Public Information Report

on

Sativex Oromucosal Spray

UK/H/961/01/DC

PLEASE NOTE:

The Assessment Report may not include all available information on the product if the assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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Module 1 – Introduction and background

An application for a marketing authorisation for Sativex Oromucosal Spray was submitted by GW Pharma Ltd in August 2006 via the European Decentralised procedure involving a number of member states with the UK acting as the Reference Member State (RMS). Before the procedure was formally concluded, GW Pharma Ltd decided to withdraw the application from final determination.
Although the marketing authorisation application was withdrawn before the end of the procedure, Sativex has been supplied on a named patient basis in the UK to approximately 1200 patients to date.

MHRA therefore considers that it is in the interest of public health to provide potential prescribers with information on the MHRA's assessment of quality, safety and efficacy of Sativex in the relief of spasticity in people with multiple sclerosis in the form of a public information report based on the information submitted by the Company in support of its application up to the date of withdrawal.

There has also been public interest in the licensing of Sativex and we wish to inform the public about its current position.

The Decentralised Procedure

There are a number of ways marketing authorisation holders (MAH or applicants) can obtain a licence (marketing authorisation, MA) for a medicinal product. One of these is using the decentralised procedure (DCP) where the MAH submits the marketing authorisation application (MAA) in all countries (member states) in which it wishes to hold a licence. This was the procedure selected by GW Pharma Limited. The MAH will select one country to act as the reference member state (RMS), all other countries involved are referred to as concerned member states (CMSs). Once the valid MAA is submitted in all the member states, the RMS has 70 days in which to assess the application and prepared the Day 70 assessment report, which is then sent to all the other CMSs and the applicant. The CMSs then have till Day 100 of the procedure to provide their comments on the application to the RMS. Following discussions and if there are unresolved issues at Day 105, the applicant has 3 months to prepare responses to the outstanding concerns of the member states. Once the applicant submits the response document the procedure restarts and the RMS then has until Day 120 to prepare and send a draft assessment report to the CMSs. If consensus is reached the procedure can be closed on Day 120. However, if there are divergent opinions between member states the CMSs have until day 145 to send their comments to the RMS. If consensus is still not reached by Day 150, there are a further 30 days (up to Day 180) in which the applicant has to resolve issues and for the member states to reach consensus. At Day 180 the RMS communicates the outstanding issues to the applicant. A break out session (BOS) can be arranged to occur before Day 205. At Day 210, the procedure can be closed if all member states are in agreement (whether that be to approve of refuse the grant of a MA).

In the case of Sativex, the applicant chose to withdraw the application from the procedure between Day 205 and 210 following the BOS.

Content of the Sativex Public information Report

In order to inform the public about the assessment position on the quality, safety and efficacy of Sativex in the relief of spasticity in people with multiple sclerosis, prior to the withdrawal of Sativex application, this report on Sativex contains summarised Assessment Reports (Quality, Preclinical and Clinical) written by the RMS. The report summarises the position of the application up to the time of withdrawal by GW Pharma Ltd from the procedure. Assessment reports have been amended after

deletion of any information of a commercially confidential nature. The report also lists, at the end, the remaining major outstanding concerns on efficacy which have not been resolved.

Module 2

Information about the procedure

Proposed name of the medicinal product in the RMS	Sativex Oromucosal Spray
INN (or common name) of the active substance(s):	Delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS) [Tetranabinex] and Cannabidiol Botanical Drug Substance (CBD BDS) [Nabidiolex], as extract of *Cannabis sativa* L.
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Pharmaceutical form(s) and strength(s):	Oromucosal Spray
Reference Number for the Decentralised Procedure	UK/H/961/01/DC
Reference Member State:	UK
Member States concerned:	DK, ES, NL
Applicant (name and address)	GW Pharma Porton Down Science Park, Salisbury, Wiltshire SP4 OJQ
Timetable	Withdrawn before Day 210

Module 3

Proposed Summary of Product Characteristics (SmPC)

Please note that, as GW Pharma Ltd withdrew from the procedure before Day 210, the SmPC was not finalised and is presented here as the last draft version submitted by the company, after deletion of information of a commercially confidential nature, before withdrawal.

1 NAME OF THE MEDICINAL PRODUCT

SATIVEX Oromucosal Spray.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
26-44mg and 35-42mg of two extracts (as soft extracts) from *Cannabis sativa* L., folium cum flore (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol and 25mg cannabidiol.
Extraction solvent: Liquid carbon dioxide

For full list of excipients, see 6.1.

Each 100 microlitre spray contains:
2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).
Each 100 microlitre spray also contains up to 0.04g alcohol.

3 PHARMACEUTICAL FORM

Oromucosal spray.
Solution in a spray container.

4 Clinical Particulars

4.1 Therapeutic indications

SATIVEX is indicated, as add-on treatment, for symptomatic relief of spasticity in patients with multiple sclerosis (MS) who have not responded adequately to other medication and who demonstrate worthwhile improvement during a 4-week trial of therapy.

4.2 Posology and method of administration

SATIVEX is for oromucosal use only.

The spray should be directed at different sites on the oromucosal surface changing the application site for each use of the product.

Patients should be advised that it might take up to two weeks to find the optimal dose and that adverse reactions can occur during this time. These reactions are usually mild and resolve in a few days, however physicians should consider reducing the dose or interrupting, at least temporarily, the treatment depending on the seriousness and intensity of the adverse drug reactions. Patients should be reviewed by the prescribing physician. If SATIVEX is well tolerated, patients should continue to receive medication for four weeks to evaluate efficacy. Only patients who are clearly benefiting from treatment with SATIVEX after this time should continue to receive the medication. The long term efficacy of SATIVEX in spasticity symptoms in MS patients has not been fully established and therefore the value of treatment should be re-evaluated periodically.

Titration period
A titration period is required to reach optimal dose. The number and timing of sprays will vary between patients.

Initial dose
On day one, patients should take one spray in the morning and one spray in the afternoon/evening.

Subsequent days
The dose should be increased by one spray each day depending on individual response and tolerability.

Maintenance period
Following the titration period, patients are advised to maintain the optimal dose achieved. The average effective dose is 8-9 sprays a day though there is variability between patients and the maximum dose is 24 sprays a day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards (without exceeding the maximum dose) or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop.

Children
No studies have been conducted in adolescents or children under 18 years of age, therefore SATIVEX is not recommended in the paediatric population.

Elderly
No specific studies were carried out in elderly patients, although patients up to 90 years of age were included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks.

Patients with significant hepatic or renal impairment.

Refer to Section 4.4.

4.3 Contraindications

SATIVEX is contraindicated in patients:

- With known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil.
- With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.

And

- In nursing women (in view of the considerable likely levels of cannabinoids in maternal breast milk and the potential adverse developmental effects in infants).

4.4 Special warnings and precautions for use

- Mild or moderate dizziness is commonly reported. This most frequently occurs during the titration period.
- SATIVEX is not recommended for use in children or adolescents as they may be more susceptible to the psychoactive effects of THC.
- Use of SATIVEX is not recommended in patients with serious cardiovascular disease. Cannabinoids may have cardiovascular effects that include tachycardia and transient changes in blood pressure including episodes of hypotension.
- Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.
- THC and CBD are metabolized in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. No specific studies have been carried out in patients with significant hepatic or renal impairment. In such individuals the effects of SATIVEX may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in this patient population.
- SATIVEX contains approximately 50% v/v of ethanol. Each actuation contains up to 0.04g of alcohol. A small glass of wine (125ml) of nominal ethanol content 12% v/v would contain approximately 12g ethanol. The maximum recommended daily dose of 24 sprays would contain less than 1g of ethanol.
- There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of SATIVEX could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

- Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in clinical trials with SATIVEX. However, patients should be warned of this possibility.
- Although no effect has been seen on fertility, independent research in animals found that cannabinoids affected spermatogenesis. Male patients with a partner of childbearing potential should ensure that reliable contraceptive precautions are maintained for the duration of therapy and for three months after discontinuation of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

See also Section 5.2 for in vitro data on the potential for interactions with other drugs metabolised by the Cytochrome P450 enzyme system.

The two main components of SATIVEX, delta-9-tetrahydrocannibinol (THC) and cannabidiol (CBD), are metabolised by the Cytochrome P450 enzyme system. In clinical trials where SATIVEX has been taken concomitantly with other drugs metabolised by the Cytochrome P450 enzyme system, no clinical consequences have been seen in these trials at clinical doses.

Amitriptyline is metabolised by CYP2C19, CYP1A2, CYP2C9 and CYP2D6. In clinical trials patients have been restricted to 75mg amitriptyline or less daily, therefore doses higher than this should be used with caution.

Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects.

Although there has been no greater rate of adverse events in patients already taking anti-spasticity agents with Sativex, care should be taken when co-administering Sativex with such agents since a reduction in muscle tone and power may occur, leading to a greater risk of falls.

SATIVEX may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly.

4.6 Pregnancy and lactation

There is insufficient experience in humans regarding the effects of SATIVEX on reproduction. Therefore men and women of child bearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

Pregnancy

SATIVEX should not be used during pregnancy unless the potential risks to the foetus and/or embryo are considered to be outweighed by the benefit of treatment.

Lactation

In view of the considerable likely levels of cannabinoids in maternal breast milk and the potential adverse developmental effects in infants, SATIVEX is contraindicated in nursing mothers (see also Section 5.3).

4.7 Effects on ability to drive and use machines

SATIVEX may produce adverse reactions such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Patients should be advised not to drive, operate machinery or engage in any hazardous activity if they are experiencing these adverse reactions. Patients should be aware that SATIVEX has been known to cause loss of consciousness.

4.8 Undesirable effects

The SATIVEX clinical program involved over 1350 patients in placebo controlled trials and long-term open label studies. Mean exposure in 444 patients with MS included in long-term extension clinical studies was 455 days.

The most commonly reported adverse reactions during placebo-controlled trials were dizziness, which occurs mainly during the initial titration period, nausea and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued (see also Section 4.2).

The frequency of adverse events with a plausible relationship to SATIVEX, from placebo controlled trials, according to System Organ Classes (SOC) are given below (some of these adverse events may be part of the underlying condition):

MedDRa SOC	**Very Common >10%**	**Common <10% - >1%**	**Uncommon <1% - >0.1%**
Infections and infestations		Pharyngitis	
Metabolism and nutrition disorders		Anorexia, appetite increased	
Psychiatric disorders		Confusion, depressed mood, disorientation, dissociation, euphoric mood,	Anxiety, hallucination (unspecified, auditory, visual), illusion, paranoia
Nervous system disorders	Dizziness	Balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, somnolence	Amnesia, memory impairment
Eye disorders		Vision blurred	
Ear and labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders		Throat irritation	
Gastrointestinal disorders	Nausea	Constipation, diarrhoea, dry mouth, mouth ulceration, oral discomfort, oral pain, vomiting	Abdominal pain,, abdominal pain (upper), glossodynia, oral mucosal disorder, stomatitis, tooth discolouration
General disorders and administration site conditions	Fatigue	Application site irritation, application site pain, asthenia, feeling abnormal, feeling drunk, thirst	
Injury, poisoning and procedural complaints		Fall	

The following further adverse reactions have also been reported in long-term open-label studies:
Common: decreased appetite, hypotension, oral mucosal discolouration, oral mucosal exfoliation, syncope.
Uncommon: delusional perception.

Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with SATIVEX. These are likely to be the result of CNS effects and are generally mild to moderate in severity. The majority of cases can be expected to resolve on reduction or interruption of SATIVEX. Disorientation (or confusion), hallucinations and delusional beliefs have also been reported. In these circumstances, SATIVEX should be stopped immediately and the patient monitored until the symptom has completely resolved.

A causal association between SATIVEX administration and suicidal ideation or psychosis cannot be ruled out.

Small increases in pulse rate and small decreases in blood pressure have been observed following initial dose introduction so caution during initial dose titration is essential. Fainting episodes have been observed with use of SATIVEX. A single case of ventricular bigeminy has been reported though this was in the context of acute nut allergy.

Adverse reactions have been reported which could be associated with the route of administration of the medicine. Application site type reactions consisted of mainly mild to moderate stinging at the time of application. Two cases of suspected leukoplakia (a potential pre-malignant condition) have been reported in patients taking SATIVEX during clinical development. Both patients were smokers. Histology was essentially normal in one case. Smear cytology results were consistent with leukoplakia in the second case which subsequently resolved. In view of this, patients who observe discomfort or ulceration at the site of application of the medicine are advised to vary the site of application within the mouth and should not continue spraying onto sore or inflamed mucous membrane. Regular inspection of the oral mucosa is also advised in long-term administration. If lesions or persistent soreness are observed, medication should be interrupted until complete resolution occurs.

The abrupt withdrawal of long-term SATIVEX treatment has not resulted in a withdrawal syndrome and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients. No increase in daily dosage has been observed in long-term use, and patient self-reported levels of 'intoxication' are low. For these reasons, dependence on SATIVEX is unlikely.

See 4.4 and 4.5 and 4.7 for Warnings, Precautions and Interactions and Effects on ability to drive and use machines.

4.9 Overdose

There is no experience of deliberate overdose with SATIVEX. Signs and symptoms of overdose/poisoning are expected to be related to the CNS and physical effects of cannabinoids, which would typically consist of an acute intoxication type reaction including dizziness, hallucinations, delusions, paranoia, tachycardia or bradycardia with hypotension.

Treatment should be symptomatic and supportive.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

ATC Code: Not yet assigned.

Mechanism of action

Mammalian tissues contain at least two types of cannabinoid (CB) receptor, CB_1 and CB_2. These are both coupled through inhibitory G protein ($G_{i/o}$), negatively to adenylate cyclase and positively to mitogen-activated protein kinase. The CB_1 receptor is also coupled through G protein to certain types of calcium and potassium channel. CB_1 receptors are present in the central nervous system and also in some peripheral tissues including pituitary gland, immune cells, reproductive tissues, gastrointestinal tissues, sympathetic ganglia, heart, lung, urinary bladder and adrenal gland. Central and peripheral neuronal CB_1 receptors are found mainly at nerve terminals and one function of these receptors is to inhibit neurotransmitter release. CB_2 receptors are present primarily on peripheral and central immune cells. Their exact roles are unclear but include the modulation of cytokine release. Thus whilst the CB_1 receptor has a neuromodulatory role, the CB_2 receptor may be immunomodulatory.

Within the brain, the distribution of CB_1 receptors is heterogeneous, including the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum. This distribution pattern is consistent with the ability of cannabinoids to alter motor function and to impair cognition and memory. Additionally, CB_1 receptors are found on pain pathways in the brain and spinal cord and also outside the central nervous system at the peripheral terminals of primary afferent neurons and it is these CB_1 receptors that are thought to mediate cannabinoid-induced analgesia in animal models.

Published literature confirms that both oral and smoked cannabis and oral, smoked or intravenous THC can cause a dose-dependent cardio-acceleration that is generally no more than 60% of resting heart rate. Review of cardiovascular clinical pharmacology and of the physiology of cannabis/THC shows there are few case reports of complications arising from cannabis use. Effects on heart rate and blood pressure can be notable, yet transient. Few clinically effects have been observed during SATIVEX administration (see Section 4.8).

Published studies showed that oral and aerosolized THC has been shown to cause bronchodilation, though results were mixed in asthmatic patients where bronchoconstriction occurred in some patients. CBD was shown to have no effect on airway conductance or any effect on the bronchodilating activity of THC. However, no clinically significant trends in vital signs have been seen with SATIVEX (see Section 4.8).

Clinical experience

SATIVEX has been studied in controlled clinical trials of up to 14 weeks duration. In MS patients, SATIVEX has shown efficacy in relieving the primary symptom of spasticity, with between 27 and 40% of patients achieving an improvement of at least 30% in self-reported severity of spasticity within six weeks, compared with 22% on placebo. In long-term use, improvement in self-reported spasticity severity has been maintained for up to 12 months. In other studies with MS patients, improvements have been seen in neuropathic pain, sleep quality and bladder dysfunction.

5.2 Pharmacokinetic properties

Absorption

There is a high degree of variability between patients in pharmacokinetic parameters.

Distribution

Following a single oromucosal administration, maximum plasma concentrations of both CBD and THC typically occur within two hours. When SATIVEX is administered oromucosally, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose. A dose of 6.65 mg of vaporised THC extract, administered by inhalation resulted in a mean plasma C_{max} of more than 100ng/ml within minutes of administration, with significant psychoactivity. With SATIVEX, a mean C_{max} of around 3 ng/ml was reached some 90-120 minutes after a 10 mg dose, and there was little evidence of significant psychoactivity. The resultant concentrations in the blood are lower than those obtained by inhaling the same dose because absorption is slower and redistribution into fatty tissues is rapid. Additionally some of the THC undergoes hepatic first pass metabolism to 11-OH THC, the primary metabolite of THC.

Table to show PK parameters for SATIVEX, for vaporised THC extract and smoked cannabis

	C_{max} THC ng/ml	T_{max} THC minutes	AUC $_{(0-t)}$ THC ng/mL/min
Sativex (providing 10 mg THC)	4.90	263	918.81
Inhaled vaporised THC extract (providing 8 mg THC	118.6	17.0	5987.9
Smoked cannabis (providing 13 mg THC)	77	9	No data

Metabolism

THC and CBD are metabolised in the liver. Human hepatic P450-2C9 isozyme catalyses the formation of 11-OH-THC the primary metabolite, which is further metabolised by liver to other compounds including 11-nor-carboxy-Δ^9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The P450-3A subfamily catalyse the formation of other hydroxylated minor metabolites. CBD is extensively metabolised and more than 33 metabolites have been identified in urine. The major metabolic route was hydroxylation and oxidation at C-7 followed by further hydroxylation in the pentyl and propenyl groups. The major oxidized metabolite identified was CBD-7-oic acid containing a hydroxyethyl side chain.

Protein binding of THC is high (~97%). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream, metabolised and excreted via the urine and faeces.

When CBD and THC were incubated together, the combination of cannabinoid extracts was shown to be an inhibitor of CYP1A2, CYP2C6, CYP2D6 , CYP2C19 and CYP3A4.

However, even the lowest IC^{50} values for any of the cytochrome P_{450} enzymes *in vitro* (1887ng/ml - 39309ng/ml) are significantly greater than mean C_{max} following dosing with SATIVEX in Phase I clinical studies (CBD: 0.99ng/ml - 3.33ng/ml and THC: 2.72ng/ml - 5.45ng/ml following a dose of 10mg CBD + 10mg THC), and is considerably greater than the highest C_{max} measured following either acute or chronic stable dosing with SATIVEX (CBD: 16.97ng/ml and THC: 28.66ng/ml). Thus, the effects seen *in vitro* are unlikely to be of clinical relevance.

Elimination
Elimination from plasma is bi-exponential with an initial half-life of one to two hours. The terminal elimination half-lives are of the order of 24 to 36 hours or longer. Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

5.3 Preclinical safety data

Effects in nonclinical toxicity and safety pharmacology studies were observed only at exposures sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. SATIVEX is not genotoxic based on a battery of *in-vitro* and *in-vivo* tests.

Reprotoxicity studies carried out with the THC and CBD extracts present in Sativex showed no adverse effects on either male or female fertility in terms of numbers of animals mating, number of fertile males and females, or on copulation or fertility indices. There was reduced absolute weights of epididymides, with a "no-effect" dosage levels of 25 mg/kg/day (154 mg/m^2) for male fertility. The "no-effect" dosage levels for effects on early embryonic and foetal survival, in rat studies, were only about 1 mg/kg/day (6.2 mg/m^2), which is close to or less than the likely maximum human dosage level of Sativex. There was no evidence to suggest any teratogenic activity in either rats or rabbits at dosage levels considerably in excess of likely human maximum dosage levels. However, in a rat pre- and post-natal study, pup survival and nursing behaviour were impaired at doses of 2 and 4 mg/kg/day (12.3 and 24.6 mg/m^2 respectively). Data from the literature have shown negative effects of THC and/or CBD on sperm number and motility.

In studies in animals, as expected, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Following repeat dosing, cannabinoids are concentrated in breast milk (40 to 60 times the plasma level) and at doses in excess of normal clinical doses may affect growth rates of breast-fed infants.

6 Pharmaceutical Particulars

6.1 List of excipient(s)

Ethanol anhydrous
Propylene glycol
Peppermint oil

6.2 Incompatibilities

None reported.

6.3 Shelf life

18 months (inclusive of in-use period).
In use: 28 days.

6.4 Special precautions for storage

Store in a refrigerator (2 to 8°C).
Once the spray container is opened, do not store above 25°C.

Store upright.

6.5 Nature and contents of container

A Type I (Ph.Eur.) glass spray container fitted with a metering pump possessing a polypropylene dip tube and elastomer neck covered with a polyethylene cap. The metering pump delivers 100 microlitre per spray.

Pack Size: 5.5ml.

5.5 ml pack size allows delivery of up to 48 actuations (sprays) of 100 microlitre.
1, 2, 3, 4, 5, 6, 10 or 12 glass sprays containers per carton.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7 MARKETING AUTHORISATION HOLDER

GW Pharma Ltd.

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10 DATE OF REVISION OF THE TEXT

Module 4
Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Sativex Oromucosal Spray as add-on therapy, for symptomatic relief of spasticity in patients with multiple sclerosis (MS) is not approvable since there remain a number of issues which have not been satisfactorily resolved, which preclude a recommendation for marketing authorisation at the present time. The details of these issues are provided in the report below.

The application for Sativex Oromucosal Spray is a full application made according to Article 8(3) of Directive 2001/83/EC submitted within the decentralised procedure with UK acting as reference member state (RMS) and DK, ES and NL as the concerned member states (CMS).

The product is a solution for use as an oromucosal spray, containing a combination of two extracts from Cannabis sativa L, equivalent to 27mg/ml delta-9-tetrahydrocannabinol and 25mg/ml cannabidiol. It is presented as 5.5ml and 10ml volumes in amber glass vials with a pump spray delivering 100µl of solution per actuation. The specified cannabinoids constitute at least 90% of the total cannabinoid content of the product.

Beneficial effects of cannabis on symptoms such as pain, urinary disturbance, tremor, spasm and spasticity have also been claimed by individuals with multiple sclerosis (MS). It is known that a substantial proportion of UK MS sufferers use cannabis medicinally (MS Society).

Sativex Oromucosal Spray has been developed with the aim of providing a standardised cannabis product that approximates in composition to the ratio of THC:CBD that would be obtained from naturally occurring cannabis.

A complete dossier is provided including quality, non-clinical and clinical modules. Pivotal preclinical and clinical studies sponsored by the applicant are supplemented by published data.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The applicant states that all clinical trials presented in the dossier are GCP compliant.

The report below contains abridged quality, pre-clinical and clinical assessments, containing non-confidential aspects derived from the initial Day 70 Preliminary Assessment Report written by the RMS, and assessments at Day 120 and 180 of the procedure of the Company's responses to questions from the RMS and each CMS. It takes into account all information – both written and verbal – provided by the applicant prior to withdrawal of the marketing authorisation application.

II QUALITY ASPECTS

INTRODUCTION

This is an application for a marketing authorisation for a cannabis-based medicinal product, Sativex Oromucosal Spray, submitted under Article 8(3) of Directive 2001/83/EC (as amended) using the decentralised procedure. The UK is the Reference Member State for the product and the Concerned Member States are Denmark, Spain and the Netherlands.

The product contains a combination of two extracts from the plant *Cannabis sativa* L dissolved in solution for use as an oromucosal spray. The applicant is applying for an indication as an add-on therapy for symptomatic relief of spasticity in patients with multiple sclerosis (MS).

Sativex Oromucosal Spray has been developed with the aim of providing a standardised cannabis product with levels of cannabinoids similar to the cannabis currently used by MS sufferers in Western Europe that approximates in composition to the ratio of THC:CBD that would be obtained from naturally occurring cannabis.

HERBAL DRUGS

Growing and production of the herbal drugs is carried out by the Applicant. The plants are cultivated in line with Good Agricultural Practice (GAP).

Two plant varieties are grown; one that contains higher levels of THC and one that contains higher levels of CBD. Dried, milled herb from the high-THC and high-CBD plants are processed and controlled separately to yield the two distinct extracts needed to make the finished product.

The applicant has provided a flow diagram and satisfactory details describing the production of the herbal drugs. The herbal drugs are cultivated under highly controlled conditions and there are no major pharmaceutical concerns arising with regard to identification or potential contaminants.

The specifications applied to the herbal drugs are satisfactory

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specifications.

All reference standards have been characterised.

The batch analysis data provided comply with the release specification.

Appropriate stability data have been generated and support the proposed retest period.

HERBAL DRUG PREPARATIONS

The herbal drug preparations (extracts) are obtained from the herbal drugs using a process that has been well detailed by the Applicant. A flow diagram that includes details of the manufacturing sites involved has also been provided.
All tests and limits included in the extract specifications are satisfactory.
Analytical methods have been appropriately validated to production scale and are satisfactory for ensuring compliance with the specifications.
Extensive batch data are presented; these data comply with the specification and are satisfactory.
The reference standards are the same as those used for the herbal drugs and are, likewise, satisfactory.
The extracts are stored in suitable conditions.
Stability studies have been carried out in accordance with ICH guidelines and support the proposed retest period for both of the extracts. .
A post-authorisation commitment has been agreed with the applicant concerning on-going work to fully characterise potential degradation products.

DRUG PRODUCT

The dosage form is a solution of the cannabis extracts in a vehicle consisting of propylene glycol and ethanol flavoured with peppermint oil, presented as an oromucosal spray.

The drug product manufacturing process is relatively straightforward and is appropriate for a product of this type.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on relevant batches and the results are satisfactory.

The finished product specification is suitably comprehensive for a product of this nature. All tests and limits are appropriate and batch analysis results are in compliance with the proposed specification.

The excipients contained in the finished product comply with their current Ph Eur monographs.

A satisfactory declaration of Transmitting animal Spongiform Encephalopathy agents (TSE) compliance has been provided.

The solution is presented in a Type I amber glass vial with a crimped-on 100µl pump spray. An 8ml vial size contains 5.5ml solution. Due to photosensitivity of the cannabinoids, amber glass has been chosen. The immediate packaging materials comply with Directive 2001/62/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

Finished product stability studies have been conducted in accordance with ICH guidelines. The results support a shelf-life of 18 months for the product when stored at 5˚C ± 3˚C, with an in-use shelf-life of 28 days for product stored below 25˚C. A post-authorisation commitment has been agreed with the applicant concerning on-going work to address precipitation of non-cannabinoid components. In addition, the applicant has provided assurance that appropriate sorption studies will be performed for the solution in the packaging materials as a post-authorisation commitment.

CONCLUSIONS

All pharmaceutical points raised during the procedure have been resolved satisfactorily. The applicant has provided assurances with regard to on-going work to characterise related substances in the herbal extracts, to address precipitation of non-cannabinoid substances present in the finished product and to investigate potential sorption onto the container/closure.

III. PRE-CLINICAL ASPECTS

The preparation of Sativex (GW-1000-02) is discussed in detail in the Pharmaceutical assessment. The terms Botanical Raw Material (BRM) and Botanical Drug Substance (BDS) have been used as applicant considered use of this terminology would provide an improved description for the MAA.

Thus, there is THC BDS and CBD BDS. The THC BDS and CBD BDS are blended to produce a mixture containing THC and CBD in approximately a 1:1 ratio.

A comprehensive search of the published literature has been performed by the applicant to identify reports related to non-clinical studies on *C. sativa*, as well as its major chemical components. In all, more than 6000 articles were identified by this search, of which approximately 2,500 non-clinical pharmacology and 300 toxicology publications were assessed for inclusion in the Non-clinical Summary. Approximately 500 references are cited in the Non-clinical Summary. In addition to the literature reports, additional information was obtained from new studies on extracts of cannabis sponsored by GW Pharmaceuticals and from the Summary Basis of Approval documentation of the United States FDA for Marinol™ (synthetic THC), obtained under the US Freedom of Information Act.

A range of new pre-clinical studies has also been submitted.

PHARMACOLOGY

The applicant has demonstrated efficacy for the proposed indication from literature data relating to two rodent models of allergic encephalomyelitis. Sativex delayed the onset of symptoms such as atonia, ataxia, paraparesis and incontinence as well as prolonging lifespan. Other pharmacodynamic activity such as anti-nociceptive activity, anti-inflammatory effects, anxiolytic action etc have also been satisfactorily described.

Results from a ‘Lead profiling Screen Data Report ‘ in which radioligand binding assays were undertaken with 60 receptor types/subtypes or ion channels and with 4 neurotransmitter transporters indicate that pure THC, pure CBD and the 1:1 combination can selectively modulate neurotransmission but only at concentrations in the micromolar and high nanomolar range. The conclusion from this study sponsored by the applicant was that ‘*it is doubtful whether this activity has clinical relevance*’.

PHARMACOKINETICS

Although no animal studies have been performed this deficiency has been covered by studies performed in healthy human volunteers.

TOXICOLOGY

The toxicology programme conducted for this product was appropriate for a product of this nature in this indication and has identified no significant preclinical issues of concern.

CONCLUSION

There are no preclinical objections to the granting of a Marketing Authorisation.

IV CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

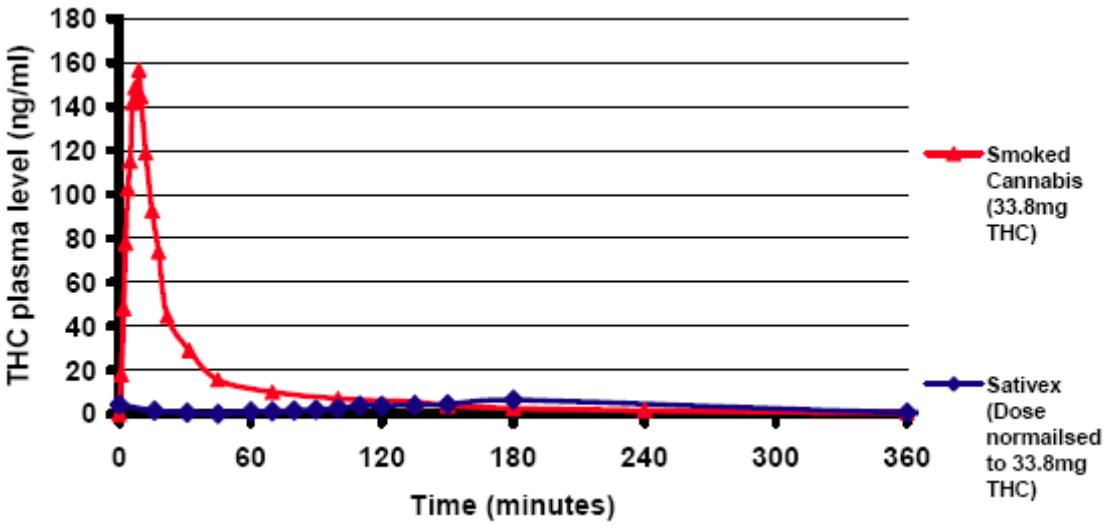
Pharmacokinetics

The proposed formulation is an oromucosal spray, which delivers 2.7mg delta-9-tetrahydrocannabinol (THC), and 2.5mg cannabidiol (CBD) per actuation. It is intended for sublingual administration.

Much of the information regarding the absorption, distribution, metabolism and excretion of the principal cannabinoids present in Sativex comes from the published literature. This is acceptable as these characteristics are well established. In addition original pharmacokinetic data were provided to characterise the pharmacokinetic profile of Sativex and to contrast with the absorption profiles of ingested and smoked cannabis.

Absorption

CBD and THC are both highly lipophilic and consequently are well absorbed following oromucosal (e.g. sub-lingual) administration. Following a single oromucosal administration, the maximum plasma concentration is reached within 2 to 4 hours. In contrast their oral bioavailability is low due to a high but variable degree of first pass metabolism. The rate and extent of absorption of the active ingredients from the Sativex oromucosal spray showed very high inter and intra-subject variation. A variable proportion of a dose of Sativex administered by the oromucosal route will be ingested and subsequently absorbed through stomach and oesophagus. This proportion will be subjected to first pass metabolism in the liver, the extent of which is itself very variable. The proportion of an oromucosally administered dose that reaches the circulation intact is therefore highly variable, resulting in high inter- and intra-subject variability in bioavailability and other pharmacokinetics parameters. For this reason dosing requirements may vary between patients and may vary with time in the same patient. Hence dose titration regimen on an individual patient basis is appropriate.



The much more rapid increase in plasma levels and the associated higher Cmax seen with the inhaled route would be expected to result in greater psychoactivity, and is the reason why smoking is the preferred method of administration for illicit cannabis users. This is consistent with the applicant's report that in Phase 1 studies vaporised THC extract administered by inhalation produced significant psychoactivity but a comparable dose of Sativex did not. This is relevant both for the occurrence of undesirable effects and for the possibility of patient unblinding to randomized treatment.

Distribution

Cannabinoids are highly fat soluble, and are therefore widely distributed and accumulate in fatty tissue. Both CBD and THC readily cross the blood brain barrier. Data on plasma concentrations are likely to correlate poorly with levels at the sites of action within the CNS, especially with long term treatment. A clear PK-PD relationship is therefore not well described. The prolonged terminal elimination half-life is due the prolonged release of cannbinoids from vessel poor fatty tissue.

This characteristic is likely to be advantageous as the aim of the product is to achieve relatively stable plasma levels without the peaks that would be associated with side effects. However long term accumulation of the drug in fatty tissues could in theory represent a safety issue.

Elimination

The metabolism of the active ingredients of Sativex has been thoroughly described in the literature. The terminal elimination half life is at least 24 to 36 hours. Pharmacokinetic sampling during chronic exposure in the extension phase of the Phase III study GWMS0001 showed no evidence of accumulation of THC or CBD in plasma, and a similar range of C_{max} values after dosing to those seen after single dose. The data showing a lack of accumulation during chronic exposure are reassuring in terms of long term safety. A reliance on literature references to establish the metabolism of THC and CBD is accepted and no particular issues are identified that might raise concerns regarding safety or efficacy.

Pharmacokinetic Interactions

Although the data do not exclude the possibility of interaction in the clinical setting, sufficient information is presented to establish that clinically relevant CYP450 mediated interactions with Sativex are not likely to be seen.

Pharmacodynamics

A substantial amount of information regarding the main pharmacological effects of the principal cannabinoids present in Sativex comes from the published literature. In addition a number of Phase I clinical pharmacology studies provided data specifically on Sativex.

Data on possible mechanisms of action specifically in the relief of associated spasticity are generally much less well established than the well known neuropsychiatric, cognitive and neuromotor aspects. There is no bio-marker for spasticity. The applicant provided a review of available data relating to the principal pharmacodynamic effects of THC and CBD that are claimed to form the basis of the claimed efficacy. It was felt that a reasonable preclinical and clinical

pharmacodynamic basis for the efficacy of cannabinoids in the relief of spasticity in MS patients had been shown.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 principal weakness of the pharmacodynamic data. However there was sufficient preclinical evidence of the effects of cannabinoids in animals models of spasticity to provide reasonable justification for the concept that stimulation of cannabinoid receptors, whether by enhancement of endocannabinoid levels or by administration of exogenous cannabinoids, might have a favourable effect on spasticity. Further pharmacodynamic data showing an effect of Sativex on the physiological phenomenon of spasticity would be highly desirable however.

It is relevant to look at the typical plasma concentration profile in patients treated with Sativex in comparison with that seen following cannabinoid inhalation. As discussed in the PK section, a dose of vaporised THC extract resulted in a relatively high Cmax, reached within minutes of administration and producing significant psychoactivity. In contrast a comparable dose of Sativex administered sub-lingually achieved a much lower Cmax and a Tmax of 90-120 minutes. This very different PK profile supports the Company's claim that the psychoactive effects seen with smoked cannabis are not problematic during treatment with Sativex. It is also an important factor when considering abuse potential and the possibility of patient unblinding in the clinical trials. However reports from the Phase I studies appear to indicate that some psychoactive effects are likely to be seen with Sativex.

Formal studies of dose response relationships have not been undertaken as they would be difficult or impossible to conduct. The wide intersubject variability in the pharmacokinetics of cannabinoids and 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.

The substantial pharmacodynamic variability that has been demonstrated between subjects, as well as the temporal variability of symptoms within the same patient and the pharmacokinetic variability, further supports the applicant's proposal that it is appropriate to allow patients to adopt a within-patient dose titration regimen. 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.

Alcohol and other CNS depressants may potentiate the effects of Sativex. There have been no specific studies of pharmacodynamic interactions with other medicinal products that are likely to be prescribed in the MS patient population, whether for spasticity or for other manifestations of the disease. The Company is relying on clinical data, since a large proportion of the patient population took such concomitant medication. The lack of pharmacodynamic interaction studies could be considered a moderate deficiency. It would be of value for example to have pharmacodynamic data to establish whether Sativex might interact with muscle relaxing agents such as baclofen and benzodiazepines, as this could be relevant in terms of maintaining muscle power and tone for example to avoid falls.

CLINICAL EFFICACY

Data from two Phase II studies and three Phase III studies conducted in patients with MS are provided in support of the indication as add-on therapy for symptomatic relief of spasticity in patients with multiple sclerosis (MS).

Phase II / dose-response studies

Phase II studies were conducted in patients with MS, investigating a number of symptoms of MS, not specifically spasticity. Studies were also conducted in patients with chronic refractory pain and/or defect of neurological function due to a range of CNS pathologies including patients with chronic pain and/or defects of neurological function due to MS, spinal cord injury, peripheral nerve or central nervous system damage. These studies were exploratory and as such cannot be considered to provide robust evidence of efficacy for the proposed indication. They are not considered in detail here.

Main studies

There are three placebo-controlled, randomised, parallel group Phase III studies in support of the proposed indication. The three Phase III studies were similar in design. The first, GWMS0001, studied a range of MS symptoms and 39 of 160 patients identified spasticity as their most troublesome symptom. It cannot be considered pivotal for the specific indication for spasticity which the Company is now requesting. In the other two studies, all patients reported spasticity as their primary symptom.

Phase III studies investigating efficacy and safety of Sativex in the treatment of spasticity in MS

Study Code (n)	**Description**	**Primary endpoint**	**Treatment Duration**
GWMS0001 n = 160 Primary spasticity group = 39 All patients with spasticity = 140	A double blind, randomised, parallel group, placebo-controlled trial of Sativex in patients with multiple sclerosis, followed by an open label assessment and study extension.	Patients identified their primary symptom from one of spasticity, pain, tremor, bladder and spasms. Primary endpoint was a 0-100mm VAS for the primary symptom severity	6 weeks
GWMS0106 n = 189	A double blind, randomised, parallel group study to assess the efficacy, safety and tolerability of Sativex compared to placebo for the treatment of spasticity in patients with multiple sclerosis	Mean daily severity of spasticity assessed with a 0-10 Numeric Rating Scale	6 weeks
GWCL0403 n = 337	A double blind, randomised, placebo controlled, parallel group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis	Mean daily severity of spasticity assessed with a 0-10 Numeric Rating Scale	14 weeks

Study GWMS0001

This was a phase III double blind, randomised, parallel group, placebo-controlled study in patients with multiple sclerosis and symptoms of pain, spasticity, muscle spasm, bladder problems or tremor.

There was no statistically significant difference between treatments for the primary endpoint, which was a composite score of target symptoms. However analyses of the individual symptom scores showed encouraging results for spasticity (39 patients).

When a trial that is negative overall has suggestive findings on a secondary endpoint, this can be a signal suggesting an avenue for further exploration. The encouraging results for spasticity in the limited number of patients in this study whose primary impairment was spasticity are viewed as hypothesis generating and cannot be considered as pivotal evidence. For this application any conclusions regarding efficacy in the treatment of spasticity in MS patients (the proposed indication) depend on the results of studies 0106 and 0403, which were specifically designed to investigate this efficacy endpoint in the patient population with MS and spasticity.

GWMS0106

This was a double blind, randomised placebo controlled, parallel group study to assess the efficacy and safety of Sativex as add-on therapy for the treatment over a 6-week period of spasticity in patients with stable MS with spasticity unrelieved - or incompletely relieved - by current therapy. The maximum permitted dose was eight actuations in any three hour period and 48 actuations (THC 130mg, CBD 120 mg) in 24 hours.

The primary endpoint was the change from baseline in the diary based Numerical Rating Scale (NRS) scores for spasticity during the last week of treatment. Secondary endpoints were composite score of Ashworth Scale in muscle groups affected by spasticity, ordinal rating scale for spasm frequency, Motricity Index scores and Patient Global Impression of Change (PGIC).

The mean (sd) number of doses per day was 9.4 (6.4) for Sativex compared to 14.7 (8.5) for placebo. The median was 6.8 for Sativex and 12.6 for placebo.

One patient was identified as an outlier on clinical and statistical grounds. This patient, who received placebo, had started treatment with beta-interferon shortly before entering the baseline period. The applicant argues that this resulted in a short-term worsening of spasticity and a high baseline NRS spasticity score which had an adverse effect on the results. Analyses for the mean and median NRS spasticity scores for Sativex and placebo at timepoints up to 6 weeks were presented with and without this outlier.

Patients receiving Sativex showed a 1.11 points reduction in NRS spasticity scores from baseline compared with a 0.59 points reduction in the placebo group (p=0.048; 95% CI: -1.029, -0.004). With exclusion of an outlier the reductions were 1.10 points in the Sativex group and 0.48 point in the placebo group (p=0.013; 95% CI: -1.118, -0.131).

Analysis of change from baseline – ITT population

	Sativex	Placebo	Difference	95% CI	p-value
Adjusted mean (with outlier)	-1.11	-0.59	-0.517	-1.03, -0.004	p=0.048
Adjusted mean (without outlier)	-1.10	-0.48	-0.625	-1.12, -0.13	p=0.013

Analysis from ANOVA with terms for treatment, centre and baseline spasticity

The difference between treatments reached statistical significance, but the p-value was not extreme for either analysis. The clinical relevance of a difference of 0.5-0.6 points on a scale ranging from 0-10 must also be evaluated.

Responder analysis - Percentage of patients with a response at endpoint – ITT population

	Sativex (n=120)	Placebo (n=64)	Difference (95% CI)	
30% response	48 (40.0%)	14 (21.9%)	18% (-5, 32)	p=0.014
50% response	21 (17.5%)	6 (9.4%)	8% (-2, 18)	p=0.189

Response: At least a 30% (50%) reduction from baseline in spasticity MRS
Analysis using Fisher's exact test

Responder analyses can be used to help assess the clinical relevance of a statistically significant difference seen on the primary scale.

The percentage of responders with greater than or equal to 50% reduction in NRS spasticity scores was 17.5% in Sativex group and 9.4% in the placebo group. Using a responder criterion of greater than a 30% reduction in NRS score gives a statistically significant result in favour of Sativex for the ITT population (40% Sativex vs. 21.9% placebo, p = 0.014).

Other efficacy endpoints

Mean Ashworth score (affected muscle groups) – ITT population

	Sativex		Placebo		Difference	95% CI	p-value
	n	mean	n	mean			
Baseline	114	2.41	63	2.44			
Change	114	-0.64	63	-0.53	-0.11	-0.29, 0.07	p=0.218

Mean Ashworth score is the average of the scores over those muscle groups with a score of ≥2 at baseline, each score ranging from 0 (no increase in muscle tone) to 4 (limb rigid in flexion or extension).
Analysis from ANOVA with terms for treatment, centre, and baseline score.

Spasm frequency – ITT population

	Sativex		Placebo		Difference	95% CI	p-value
	n	mean	n	mean			
Baseline	123	2.27	64	2.54			
Change	120	-0.39	63	-0.22	-0.17	-0.39, 0.06	p=0.141

Analysis from ANOVA with terms for treatment, centre, and baseline score.
5 point scale: 0= no spasm, 1 = one or fewer spasms per day, 2= between one and five spasms per day, 3= six to nine spasms per day, 4 = ten or more spasms per day or continuous contraction.

Motricity index – ITT population

	Sativex		Placebo		Difference	95% CI	p-value
	n	mean	n	mean			
Affected arms							
Baseline	32	68.59	16	63.19			
Change	25	3.91	15	2.61	1.30	-7.47, 10.07	p=0.766
Affected legs							
Baseline	113	53.08	61	51.49			
Change	103	5.71	56	1.85	3.86	-0.06, 7.78	p=0.054

Patient's global impression of change – ITT population

	Sativex (n=124)	Placebo (n=65)	Difference	95% CI	p-value
Very much improved	2 (2%)	0			
Much improved	24 (21%)	11 (17%)			
Minimally improved	40 (34%)	20 (31%)			
No change	38 (33%)	26 (41%)			
Minimally worse	10 (9%)	5 (8%)			
Much worse	2 (2%)	2 (3%)			
Very much worse	0	0			
Nor recorded	8	1			
% Improved	57%	48%	8%	-7, 24	p=0.349

p-value from Fisher's exact test

Assessors' Conclusions on study GWMS0106

On the primary efficacy measure Sativex was more effective than placebo both in analyses including the outlier (p=0.048) and without the outlier (p=0.013). The difference reached statistical significance but the p-value was not extreme in either analysis. It must also be considered to what extent the difference between treatments of around 0.5 to 0.6 points on a scale ranging from 0-10 represents a meaningful clinical benefit in the population studied.

Consideration of responder rates can help address the question of the clinical relevance of a statistically significant effect seen on the primary scale. An additional 8% of patients achieved >50% improvement and an additional 18% of patients achieved >30% improvement in their spasticity. These estimated improvements in response rate could be clinically valuable. Improvement in spasticity can improve quality of life substantially in these patients. Even if significant improvement is achieved only in a minority of individuals, with many patients failing to respond, this could still represent important efficacy, especially if it can be established quickly whether patients will respond to treatment so that exposure to risk without benefit is minimised. Regarding the latter point, it is difficult in a short term study with only six weeks on treatment to establish the time pattern of when responses occur.

The CHMP guideline for applications with one pivotal trial describes the criteria which must be met for an application to be successful with only one trial providing pivotal evidence. These include noting that statistical evidence considerably stronger than $p<0.05$ is usually required; the estimated size of treatment benefit must be large enough to be clinically valuable; all important endpoints should show similar findings. It is not considered that this particular trial

would clearly satisfy these requirements. The primary endpoint reached statistical significance, but the level of evidence was not extreme, even with the outlying patient removed. With the outlier included the result was the definition of borderline (p=0.048). It would not be acceptable if the decision on the efficacy of a product was dependent on the inclusion or exclusion of a single patient; any decision made must be much more robust than that.

The difference seen does not seem overly impressive on the mean scale (a difference of 0.5 – 0.6 points on a scale ranging from 0-10); however the differences seen in response rates could be of more clear clinical relevance.

There were no significant findings in any of the secondary endpoints, weakening the internal validity of the trial. With the possible exception of the motricity index (p=0.054) there were at best small trends of questionable clinical relevance in these supportive endpoints,

In conclusion this trial showed some evidence of efficacy but could not stand on its own as a single pivotal trial, and it is necessary to have data from a second pivotal trial.

Study GWCL0403

This was a randomised, double-blind, placebo-controlled study of Sativex as add-on therapy in the treatment of patients with symptoms of spasticity due to multiple sclerosis. The duration of the placebo controlled period of this study was 14 weeks. Otherwise the study design was very similar to that of study GWMS 0106.

The primary endpoint was the change from baseline to the end of the evaluable period in the patient recorded 11 point numerical rating scale, scores ranging from 0 (no spasticity) to 10 (worst ever spasticity).

In the primary efficacy analysis (ITT population) no significant difference was seen between Sativex and placebo on the spasticity NRS score.

The results on the analysis in the per-protocol population appeared more encouraging and the applicant places some emphasis on this analysis. However the per-protocol population is not a comparison of fully randomised groups. Use of this population can provide an extremely biased treatment comparison, especially in this study where inclusion in the analysis is based in part on response to treatment – early treatment discontinuations are excluded, and such discontinuations are likely to be a consequence of reactions to treatment such as efficacy and adverse events. Hence there is a possibility of large biases when considering the treatment effect. Efficacy assessments should be based on the ITT population.

<u>Secondary efficacy analyses</u>
There were a number of secondary efficacy measures including specific measures of spasticity and the associated disability, and more general measures. The results for all of the secondary efficacy endpoints were all consistent with the findings of the primary endpoint. There were no significant differences between the treatments for any efficacy measures. The trends in general

favoured Sativex, but they were very modest, did not approach statistical significance, and the treatment differences were mostly smaller than the differences seen at baseline.

Overall summary of efficacy for study GWCL0403

There were no statistically significant differences seen between Sativex and placebo in this trial when using the full analysis set. There were modest trends in favour of Sativex for the majority of endpoints, but these differences fall some way short of being of a clinically important magnitude. In general the estimated treatment differences were smaller than the differences seen at baseline.

Some significant differences were seen using the per-protocol population, but analyses using this population are considered to be biased and not to provide evidence of efficacy.

Meta-analysis of the pivotal studies 106 and 403 including responder analyses

A meta-analysis of the pivotal studies 106 and 403 (but not including data from GWMS0001 as this was exploratory for the spasticity indication) was presented. Each study examines the use of the same drug product, in a very similar patient population, using the same efficacy endpoints, in the same trial design (randomised, placebo-controlled, parallel group) and a combined analysis is appropriate. A total of 526 patients were included in the pooled analysis (Sativex: n=291; placebo: n=235).

The key outcome measures in the meta-analysis were the mean between-group treatment difference for the NRS, the odds ratios for responder rates and for the global impression of change, and the between group difference for the Ashworth score. All of these key outcomes, with the exception of the Ashworth Score, reached statistical significance at the $p<0.05$ level but not at the $p<0.01$ level.

However the magnitude of the mean treatment difference between Sativex and placebo (-0.34 points on a 10 point scale) was small and of questionable clinical relevance. The Company presented an argument that the efficacy of Sativex can be assessed not just by looking at mean treatment effect but also by using a responder analysis. The assessor agreed that the Company had provided a reasonable definition for characterising a responder.

The cornerstone of the Company's response is that the total population – both in the trial and in the wider patient population – includes a substantial proportion that will be non-responders, so that the magnitude of the treatment effect in those that do turn out to be responders will be substantially greater than 0.34 points. Hence the clinical relevance of efficacy can be assessed by examination of the benefits in the responder population.

The Company presented data showing the proportions of Sativex and placebo patients achieving an improvement in spasticity at a range of percentage levels. At all levels, the proportion of Sativex responders was greater than placebo, and the difference was statistically significant for most of the levels of response analysed. The difference in the responder rate is fairly consistent regardless of the definition of responder employed (although it reduces, as it must, when the response rate drops in both groups for the tougher definitions). The odds ratio is also quite consistent.

The Company also presented an alternative analysis of the proportions of patients achieving certain absolute reductions from baseline in spasticity scores. It yields similar results. At all levels, the proportion of Sativex responders was greater than placebo, and the difference was statistically significant for most of the levels of response analyse.

The CHMP points to consider document on applications with a meta-analysis or one pivotal trial lists some prerequisites for a meta-analysis to provide sufficient evidence for a claim. Among these are that some studies should be clearly positive; that inconclusive studies show positive trends in the primary variable; and the pooled 95% confidence interval should be well away from zero. This final requirement is an alternative way of stating that statistical evidence considerably stronger than $p<0.05$ is required, which is the way that the same requirement is worded in the single pivotal trial section.

It is conceivable that the first two requirements have been met. GWMS0106 is positive, while GWCL0403 trends in the right direction. However it is difficult to argue that that the pooled confidence interval is well away from zero. The upper bound of -0.04 seems fairly close to zero, while the p-value of 0.027 does not seem to provide considerably stronger evidence than $p<0.05$. For example, a value of $p=0.00125$ would be needed to replicate the evidence from two pivotal trials positive at the 0.05 level. This suggests that further data are required to gain the strength of evidence we would usually expect.

An argument can be made that an important treatment effect in a substantial minority of patients might be masked to some extent by the data “noise” from a larger number of non-responders in an analysis of mean changes. If it can be shown that it is possible reliably to identify non-responders without exposing them to ineffective treatment for a prolonged period, a therapeutic trial to identify responders could be a reasonable approach. In this situation a responder analysis is of value in assessing the clinical relevance of a difference in means observed on a scale and identifying a clinically relevant treatment effect in a proportion of patients.

It is important to note that quoting the Sativex response rate in isolation is not useful. It is essential to look at this as a difference in responder rates from placebo rather than just looking at the responder rate on active treatment in isolation, as the placebo response in these trials is substantial.

Sativex consistently achieved more responders than placebo regardless of the definition of responder. The difference between responder rates observed between Sativex and placebo could reasonably be considered to be of clinical relevance and could in principle lead to a positive risk-benefit conclusion. Responder rates such as these are not out of line with those seen in clinical trials for medicines known to be efficacious in other conditions where measurement of the key efficacy parameter is difficult, such as in various psychiatric conditions.

The Company provided analyses of the ability of a four-week therapeutic trial of Sativex to correctly predict patient outcomes. While these results are not unpromising and suggest that a 4 week therapeutic trial might be a way to allow responders access to treatment without subjecting non-responders to long-term treatment, it must be remembered that it all comes from an unplanned post-hoc analysis. This exercise in designing a rule to be used for a therapeutic trial is interesting and generates a possibly useful hypothesis. However further confirmatory data are required before it could be used with confidence.

Maintenance of Blinding to Treatment Allocation

Given the substantial observed differences from placebo in side effects such as dizziness, concerns were raised that if a significant proportion of patients became unblinded to treatment allocation there could be a potential for measurement bias, especially since the primary efficacy endpoints of the pivotal clinical trials are patient reported and subjective. The fact that a substantial proportion of patients had previously taken illicit cannabis as self medication increases these concerns, firstly because this may have enabled them to recognise Sativex by its psychoactivity, and secondly because they might have greater expectations of benefit from Sativex treatment than would cannabis naïve patients.

Analyses conducted by an independent statistician and provided by the Applicant concluded that "there is no evidence to suggest that the blinding has been seriously compromised in these three studies" and that "if any subjects did become unblinded then there is no evidence in these three studies of any bias in the assessment of the treatment difference between Sativex and Placebo for efficacy, adverse events or study drug dosing.". However differences from placebo on efficacy measures were small and there was concern that such differences could be accounted for by unblinding and measurement bias.

It is important to note that the PK profile of Sativex is very different from that of smoked cannabis. The rapid rise in plasma levels and high C_{max} achieved by the inhaled route results in obvious psychoactivity. In contrast Sativex does not produce such peaks and instead plasma levels are relatively stable, especially with maintenance treatment when the substantial reservoirs of drug in body fat further stabilise plasma levels. 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 fluctuation. Plasma levels during treatment with Sativex are approximately 30 times lower than those obtained by smoking cannabis.

In conclusion there is no clear evidence that an important degree of bias has been introduced although the pattern of CNS side effects such as sedation is highly suggestive that some unblinding is possible. The presented analyses are not able to refute the possibility of bias arising as a result but at least there is no evidence of a major problem. The smaller the differences between active and placebo, the greater is the concern that a relevant contribution of that apparent difference may not be real. This still needs to be considered in the overall evidence of efficacy but if a compelling treatment effect can be shown it might be concluded that the possibility of unblinding might not represent a major concern.

Validity of the primary efficacy measure

The validity of the NRS primary end point as a measure specifically of spasticity appears unclear. The proposed indication is specifically for spasticity and there is concern to what extent a difference in the patient reported NRS score reflects a difference in the severity specific to the physiological

phenomenon of spasticity in this patient population, as opposed to other symptoms that a patient might complain of, and general well being.

Dose-response

The lack of any evidence of a dose-response relationship is a weakness of the dossier. It is agreed that showing dose-response in terms of clinical efficacy would be very difficult because it is difficult enough to show a substantial treatment effect at all. Although the UK has not considered the lack of evidence of a dose-response relationship to be a major objection, any information that could be generated, using either a clinical or pharmacodynamic measure (or both) would make an important contribution to the overall evidence of efficacy which currently falls short of the required level.

Open label studies/long-term efficacy

Two long term open label non-comparative studies were presented. Their major objective was to assess the safety and tolerability of long-term therapy with Sativex, efficacy measures being part of the secondary objectives. These studies in a small number of patients cannot provide robust evidence of long-term maintenance of efficacy. Any trends or notable features of the efficacy measures could be attributable to a variety of causes, including changes in the underlying disease across time or changes in the set of subjects in the study and efficacy related withdrawals, with no possibility of comparing with a reference treatment or placebo. Controlled data are necessary to assess the long-term efficacy of Sativex in MS patients.

CLINICAL SAFETY

Patient exposure

The extent of exposure to Sativex in clinical studies included in the integrated sub-populations is discussed and tabulated below (figures from initial submission).

Summary of Drug Exposure (Sativex) for the MS, Non-MS and Cancer Sub-sub-populations

	Extension Studies		Comparative Studies				Cancer Sub-population Comparative Study	
			Sativex		Placebo			
	MS Sub-pop.	Non-MS Sub-pop.	MS Sub-pop.	Non-MS Sub-pop.	MS Sub-pop.	Non-MS Sub-pop.	Sativex	Placebo
Number of Subjects (n)	444	218	496	148	434	153	60	59
Mean Exposure (Days)	455	314	56	26	62*	27	14	14
Total Exposure (Subject Years)	554	187	77	11	74	11	2	2

The size of the safety database is acceptable in principle. Much is known about the safety profile of cannabinoids from the published literature although some safety issues, in particular the potential for psychiatric adverse events, are still not clearly defined. The key points that the Sativex safety database is required to address include issues specific for Sativex (e.g. related to the formulation and route of administration), issues specific for the MS patient population, and clarification of the effects of this medication on psychological health and the potential for it to cause psychiatric morbidity.

Adverse events

The table below shows the number of treatment related events with a plausible causal relationship to Sativex described by patients taking Sativex in phase III long-term extension studies and both Sativex and placebo in short-term (comparative) phase III parallel group studies. The same patient may have described adverse events in more than one category. All long-term extension studies were open label single group non-comparative trials.

		Extension Studies GWEXT0102 + GWMS0001 All patients (n=662)		Comparative Studies Sativex Oromucosal Spray (n=644)		Comparative Studies Placebo (n=587)	
		n	%	n	%	n	%
Ear and Labyrinth disorders							
	Vertigo	15	2.3%	28	4.3%	8	1.4%
Eye Disorders							
	Vision Blurred	7	1.1%	14	2.2%	2	0.3%
Gastrointestinal Disorders							
	Abdominal pain	4	0.6%	6	0.9%	0	0%
	Abdominal pain upper	8	1.2%	5	0.8%	2	0.8%
*	Oral mucosal exfoliation	7	1.1%	0	0%	0	0%
	Diarrhoea	76	11.5%	19	3.0%	9	1.5%
	Dry mouth	55	8.3%	51	7.9%	14	2.4%
*	Glossodynia	37	5.6%	6	0.9%	8	1.4%
*	Mouth ulceration	31	4.7%	9	1.4%	3	0.5%
	Nausea	85	12.8%	68	10.6%	31	5.3%
*	Oral discomfort	19	2.9%	17	2.6%	16	2.7%
*	Oral mucosal disorder	23	3.5%	2	0.3%	2	0.3%
*	Oral Pain	51	7.7%	21	3.3%	23	3.9%
*	Tooth discolouration	25	3.8%	2	0.3%	2	0.3%
	Vomiting	40	6.0%	17	2.6%	9	1.5%
Administration Site Conditions							
*	Application site irritation	20	3.0%	10	1.6%	14	2.4%
*	Application site pain	33	5.0%	21	3.3%	20	3.4%
General Disorders							
	Fatigue	67	10.1%	84	13.0%	46	7.8%
	Feeling Abnormal	21	3.2%	17	2.6%	3	0.5%
	Feeling Drunk	29	4.4%	29	4.5%	2	0.3%
	Thirst	9	1.4%	7	1.1%	1	0.2%
	Asthenia	26	3.9%	33	5.1%	13	2.2%
Injury, Poisoning and Procedural Complications							
	Fall	15	2.3%	8	1.2%	3	0.5%
Metabolism and Nutrition Disorders							
	Anorexia	14	2.1%	10	1.6%	1	0.2%
	Decreased appetite	9	1.4%	0	0%	1	0.2%
	Increased appetite	6	0.9%	13	2.0%	3	0.5%
Nervous System Disorders							
	Amnesia (short term)	13	2.0%	4	0.6%	0	0%

		Extension Studies GWEXT0102 + GWMS0001 All patients (n=662)		Comparative Studies Sativex Oromucosal Spray (n=644)		Comparative Studies Placebo (n=587)	
		n	**%**	**n**	**%**	**n**	**%**
	Balance disorder	28	4.2%	16	2.5%	4	0.7%
	Disturbance in attention	29	4.4%	29	4.5%	0	0%
	Dizziness	183	27.6%	206	32.0%	60	10.2%
	Dysarthria	14	2.1%	12	1.9%	2	0.3%
*	Dysgeusia	53	8.0%	30	4.7%	10	1.7%
	Lethargy	22	3.3%	14	2.2%	5	0.9%
	Memory impairment	23	3.5%	6	0.9%	1	0.2%
	Somnolence	54	8.2%	57	8.9%	16	2.7%
	Syncope	8	1.2%	0	0%	0	0%
Psychiatric Disorders							
	Anxiety	12	1.8%	4	0.6%	3	0.5%
	Delusional perception	1	0.2%	0	0%	0	0%
	Depressed mood	17	2.6%	8	1.2%	2	0.3%
	Disorientation	23	3.5%	31	4.8%	5	0.9%
	Dissociation	9	1.4%	16	2.5%	1	0.2%
	Euphoric mood	25	3.8%	17	2.6%	6	1.0%
	Hallucination	6	0.9%	5	0.8%	1	0.2%
	Hallucination, auditory	0	0%	2	0.3%	0	0%
	Hallucination, visual	3	0.5%	2	0.3%	0	0%
	Illusion	4	0.6%	1	0.2%	1	0.2%
	Paranoia	5	0.8%	6	0.9%	1	0.2%
Respiratory, thoracic and mediastinal disorders							
*	Throat irritation	8	1.2%	6	0.9%	1	0.2%
Vascular disorders							
	Hypotension	12	1.8%	1	0.2%	3	0.5%
* - Possible Application Site Reactions							

The AE profile is broadly in line with that expected from the known pharmacology of cannabinoids. The issues are mostly of tolerability rather than safety. However some of the reported undesirable effects could have the potential for Sativex to worsen overall disability or to increase the risk of accidental injury. These are the principal potential concerns that are identified.

Serious adverse events in placebo controlled trials

The following table shows treatment emergent related non-fatal, SAEs in MS subjects and non-MS subjects in the comparative studies.

Cases on Sativex		**Cases on Placebo**	
MS subjects	**Non-MS subjects**	**MS subjects**	**Non-MS subjects**
N=496	**N=148**	**N=434**	**N=153**
Total Number of Subjects with SAEs			
9	**1**	**3**	**0**
Description of Serious Adverse Events			
Vomiting in one patient		Vomiting and Dizziness in one patient	
Urinary Infection in one patient		Urinary Retention in one patient	
Haemorrhagic Cystitis and Dehydration in one patient			
Multiple Sclerosis Relapse in one patient		Hypotonia in one patient	
Aggression, Agitation, Delusions, Insomnia, Irritability and Muscle Spasms in one patient			
Confusional state in one patient	Confusional state and paranoia in one patient		
Worsened depression with Suicidal Ideation and Drug Dependence in one patient			
Respiratory Distress in one patient			
Transient Ischaemic Attack in one patient			

Most of these SAEs are of a nature and frequency that would be expected in this patient population regardless of study medication. Numbers are small and in statistical terms the greater number of cases in Sativex treated patients could reasonably be due to chance. It is reassuring that no events indicating an adverse effect of Sativex in terms of worsening overall disability, for example by reducing muscle power or the ability to maintain posture, are reported as SAEs. The only area of potential concern that is identified here is the occurrence of psychiatric disorders and confusional state in a small number of patients. This is considered in more detail below.

Serious adverse events in the extension studies (open label Sativex)

The following table shows treatment emergent related non-fatal, SAEs in MS subjects and non-MS subjects in the open label extension studies.

MS subjects	Non-MS subjects
N=444	**N=218**
Total Number of Subjects with SAEs	
15	**7**
Description of Serious Adverse Events	
Circulatory Collapse with ventricular bigeminy and extrasystoles in one patient	Upper Abdominal Pain in one patient
Diarrhoea and vomiting in one patient	Diarrhoea in one patient
GI bleed (haematemesis and blood in stool) in one patient	Asthenia, Dysarthria and Somnolence in one patient
Nausea, dizziness, abnormal coordination, paraesthesia, and tremor in one patient	Chest Pain, Cholelithiasis and Abnormal Liver Function Tests in one patient
Asthenia in one patient	Suicidal Ideation in one patient
Convulsion in two patients	Urticaria (localised and generalised) and eyelid oedema in one patient
Chest Pain in one patient	Somnolence in one patient
Pneumonia in one patient	
Abnormal Liver Function Tests in two patients	
Balance disorder in one patient	
Multiple Sclerosis Relapse in one patient	
Epistaxis in one patient	
Delusions and paranoia in one patient	

Most of the SAEs 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 in one and suicidal ideation in another. However the numbers are too small to draw any conclusions and MS is associated with psychiatric morbidity in any case. The SAE rates were similar in MS and non-MS patients. There do not appear to be any reported SAEs in which CNS side effects caused major personal safety incidents, such as with food and hot drink preparation. The occurrence of a single case of circulatory collapse with ventricular extrasystoles and bigeminy is likely to be unrelated to Sativex. However it should be included in the SPC, particularly in view of the cardiac effects reported from the literature in the clinical pharmacology summary (enhanced sinus node automaticity and sinoatrial and AV conduction in humans, P-R prolongation and/or second degree AV block in animals) and reports of ventricular ectopy in published studies (e.g. Miller et al). Abnormal liver function tests should also be added to section 4.8 of the SPC. Otherwise the SAEs reported here are adequately addressed in the SPC.

Loss of consciousness

In all, there were 22 events, 13 of which were considered treatment related. Of these only one was a loss of consciousness and described as “unresponsive”. The patient recovered the same day and continued treatment with Sativex. Of the remaining 12 subjects, 11 continued treatment. The one discontinuation was for intoxication-like symptoms. None of these events were considered to be serious. Of the nine events which were not considered treatment-related, two were events of “loss of consciousness” and were deemed to be serious. Another, termed as a blackout, was considered non-serious. There were two cases of syncope, of which one was in the placebo group and the other occurred during the pre-randomisation period.
Although loss of consciousness may be a feature of MS and could be associated with concomitant medication, a causal association with Sativex cannot be excluded.

Psychiatric adverse events

There is some potential concern regarding association of psychiatric adverse events such as psychosis and suicidal ideation with long-term use of Sativex. Adverse events which code to the System Organ Class of Psychiatric Disorders are common with Sativex and are said by the Company to be consistent with events seen with recreational cannabis and synthetic THC medications. The majority of the events seen are reported to have been of mild severity, transient and did not require cessation of treatment.

Psychosis
Psychosis is reported in two clinical trial patients in association with Sativex. In one of these cases the patient also had paranoia. In one case psychosis developed six days after stopping treatment and improved with antibiotics prescribed for infection. The investigator did not feel that the event was related to the study medication. In the second case the patient developed confusion, which was initially thought to be related to the study medication. However the confusion did not improve after ceasing the medication, and the patient deteriorated further.

There is clear evidence that recreational cannabis can produce a transient toxic psychosis in larger doses or in susceptible individuals,and transient psychotic episodes as a component of acute intoxication are well documented. It is thought that regular long-term cannabis smoking by young adults may increase the risk of developing functional mental illnesses such as schizophrenia in later life although a causal link has not yet been definitively established. 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 the level of risk might be quite different. Nevertheless, the clinical safety data for Sativex are insufficient to establish whether there is a significant risk of psychosis or not, either in the short/medium term or the long term.

Hallucinations
There were three serious adverse events listed under the preferred terms `Hallucinations’, `Visual Hallucinations’ and `Auditory Hallucinations’. All three events were considered unrelated to the study medication. Two of the events were attributed to septic episodes, and the third was attributed to brain metastasis as a progression of known lung cancer. 16 patients

developed non-serious adverse events listed under the same preferred terms. All were considered related to the study medication.

Transient hallucinations are well known to occur in association with recreational cannabis use (Johns 2001) but the level of risk in relation to the use of Sativex is unclear. The proposed SPC includes "hallucination (unspecified, auditory, visual)" in the section 4.8 listings. This is satisfactory.

Paranoia

Paranoia, was reported in 12 patients in association with Sativex, and was part of a psychotic syndrome in one (paranoia does not necessarily indicate psychosis unless held with delusional intensity). This case occurred after sepsis and the investigator felt the event to be unrelated to the study medication.

Of the remaining 11 patients on Sativex who reported paranoia as an adverse event, all cases were considered to be related to the study medication. All patients recovered spontaneously, or on discontinuation of the study medication. Additionally, there was one patient found with an episode of paranoia on placebo, which was not considered serious.

Paranoia is well recognised as a manifestation of acute intoxication during recreational cannabis use (Tart 1970) and it may occur in association with Sativex. The majority of cases have been transient and of mild to moderate intensity. Paranoia is listed in the proposed SPC.

Applicant's comment on psychiatric safety profile

The data suggest 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 most of the early adverse events have resolved, psychiatric adverse events are more common in placebo-treated patients.

A large majority (90 of 103) of patients reporting psychiatric adverse events do so during the first 28 days of exposure to Sativex. This contrasts with placebo, where 19 of 36 patients report events during the first 28 days. Thus, for a large majority of patients treated with Sativex, a propensity to psychiatric AEs will become evident to the prescribing clinician within the proposed 4 week therapeutic trial. This provides reassurance regarding the risk benefit assessment in patients who respond to Sativex, since it is evident that there is a relatively low risk of experiencing new psychiatric adverse events after the period of the therapeutic trial – in fact, numerically lower than the risk on placebo.

Few (14 of 103) patients with psychiatric adverse events discontinued study therapy on Sativex, and therefore it is apparent that the large majority resolve spontaneously whilst the treatment continues. At the end of the study period, only 20 out of 103 (19%) patients had unresolved psychiatric adverse events on Sativex compared with 17 of 36 (47%) on placebo. Thus patients with MS experiencing a psychiatric AE on placebo were less likely to reach resolution of the AE by the end of the study than patients on Sativex. This was especially notable for the AEs of depressed mood and depression.

Psychiatric Serious Adverse Events have been reported in three subjects in placebo-controlled clinical trials, compared with none on placebo. These subjects have been previously described in

the safety overview of this application. All three SAEs occurred in Study GWCL0403. One female patient developed depression and transient suicidal ideation after stopping treatment, which was described as psychological dependence. One female patient developed acute confusion and withdrew from treatment; and one male developed agitation, irritability and sleeplessness after stopping treatment. All these events resolved with no sequelae.

The data summarised above show that while psychiatric adverse events occur frequently in patients with MS who take Sativex, the large majority occur within the period of the proposed therapeutic trial, are predominantly of only mild or moderate intensity, and are likely to resolve spontaneously. For Sativex responders, there is only a small risk of developing new psychiatric adverse events after the completion of the therapeutic trial. The pattern, severity and outcome of the psychiatric adverse events seen in clinical trials does not suggest that Sativex carries a high risk of psychological or psychiatric morbidity.

Assessor's comment on psychiatric safety profile

A causal association between Sativex administration and suicidal ideation cannot be ruled out. There were two cases of suicidal ideation, and a single case of suicide, during the use of Sativex, reported as serious adverse events. Similarly there is nothing in the applicant's submission that rules out occurrence of psychosis in patients on Sativex. The possibility of psychosis is mentioned in Section 4.8 of the SPC, as are hallucination and paranoia.

Anxiety and depression are common in patients with chronic symptomatic disease. Suicidal ideation and attempted or completed suicide are well documented as occurring with an increased frequency in subjects with MS. There have been no non-serious adverse events involving suicidal ideation on Sativex. The three cases reported on Sativex all had a previous history of psychiatric problems, or other confounding factors. Though the association cannot be ruled out, none of these events appear convincingly related to the study medication.

There is no evidence of a different incidence of psychiatric adverse events in Sativex-treated patients with prior experience of cannabis compared to cannabis-naïve-treated patients.

Application site reactions and leukoplakia

Application site type reactions have been documented with the use of Sativex, including dry mouth, application site pain, application site burning, oral discomfort, oral pain, oral mucosal disorder, dysgeusia, desquamation mouth, glossodynia, tooth discolouration, throat irritation and mouth ulceration (See Common Adverse Events). As the events also occur to a similar extent with placebo, it is likely that the excipients, including alcohol, are primarily responsible. These reactions typically consist of mild to moderate stinging at the time of application.
There have been two SAEs diagnosed as oral leukoplakia plus one "non-serious" case. All three subjects were smokers and a causal relationship with Sativex has not been established. However in view of the known association of leukoplakia with oral irritation, a causal relationship cannot be excluded.
Application site reactions could be underreported, as they may be more likely to increase with time of use of the medicine.

Discontinuation due to AEs
The overall withdrawal rate was quite low but there was a three to four fold higher withdrawal rate in the Sativex group compared to the Placebo group. 69 subjects (10.7%) out of a total of 644 receiving Sativex and 19 (3.2%) subjects out of 587 receiving placebo withdrew in MS and Non-MS comparative studies due to adverse events (all causality). 107 subjects (16.2%), receiving Sativex out of a total of 662 were withdrawn from the extension studies due to adverse events (all causality). The incidence of adverse events leading to withdrawal were similar in the MS and non-MS populations. The reasons for withdrawal were very similar to the common AEs and were primarily CNS effects or application site reactions. Only dizziness and nausea led to withdrawal in 2% or more of subjects. No particular concerns are raised by these data. The side effects leading to withdrawals were those that occur particularly in the initial titration phases and in most cases can be satisfactorily managed by adjustment of the dose and/or titration rate. They are issues of tolerability rather than safety.

Deaths
The pattern of deaths was as would normally be expected in the studied patient populations. No unexpected concerns were identified from detailed reviews of fatal events.

Laboratory findings
No safety signals were identified from the laboratory data.

ECG and QT findings
Detailed ECG analysis was undertaken during two phase I studies and before and after treatment ECGs were taken in the three Phase 3 studies. No clinically relevant QT prolongation or other ECG abnormalities were found in association with Sativex and there is no evidence of any ECG/QT issues.

Prior Cannabis Use
The AE profile does not appear to be substantially influenced by prior cannabis use.

Safety related to drug-drug interactions and other interactions
Some interaction with other CNS depressant medicines is to be expected. The presented data raise no significant issues with regard to possible clinically significant pharmacodynamic interactions between Sativex and these common concomitant medications. The SPC states that care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation. A suitable statement is also provided regarding alcohol.

Drug abuse, tolerance, withdrawal and rebound
The Company reports that there have been no reports of drug abuse associated with Sativex. Although Sativex clearly has some abuse potential, this would seem to be quite limited because of its PK profile, lacking as it does the rapid absorption and high peak plasma levels obtained by smoking cannabis.

There is no clear agreement in the published literature regarding tolerance to the psychoactive effects of cannabis. In the long-term extension studies there was no indication of an increase in

dosage over time although the number of patients exposed to long term therapy is not high. Psychological dependence on cannabis is estimated to be about 1% of recreational cannabis smokers. The applicant argues that the problem is minuscule compared to that observed with alcohol.
A drug interruption sub-study was performed. Abstinence from Sativex was reported to be associated with re-emergence of MS-related symptoms in most subjects but there were no SAEs associated with the drug interruption. The results suggest that the consequences of abrupt withdrawal from Sativex in clinical practice are likely to be limited to transient disturbances of sleep, emotion or appetite in some subjects.
In the context of the proposed indication and patient population abuse of Sativex is not considered to be an issue of great concern, subject to sensible precautions. Drug usage measures show no evidence of significant tolerance with long term treatment although there is a lack of long term efficacy data to assess this. It seems that some withdrawal reactions may occur but whether this may result in dependence, either physical or psychological, is unclear. It is not possible to assess whether withdrawal from Sativex might cause symptom rebound as there are no adequate controlled long term efficacy data.

Post marketing experience and spontaneous reports
Post marketing reports from Canada, where the drug is provisionally licensed and spontaneous ADR reports from the UK are provided including PSURs. These data provide more than 1,000 patient years of exposure in addition to that derived from clinical trials. 59 patients have received Sativex continuously for more than 5 years. All SAEs and fatalities that have occurred during this use of Sativex are presented in the main body of the safety summary and have been considered above. No new issues are identified from this exposure.

Safety profile in a 4 week therapeutic trial

The potential risks of a 4 week Sativex treatment period would need to be outweighed by the potential benefits, the concern being that substantial numbers of patients might be exposed to the risks without at the end of the day obtaining any benefit. The adverse event profile apparent after 4 weeks of Sativex therapy is very similar to that at the end of the study. Whilst this might enable both the risks and benefits of Sativex in a particular patient to be reliably assessed at the end of the 4-week therapeutic trial it also means that patients are exposed to the full range of potential adverse events during the efficacy evaluation period.

The incidence of adverse events during the first 4 weeks that represent a hazard as opposed to a tolerability issue is quite low. The occurrence of events such as dizziness, dry mouth, dysgeusia, constipation, fatigue, somnolence, and headache are not of major concern in this context. Of more concern is the possibility of psychiatric adverse events. There are sufficient psychiatric adverse events such as disorientation, depressed mood, dissociation, apathy and confusional state recorded as severe or resulting in discontinuation, for there to be cause for concern. It would be necessary for patients undergoing a therapeutic trial with Sativex to be monitored for these psychiatric adverse events.

Assessor's overall conclusions on clinical safety

The size of the safety database is acceptable in principle. Much is known about the safety profile of cannabinoids from the published literature although some safety issues are still not clearly defined and there are additional issues specific for the MS patient population.

The adverse event rate was much higher in the Sativex treated groups than in the placebo groups. This as such is not unexpected but these issues would need to be clearly outweighed by the therapeutic benefits.

There are safety issues relating to the potential for oral mucosal lesions. For the most part these are issues of tolerability that in most cases can be managed by varying the application site. The possibility remains that there might be an increased incidence of pre-malignant leukoplakia although the available data do not indicate a serious concern. Until there is more experience vigilance backed up by suitable SPC wording is an acceptable approach. Otherwise there are no major safety issues relating to the formulation and route of administration.

The profile of AEs and SAEs is broadly in line with that expected from the known pharmacology of cannabinoids. The main safety and tolerability issues are related to CNS events. The side effects that are relatively common on initiation of treatment and during dose titration may limit tolerability of Sativex. There is also the potential for Sativex to cause worsening functional impairment, particularly in psychomotor function during this period, which could result in personal injury. It is reassuring that no SAEs of this kind are reported although precautions will clearly be necessary. There could be more problems of this nature in the real world than in the highly controlled clinical trial situation.

There continue to be concerns regarding the potential for psychological and psychiatric morbidity. A number of important psychiatric events including SAEs were reported. However such events are common in the MS patient population and there are insufficient data to establish whether there might be a causal association with Sativex. The information regarding mental health with long term Sativex treatment is especially limited. As there is no clear indication of a problem this is an issue that may reasonably be managed with post marketing risk management and robust SPC and PIL advice.

As part of the CNS pathology of MS, patients have a high prevalence of psychiatric morbidity. There is insufficient information at this time to establish whether MS patients might have greater susceptibility to psychiatric adverse effects from cannabinoids than the general population.

There was no indication of any increased or decreased susceptibility to psychiatric adverse effects from treatment with Sativex in patients who have previously taken cannabis as self medication or recreationally.

The occurrence of certain other AEs such as loss of consciousness similarly requires long term experience to provide reassurance.

The data clearly show a significant excess of a wide range of psychiatric AEs over placebo (21% vs. 8%) over 4 weeks. This is almost certainly statistically significant, as is the fact that 20 of the 22 AEs in this list show an excess for Sativex over placebo. Only anxiety and insomnia were less common with Sativex. The safety implications of therapeutic trials in substantial numbers of patients who will ultimately not show a favourable response to treatment remains of concern and should be fully addressed in a subsequent pivotal clinical trial.

In conclusion the safety profile is considered acceptable in principle for the proposed patient population and indication, providing sufficient efficacy is demonstrated. However there remain important safety issues that as yet are not clearly quantified and occur during the proposed 4 week trial period. It will be necessary to demonstrate clear potential efficacy if these safety issues are to be outweighed so that a positive risk-benefit might be concluded.

Overall Summary and Conclusions on Pharmacokinetics

The Company's responses are considered satisfactory. No additional PK studies or SPC warnings are considered necessary.

Overall Summary and Conclusions on Pharmacodynamics

The Company's responses to the pharmacodynamic questions are considered satisfactory and there are no remaining major objections relating to the pharmacodynamic data. Further data showing an effect of Sativex on the physiological phenomenon of spasticity would be highly desirable.

Overall Summary and Conclusions on efficacy

The evidence of efficacy is not considered to be sufficient at present. The magnitude of the estimated treatment effect of Sativex on the self reported measure of spasticity in the pivotal trials GWMS0106 and GWCL0403 appears small in the overall patient population. The applicant has presented post hoc analyses supporting an argument that non responders can be identified in a 4-week therapeutic trial, and that the mean treatment effect in the remaining patients who would continue to receive treatment, would be clinically significant. There is however a lack of clinical data investigating such conditions of use, as no such therapeutic trial followed by exclusion of non-responders was used in the pivotal trials. Further clinical data are necessary to investigate the effectiveness and safety of the proposed 4-week therapeutic trial in identifying responders and excluding non-responders, and to clarify the magnitude and clinical relevance of the efficacy achieved in the subgroup of patients who continue to be treated with Sativex following a successful therapeutic trial. The validity of the NRS as a measure specifically of spasticity appears unclear. Further information is required on the clinical relevance of the observed treatment effect specifically to the physiological phenomenon of spasticity in patients with MS. Since MS is a chronic disorder, there is a lack of evidence of maintenance of efficacy with long-term treatment.

Overall Summary and Conclusions on safety

The evidence of safety for the proposed patient population and indication would be in principle sufficient to support a marketing authorisation provided that a satisfactory risk management plan is

implemented in order to identify and characterise uncommon serious adverse events, in particular psychiatric morbidity and other undeniable CNS effects, assuming efficacy had been demonstrated. However there are some important safety issues that would need to be outweighed by significant benefit in terms of efficacy.

Overall Conclusions on risk-benefit

In conclusion a positive risk-benefit has not been sufficiently demonstrated at this time.

Information provided by the company after the issue of the Day 180 Assessment report and before the withdrawal from the procedure.

A panel of independent clinical experts specialising in the treatment and rehabilitation of people with MS and in clinical trial design was asked to review and comment on the Sativex data and the MHRA's assessment thereof. This panel was chaired by Lord Walton of Detchant, (a British neurologist and past president of the Royal Society of Medicine and the General Medical Council of Great Britain). Their report is summarised below. Note that statements included here do not necessarily reflect the views of the MHRA and if quoted should be attributed correctly.

Summary of Experts Report provided by the company:

The clinical assessment of Sativex by the MHRA has concluded that the improvement seen in patients with Multiple sclerosis 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.

Analysis of randomised controlled clinical trials of Sativex provides clear evidence that a statistically significantly greater proportion of patients achieve a clinically relevant and meaningful level of improvement on Sativex when compared with placebo. The data also show clear statistical evidence of improvement in the patient's global impression of change, and in the carer's global impression of change, adding confidence to the robustness of the conclusions.

The improvement from baseline seen in patients who respond to Sativex is substantial. Data from long-term studies confirm that this improvement is maintained for at least 1 year, with no increase in the dose of Sativex taken. In a population whose spasticity, if anything, would be expected to deteriorate over that time period, this indicates a clinically meaningful effect.

This improvement is seen with a low adverse event burden. Sativex is used as a prescription medicine in Canada, on a regional government sponsored compassionate use programme in Catalonia, and as an unlicensed medicine in the UK. During this 'real-world' exposure the experience of psychiatric adverse events has been reassuring. In short, there is no evidence of a significant risk of psychiatric morbidity in adult patients or subjects taking Sativex.

More than 1200 patients have been prescribed Sativex in the UK. In a recent postal survey of UK physicians who have prescribed Sativex to at least 2 of their patients, 80% of physicians indicated that Sativex provided useful clinical benefits to their patients and 88% regarded Sativex as a useful addition to their therapeutic options.

A carefully constructed questionnaire was also sent to patients who have been receiving Sativex over a period of at least 1 year. The results of this questionnaire confirm that relevant functional improvements are being achieved, and these improvements are independently confirmed by their carers. A remarkable 19% of patients report a reduced need for either supportive equipment or specific assistance to improve their mobility. 94% of respondents report an improvement in general

life benefits from the improvement they have experienced on Sativex. These reports are exactly what doctors rely on when assessing the clinical relevance of treatments for spasticity, and indicate that Sativex does produce relevant benefits and functional improvements. A notable 71% of carers report that night-time care of the patient is less burdensome.

In summary, we note that all the elements which are required to conclude that Sativex is providing worthwhile clinical benefit at low risk are present in the data we have seen. Controlled clinical trials show statistical significance, and analyses of the improvement seen, especially in responders, show clear evidence of clinical relevance. Long-term use confirms maintenance of the treatment effect without the emergence of new adverse events, and with no evidence of tolerance. Questionnaire responses confirm that independence is improved in long term use, a view expressed by patients and confirmed by carers. Prescribers overwhelmingly agree that Sativex provides them with a valuable treatment option.

We conclude that Sativex meets a currently unmet medical need in patients where there is no other conservative treatment option. 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 the MHRA to do so.

V List of outstanding major objections at the time of withdrawal of the application

The following major objections were agreed unanimously by the Reference Member State (UK) and all Concerned Member States in the procedure. For the purpose of this Public Information Report there are some amendments to the wording adopted formally. In addition there were a number of points for clarification which are not listed here.

Quality aspects

None.

Non clinical aspects

None

Clinical aspects

The evidence of efficacy is not considered to be sufficient at present. The following are the key issues that need to be resolved:

a. The magnitude of the estimated treatment effect of Sativex on the self reported measure of spasticity in trials GWMS0106 and GWCL0403 was small in the overall patient population. The applicant has presented post hoc analyses supporting an argument that non responders can be identified in a 4 week therapeutic trial, and that the mean treatment effect in the remaining patients who would continue to receive treatment, would be clinically significant. This approach is welcomed. However, it has not been prospectively investigated whether the effect calculated in the post-hoc analysis can been translated into a pre-specified meaningful benefit for the patient. There is a lack of clinical data investigating such conditions of use, as no therapeutic trial followed by exclusion of non-responders was used in the pivotal trials. Further clinical data are necessary to investigate the effectiveness of the proposed 4 week therapeutic trial in identifying responders and excluding non-responders, and to clarify the magnitude and clinical relevance of the efficacy achieved in the subgroup of patients who continue to be treated with Sativex following a successful therapeutic trial. The pivotal clinical trial data should clarify the potential efficacy benefits in a subgroup of patients against the potential risks to a larger number of patients of a 4 week therapeutic trial of Sativex.

b. Since MS is a chronic disorder, there is a lack of evidence of maintenance of efficacy with long-term treatment.

c. The validity of the NRS as a measure specifically of spasticity appears unclear. Ongoing reassurance is required on the validity of the primary efficacy measure.

d. The pattern of CNS side effects such as sedation is highly suggestive that some unblinding is possible. Although there is no clear evidence that an important degree of bias has been introduced as a result of patient unblinding, the presented analyses are not able to refute this possibility. This issue still needs to be considered in the overall

evidence of efficacy. The smaller the differences between active and placebo, the greater is the concern that a relevant contribution of that apparent difference may not be real if a source of bias exists. If a compelling treatment effect can be shown it might be concluded that the possibility of unblinding might not represent a major concern.