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

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
Relief of pain in cancer

PROPOSED DOSAGE: Self-titration

BACKGROUND

Neuropathic pain and spasticity are common disabling problems in patients with multiple sclerosis (MS) for which treatment is often unsatisfactory. Sativex contains the cannabinoids Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) derived from *Cannabis sativa*. Sativex was approved in Canada for treatment of neuropathic pain in MS in April 2005 and the relief of pain in advanced cancer in August 2007. A marketing application was submitted in August 2006 in four countries in Europe for the indication of relief of spasticity in MS, but more efficacy data was requested and the application was not approved. The company is seeking approval under Section 23.

PART III: PHARMACOTOXICOLOGICAL (PRECLINICAL) DATA

Most of the preclinical data was derived from studies in which THC and CBD were tested individually.

A. Animal Pharmacology

1. Pharmacodynamics

There are 2 types of cannabinoid receptor (CB_1 and CB_2). CB_1 receptors are present in the central nervous system (CNS), but both types are found in certain peripheral tissues. Central and peripheral neuronal CB_1 receptors are found mainly at nerve terminals. Auto-radiographic studies in a variety of mammalian species have shown a high density of CB_1 receptors in the cerebral cortex, hippocampus, basal ganglia and cerebellum, and lower densities in the hypothalamus and spinal cord. CB_1 receptors are sparse in brain stem respiratory centers. Many of the CNS effects of the cannabinoids are mediated by the CB_1 receptor. Modulation of activity in the prefrontal cortex and hippocampus probably is the basis for the effects on higher

cognition and patterns of abuse. CB_1 receptor expression in the spinal cord is concentrated on the spinal interneurons. Peripheral CB_1 receptors have a widespread distribution. CB_2 receptors are localised mainly to the immune system.

The CB_1 receptor belongs to the G-protein-coupled receptor subfamily. Cannabinoids inhibit adenylyl cyclase activity through interaction with the inhibitory G-protein. As a result, adenylyl cyclase cannot catalyse the conversion of ATP to cyclic AMP. Not all effects of the cannabinoids can be explained by binding to CB receptors. Some effects are mediated by anti-oxidant activity, alteration of membrane fluidity and modulation of neurotransmitter systems.

There is evidence in animal models of MS that endogenous cannabinoids are involved in spasticity. In EAE (experimental allergic encephalomyelitis) the anti-spasticity effects of THC were compared with a cannabis extract matched for the THC content. Both materials inhibited spasticity to a similar extent, but the extract caused a more rapid onset of action than THC alone. Treatment with a THC-free extract or with CBD alone did not inhibit spasticity. THC reduced symptoms and increased life span in EAE.

No studies have examined the effects of CBD alone in animal models of MS, but there is evidence that CBD has activity that may be useful in treating spasticity. CBD decreases the amplitude of excitatory postsynaptic potentials in cat spinal motor neurons. Oral CBD did not produce analgesia in mice or rats in one study, but in another study in mice, lower doses of CBD were more effective in inhibiting pain than either THC or aspirin.

The anti-nociceptive activity of THC has been demonstrated in mice, rats, rabbits and dogs using a variety of test systems. CB_1 receptors, which are present on pain pathways in the brain and spinal cord and on the peripheral terminals of primary afferent neurons, may be involved in the analgesic effects of THC. The analgesic activity of THC is also partly due to its interaction with other CNS neurotransmitters. CBD produces analgesia by inhibition of adenosine uptake and as an agonist of the TRPV-1 (vanilloid) receptor.

Several pharmacological interactions occur between THC and CBD. CBD may add to the anti-inflammatory and analgesic effects of THC, but reduce its psychomotor stimulation.

THC and CBD have mild effects on the cardiovascular system in animals. There is some evidence that tolerance develops to the cardiovascular effects of THC. These effects of THC may be attenuated by simultaneous administration of CBD.

In animal studies, THC has been associated with mood changes, pro- and anti-convulsant effects, impaired short-term memory and impaired learning in young animals. CBD can have anxiolytic and anticonvulsant effects.

In most studies cannabis and THC cause reversible suppression of immune function: modulation of lymphocyte proliferation, modulation of cytokine production, and suppression of NK cell activity, suppression of macrophage function and neutrophil function, and suppression of antibody production. Some reports have found a

stimulatory effect on other components of the immune system. CBD probably has a weaker effect on immune function.

THC appears to have lower addictive properties than opioids, cocaine and amphetamines. CBD probably has little or no abuse potential. Withdrawal effects after long-term THC treatment appear to be minor.

Summary
Animal data show that THC has analgesic activity, but there is a less marked analgesic effect from CBD. Animal data suggest THC could relieve spasticity. Both compounds have psychotropic effects that may be beneficial in MS. The combination of THC and CBD may be more effective than THC alone, but the evidence is not especially convincing.

2. Pharmacokinetics
Animal pharmacokinetic studies with Sativex have not been performed, but the pharmacokinetics and metabolism of THC and CBD have been evaluated. None of these studies used the oromucosal route intended for Sativex, because of the difficulty administering drugs by this route to animals.

THC. Oral administration results in variable blood levels, because of destruction of the drug in the stomach and extensive first-pass hepatic metabolism. The oral bioavailability is only 10-20%. THC is rapidly absorbed and distributed after oral administration. The terminal elimination $T_{½}$ after IV administration is 2-3 days in rabbits and 8 days in dogs. THC has a large volume of distribution. The highest tissue levels occur in fat. THC is more lipid-soluble than CBD. THC can cross the placenta. The principal route of metabolism in most animals and in man is by hydroxylation to form 11-OH-THC. Excretion, mainly as metabolites, is via the faeces and urine. After oral or IV administration of radiolabelled-THC, 56-67% of the dose is excreted within 96 hours. In rats, a substantial proportion is excreted in bile.

CBD. In rats CBD is rapidly absorbed and distributed. The terminal $T_{½}$ after IV or oral administration is about 11 hours. The disappearance of THC from the blood after IV administration shows a rapid distribution phase ($T_{½}$ 2 min) and a much slower terminal phase ($T_{½}$ 11 hours). In dogs, CBD is rapidly distributed after IV administration and slowly eliminated ($T_{½}$ 9 hrs); it has a large volume of distribution (~100 L) indicating widespread tissue distribution. CBD undergoes hepatic metabolism and oral bioavailability is 20%. The principal metabolites are hydroxylated derivatives. There is little information on the excretion of CBD.

Pharmacokinetic interactions. At high doses, CBD inhibits P450 isozymes for which THC is a substrate. However, at doses similar to those in Sativex, CBD is unlikely to have an immediate effect on tissue and brain levels of THC and its metabolites. Long-term administration of CBD may modify the metabolism and distribution of THC. CBD has the potential to alter the metabolism of other drugs.

Toxicology. Single oral dose studies with THC and cannabis extract suggested low acute toxicity in several laboratory species. Signs of toxicity were anorexia, weight loss, sedation, dyspnoea and hypothermia. Female rats were more susceptible than males to the toxic effects of THC or cannabis extract. Post-mortem findings were

unremarkable. THC showed more acute toxicity (including convulsions) when administered IV. LD_{50} values for oral THC were generally >1 g/kg in rats, 3 g/kg in dogs and 9 g/kg in rhesus monkeys, suggesting a wide margin of acute safety in man for Sativex. IV LD_{50} values were much lower: 15-20 mg/kg in rats, 62.5 mg/kg in rhesus monkeys and 1,000 mg/kg in dogs.

Comparison of IV LD_{50} values suggests that CBD is less acutely toxic than THC. The IV LD_{50} in rats for CBD was 235-252 mg/kg. Clinical signs of toxicity were similar to those reported with THC. Deaths after CBD in rodents mainly resulted from hypothermia. The main post-mortem finding in animals treated with IV CBD was a dose-related increase in liver weight.

Repeat-dose studies suggested there was cumulative toxicity for THC and cannabis extract in the early stages of treatment. The signs of toxicity were similar after single or repeat doses, apart from a change in behaviour following repeat dose. Deaths following repeat doses of THC were mainly due to hypothermia. Repeat oral doses of CBD had a similar toxicological profile to THC.

Both CBD and THC produced a reversible reduction in the weight of sex organs. Both compounds increased the weight of the liver and adrenal glands, but these effects were not associated with any marked histopathological changes.

Genotoxicity. THC and CBD have a very low potential for causing genotoxicity.

Carcinogenicity. In mice there was an increase in thyroid follicular cell tumours at a single dose. There was no dose-response relationship and there was no evidence that hyperplasia of thyroid follicular cells progressed to adenomas or carcinomas.

Reproductive and Developmental Toxicity. Repeat doses of both THC and CBD were associated with reduced uterine and testicular weight, increased oestrous cycle length and inhibition of spermatogenesis. These effects were mediated by effects on the hypothalamus and pituitary, resulting in reduced circulating levels of testosterone, progesterone, LH, FSH and prolactin.

In pregnancy, cannabinoids had a dose-related adverse effect on the number and weight of offspring and their survival. THC may exert adverse effects on reproductive function at relatively low doses. THC was associated with increased embryo-fetal mortality in several species. In some mouse studies, high doses of THC had teratogenic effects, but THC was non-teratogenic in rats, rabbits and rhesus monkeys.

THC caused alterations in fetal sexual and behavioural development when administered in doses as low as 1 µg/kg to pregnant rats or sexually immature offspring. CBD probably has a similar effect to THC on embryo-fetal development.

GLP-compliant studies using a 1:1 mixture of THC and CBD confirmed that cannabinoids have adverse reproductive effects. The "no-effect" dose on early embryonic and fetal survival in rats was only ~1 mg/kg/day (similar to the likely maximum dose for Sativex). There was no evidence of teratogenic activity for 1:1 THC and CBD in rats or rabbits at doses exceeding human maximum doses. In a rat

pre- and post-natal study, pup survival and nursing behaviour were impaired at doses of 2-4 mg/kg/day.

Local Tolerance. No irritation of the buccal mucosa was observed in two GLP-compliant studies.

Summary of the pharmacotoxicological data. The results suggest Sativex should not be used during pregnancy or breast-feeding.

PART IV: CLINICAL DATA

A. Clinical Pharmacology

1. Pharmacodynamics

2. Pharmacokinetics

Cannabinoids have low oral bioavailability, because of first-pass hepatic metabolism. The degree of first-pass metabolism varies widely between subjects. For this reason, a within-patient dose titration using a small-unit sublingual dose was selected.

Most of the pharmacokinetic data was obtained from single dose studies in healthy volunteers. Sativex appears in the plasma within 15-30 minutes; T_{max} 90 mins. C_{max} and exposure to THC were greater than for CBD, suggesting that THC may have a slightly greater bioavailability. Individual values for C_{max} and exposure show a high degree of patient variability (providing the rationale for within-patient dose titration).

There has been no systematic study of multiple dose pharmacokinetics, or pharmacokinetic studies in different patient populations. In a phase III study, a cohort of patients had plasma levels measured at two time points during chronic exposure. There was no evidence of accumulation of THC or CBD in the plasma. The range of C_{max} after chronic dosing was similar to the range after a single dose. There was variability between patients in plasma levels.

The first metabolites are hydroxylated derivatives, which then undergo oxidation by CYP450 isoforms. Excretion of metabolites of THC is largely fecal and renal. There is little data on the excretion of CBD. Structurally, THC and CBD are similar. Both are highly lipophilic, leading to rapid uptake into tissues and a high volume of distribution. Radiotracer studies show that THC and CBD both cross the blood-brain barrier.

In vitro studies suggest 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.

B. Efficacy

A trial using Sativex in patients with brachial plexus injuries was included in the dossier, but has not been reviewed.

Trials in patients with multiple sclerosis

GWN19901A. This was an exploratory trial in patients with various symptoms, including chronic refractory pain of neurological origin. Only 16/34 patients had MS. The primary objective was to identify the therapeutic windows in which patients may benefit from Sativex. The results do not help in determining the efficacy of Sativex in the treatment of pain in MS.

GWMS0001. This was a double-blind, randomized, 6-week, parallel group, placebo-controlled trial of THC + CBD in patients with MS. Five symptoms were assessed: pain, spasticity, spasms, bladder problems and tremor. 160 patients were randomized and 154 completed the randomised part of the study. 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 ($p = 0.124$; 95% CI –13.52, 1.65 mm). The estimated treatment difference for spasticity was 7.10 mm in favour of Sativex (non-significant; $p = 0.062$; 95% CI –14.56, 0.37 mm). In a subgroup of 39 patients in whom spasticity was the primary symptom, the results were statistically significantly in favour of Sativex: difference of 22 mm with placebo; $p = 0.001$.The estimated treatment differences for other impairments were all in favour of Sativex, but were not statistically significant. The traditional clinician-reported assessment of spasticity (Ashworth Scale) was not used.

GWMS0107. This was a single center, double-blind, randomised, placebo-controlled parallel group study. 66 patients with MS and central neuropathic pain [Box Scale 11 (BS-11) ≥4] and stable analgesic medication for the previous 2 weeks were recruited. After a 7-10 day baseline period, patients were randomised to a 4-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 4 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 ($p = 0.005$, 95% CI –2.11 to –0.39 boxes). The main secondary efficacy measure, the neuropathic pain scale (NPS) also favoured Sativex over placebo: estimated treatment difference 6.59 ($p = 0.044$; 95% CI –12.98, -0.20). 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. More patients treated with Sativex achieved a 1-box improvement 29/33 vs. 18/32; $p = 0.0057$), 2-box improvement (Sativex 19/33 vs. placebo 10/32; $p = 0.0464$) and 3-box improvement (Sativex 16/33 vs. placebo 4/32; $p = 0.0027$). The level of sleep disturbance and the Patient Global Impression of Change favoured Sativex. Results of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) showed a trend to improvement after 4 weeks in both groups. The only statistically significant treatment difference occurred with the long-term memory storage score, which was in favour of placebo. There was no difference between groups in the Hospital Anxiety and Depression Scale, MS Functional Composite Score and Guy's Neurological Disability Scale.

GWPS0105. This 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 decreased by 1.3 boxes in the Sativex group and 0.9 boxes in the placebo group: treatment difference 0.39 boxes ($p = 0.332$;

95% CI –1.18, 0.40). The median percentage of days that patients in the Sativex group took escape medication was 4.8% vs. 45% in the placebo group (p = 0.006). The difference in the use of escape medication between the two groups confounded the primary endpoint. The results for the subgroup with MS were similar to the overall results.

GWMS0106. This was a pivotal Phase III study in patients with MS complicated by spasticity (Ashworth Score ≥2 in 2 or more muscle groups unrelieved by existing treatment). Sativex was used as an add-on treatment for 6 weeks. The primary outcome measure was change from the baseline Numerical Rating Scale (NRS). In the intention-to-treat (ITT) population, the change in the NRS was –1.11 for the Sativex group and –0.52 for placebo (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). Responders (patients achieving ≥30% improvement) were seen in 40% of the Sativex group and 22% of the placebo group (p = 0.014). Secondary efficacy measures, including the Ashworth Scale (p= 0.22), spasm frequency (p = 0.14) and Motricity Index (p=0.054) also favoured Sativex, but the differences were not significant.

GWCL0403. This 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: change in the NRS from baseline was –1.05 for Sativex (n = 166) and –0.82 for placebo (n = 169); p = 0.21. For the "per protocol population", the change in the NRS was –1.30 for Sativex and –0.84 for placebo (p = 0.035). The frequencies of responders in the ITT populations were 31% in the Sativex group and 25% in the placebo group (NS).

GWEXT0102. This was a long-term, open-label, safety and tolerability study of Sativex in patients who had had a positive response in earlier trials. The study was not limited to patients with MS, or to patients with pain. The mean duration of exposure to Sativex was 463 days. There was no loss of analgesic activity during the first year. Only 12/156 patients withdrew due to lack of efficacy. There was no increase in Sativex usage or use of other analgesic medications over time.

Spasticity: pooled results. The results of 3 Phase III trials (GWMS0001, GWMS0106 and GWCL0403) that assessed the response of spasticity were pooled. The pooled results for the ITT populations (666 patients) were used. The difference between Sativex and placebo in the NRS at the study end was –0.32, 95% CI –0.61, -0.04, p = 0.027. The proportion of 30% responders at the study end was 37% for Sativex and 26% for placebo; OR 1.62; 95% CI 1.15, 2.28, p = 0.0073. Efficacy was maintained in long-term, open-label extension studies.

Pain in Cancer

There has been one randomised controlled study in patients with cancer pain

GWCA0101. This was a 2-week, multicentre, double-blind, randomized, 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 3 groups: Sativex, THC alone or placebo.

Medication was self-titrated (maximum of 48 actuations in 24 hours). The pain NRS was the primary efficacy variable (0 = no pain, 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 the ITT population were: Sativex –1.37, THC –1.01, placebo –0.69. The estimated treatment difference between Sativex and placebo was –0.67 (p = 0.014; 95% CI –1.21, -0.14). There was an estimated treatment difference of 0.32 points in favour of THC over placebo, but this was not statistically significant (p = 0.245, 95% CI –0.86, 0.22). 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 patients on Sativex achieved a "clinically relevant" 30% improvement in pain vs. 21% of patients on placebo (odds ratio 2.81; 95% CI 1.22-6.5).

GXEXT0101. Patients recruited in 0101 were invited to participate in an open-label study. 42/72 eligible patients entered the extension study. By 6 months, only 11 patients (28%) remained on treatment and the median duration of exposure was only 25 days. The beneficial effects reported in 0101 were generally maintained. A stable dose was reached by Day 6 and there was no tendency for the dose to increase over time.

C. Safety

The overall numbers of patients included in controlled studies were (1) MS: 496 Sativex and 434 placebo; (2) in all placebo-controlled studies (regardless of indication): Sativex 921, placebo 853 and (3) in patients with cancer pain: Sativex 60, placebo 59.

In the MS studies, the following AEs occurred more frequently in the Sativex group compared with placebo group: (1) gastrointestinal: nausea (10.8% vs. 6.5%), dry mouth (6.7% vs. 2.8%), vomiting (3.4% vs. 2.1%), constipation (3.2% vs. 0.7%); (2) general: fatigue (14.9% vs. 10.8%), asthenia (7.9% vs. 3.9%), "feeling abnormal" (2.6% vs. 0.5%), feeling drunk (3.4% vs. 0.2%); (3) nervous system: dizziness (32.7% vs. 10.8%), somnolence (7.9% vs. 3.9%), dysgeusia (3.6% vs. 1.2%), disturbance in attention (4.8% vs. 0), dysarthria (2.4% vs. 0.5%); (4) psychiatric: depression (3% vs. 1.8%), confusion (5.4% vs. 1.2%), (5) ear and labyrinth: vertigo (5.4% vs. 1.6%). The frequency with which these mild and moderate AEs occurred does suggest that the development of these symptoms may have unblinded 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 vs. 3.5% on placebo. The two most common AEs, which led to discontinuation of study medication were dizziness in 12 patients (2.4%) and nausea in 2.2%. In the Sativex-treated patients, 4 AEs were severe in >1% of the total patient population: dizziness (22 patients), asthenia (9 patients), vertigo (6 patients), fatigue (5 patients). SAEs occurred in 22 patients on Sativex (4.4%) and 15 patients (3.5%) on placebo. The events were classed as treatment-related in 8 patients on Sativex (1.6%) and 3 on placebo (0.7%). SAEs occurring in patients receiving Sativex (1 patient each) were vomiting, urinary tract infection, dehydration and cystitis,

respiratory distress, confusion, depression and suicidal ideation, muscle spasms and agitation and transient ischaemic attack.

In long-term open label studies in patients with MS, 662 patients have taken Sativex for a mean of 409 days. A long list of AEs occurred in >3% of patients which were judged to have at least a possible causal relationship to Sativex. Those AEs that occurred in >10% of patients were nausea (10.8%), diarrhoea (13.1%), fatigue (11.0%) and dizziness (27.5%). Most AEs occurred early after exposure. The withdrawal rate due to AEs was 15.8%. The most common reasons for withdrawal due to an AE were nausea (2%) and dizziness (1.8%).

In patients with cancer, AEs were reported in 85% of patients receiving Sativex vs. 70% on placebo. The most common treatment-related AEs in cancer patients on Sativex were somnolence (13%), dizziness (12%), nausea (10%) and confusion (7%). The pattern of AEs was similar to the AEs observed amongst patients with MS. Most AEs were mild or moderate in severity. Ten (17%) patients receiving Sativex terminated study treatment due to an AE (vs. 3 patients on placebo). No death was attributed to the study drug. SAEs occurred more commonly in the Sativex group: 13/60 (22%) vs. 7/59 (12%). However, none of the SAEs were judged to be related to treatment. The pattern of AEs seen in the long-term study reflected that seen in the controlled study.

Clinical laboratory results. There have been some reports of abnormal liver enzymes, most commonly an isolated increase in GGT. There were no other unexpected results.

Serious adverse events and deaths in non-cancer clinical studies. There have been 46 deaths during all use of Sativex. 27 of these deaths occurred in patients with cancer. Of the remainder, 3 were considered to have a possible relationship to Sativex: adult respiratory distress and acute tubular necrosis in a patient with diabetes and neuropathy, aspiration pneumonia in a patient with MS and mesothelioma in a patient with a spinal cord injury.

Safety of Marketed Product. Sativex has been marketed in Canada and the UK. About 2500 patients have been prescribed Sativex in this way. 24 patients have had a SAE, which was deemed to be related to Sativex in 13.

C. Summary of clinical data

For neuropathic pain in multiple sclerosis. The results of 3 randomised, placebo-controlled trials were presented in support of this indication. In one of these studies (GWMS0107) there was a statistically significant benefit in short-term pain relief compared with placebo, but in the other two trials (GWMS 0001 and GWMS 0105) there was only a non-significant trend towards benefit from Sativex. Interpretation of GWMS0107 was 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.

For relief of spasticity in multiple sclerosis. In GWMS0001, there was 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 primary

symptom. Two pivotal Phase III, placebo-controlled trials assessed the role of Sativex in the treatment of spasticity. In GWMS0106 there was a marginally significant benefit for Sativex over placebo in the ITT population ($p = 0.048$), but there was a statistically significant benefit in the per protocol population. A significantly greater number of patients treated with Sativex achieved a ≥30% improvement (defined as a clinically significant improvement). In the other pivotal study (GWMS0403), there was no statistically significant difference between Sativex and placebo in the IIT population, but a significant benefit was demonstrated in the per protocol population. When the results of these three studies were pooled, there was a significant benefit for Sativex over placebo.

For relief of pain with cancer. The results of one placebo-controlled randomised trial were presented and in this study there was a statistically significant benefit of Sativex over placebo for pain relief. This benefit may be clinically significant, because the study was performed in a population of patients in whom pain was incompletely controlled by opioid medications.

Safety. Adverse events were common, but the vast majority of these AEs were mild or moderate in severity. Severe AEs were uncommon. In summary there were no major concerns about safety.

DATA SHEET

OVERALL SUMMARY

The trials suggest that Sativex may reduce central pain in patients with MS, but there is insufficient evidence to support this indication.

There is better evidence that Sativex reduces spasticity in patients with MS, but even for this indication only 1 of 3 placebo-controlled trials showed a statistically significant benefit in the primary endpoint in the ITT population. The pooled results did show a statistically significant benefit.

There has only been one medium-sized trial in patients with cancer pain. This trial did show a statistically significant benefit for Sativex, but further evidence of efficacy for this indication is required.

Mild AEs were common and while these events do not raise any major safety issues, they do suggest that the patients receiving Sativex in the placebo-controlled trials may have been unblinded.