and a maximum of 579 days. The benefits were maintained in longer term follow-up. There was no tendency for pain levels to return to pre-study values.

Dosing Patterns

Titration period appears to last around five days at which time a stable dose has been reached. Thereafter the mean number of daily sprays is very consistent showing no apparent tendency to increase over time. In MS patients long term dosing mean was 7.6 sprays per day with a daily median of 6.0 sprays. Cancer patients the mean daily dose was 5.4 sprays.

Clinical Safety

The key points that the Sativex safety data base is required to address include issues specific for Sativex such as formulation and route of administration, issues specific for MS patient population and clarification of the effects of this medication on psychological health and the potential for it to cause psychiatric morbidity. There is already a lot of information regarding the safety profile of cannabinoids in general. The main adverse effects appear to be dizziness 32% vs 10%, nausea 10.6% vs 5.3% fatigue 13% vs 7.8%. In regard to anorexia 1.6% vs 0.2% but increased appetite 2% vs 0.3%. In regard to psychiatric disorders, disorientation, dissociation and euphoric mood are higher than placebo (approximately 3% vs 1%). Somnolence is 8.9% vs 2.7%. It is stated that most of the SAE's observed in Sativex clinical trials and extension studies are of a nature and frequency that would be expected in this patient population, with the possible exception of an apparent systemic allergic reaction in one patient and psychiatric disorders in two patients (paranoid delusion and suicidal ideation). There is some report of cardiac conduction changes and also some abnormality of liver function tests. There is some potential concern regarding association of psychiatric adverse events such as psychosis and suicidal ideation with long term use of Sativex. There is clear evidence that recreational cannabis can produce a transient toxic psychosis. The level of cannabinoid exposure and especially peak plasma levels achieved with regular recreational cannabis smokers is in general substantially greater than that in patients treated with Sativex and therefore it is considered that the level of risk might be quite different. Nevertheless, the clinical safety data for Sativex is insufficient to establish whether there is a significant risk of psychosis or not either in the short medium term or in the long term. The data suggests that during the first 28 days of treatment, psychiatric adverse events occur more frequently in people with MS who are treated with Sativex than in those treated with placebo. However once treatment continues beyond 28 days, at which time the earlier adverse events have resolved, psychiatric adverse events are more common in placebo treated patients.

The overall withdrawal rate was quite low but there was a 3-4 fold higher withdrawal rate in the Sativex group compared to placebo (10.7 vs 3.2%).

B. Clinical experience

Post marketing reports from Canada and the UK have provided more than 1000 patient years of exposure in addition to that derived from clinical trials. 59 patients have received Sativex continuously for more than five years. No new issues have been identified from this exposure.

An interesting questionnaire was sent out to patients and carers asking the following three questions. Has Sativex benefited your life generally? The answers were mainly positive "only a MS sufferer can understand (that) any help, no matter how small can be priceless". The second question was "Would you like to continue taking Sativex? If so why?" Again there was a general sense of wellbeing and improvement in quality of life. The third

question was directed to Carers, "Do you feel that there is benefit to your life from them taking Sativex?". Again positive responses were obtained.

C. Summary of the clinical data

This is a very unique application for a number of reasons. Firstly it is a combination of cannabinoids and it is well recognised that cannabis is an illicit substance comprising a multitude of cannabinoids. The main offender is the principle cannabinoid THC. Sativex is a 50/50 combination of THC and CBD. Certainly the latter has quite different pharmacodynamics and in terms of kinetics it does generally have a lower plasma level. The combination when administered via the orobuccal mucosa is relatively slowly absorbed with much lower kinetic profiles than the smoked components. Animal pharmacological data does not suggest any major adverse effects and obviously there is concern about some of the untoward CNS effects. No dose response information has been provided. Dosing in humans is achieved by infra-patient responsiveness. Cannabinoids do have effects on the immune system which are obviously complex. There is no evidence to demonstrate deterioration in neurological deficit.

MS is a complex illness with almost 85% of patients presenting with a relapsing remitting form. Therefore assessment of efficacy of a symptom-relieving agent is more complex. GW Pharmaceuticals have demonstrated efficacy particularly for the neuropathic pain associated with MS. In regards to spasticity the evidence is not as strong. Patient feedback has been positive. In regard to cancer analgesic efficacy has been demonstrated. Long term evidence is presented. Importantly tolerance has not been observed. Nor has dependence (though there is concern about the misuse of such an agent. There is no evidence about the long term effect on MS outcome with this agent particularly if there are effects on immunity. We have not been presented with any information as to whether this agent could be delivered by inhalation and therefore increase the absorption kinetics. That would be of concern. Finally, I am not sure how much credence we should give to [redacted] of The Old Piggery) report.

Recommendation

I would recommend Section 23 approval for pain relief in terminal cancer and MS.

DATA SHEET [OR SUMMARY OF PRODUCT CHARACTERISTICS]

Comprehensive. Boxed warning for abuse and CNS/CVS risk.
Appropriate contraindications
Adverse effects well documented, particularly site irritation.

MEDICINE CLASSIFICATION

Controlled prescription.

OVERALL SUMMARY/DISCUSSION

Unique medication, providing symptomatic relief in terminal and severe physical disability patients. Longterm efficacy demonstrated without tolerance. Equivocal data on spasticity outcome. THC toxicity appears to be balanced by CBD.

OUTSTANDING ISSUES

1. Complex pharmacology with significant interpatient variability

2. Only registered in Canada

3. Suspect reluctance to register due to marijuana stigma

4. Is 50:50 ratio appropriate?

5. Longterm safety and outcomes in MS is still to be determined. May in fact have immune/neuroplasticity benefit.