Public Assessment Report

Decentralised Procedure

Sativex Oromucosal Spray

UK/H/2462/001/DC

UK licence no: PL 18024/0009

GW Pharma Limited

LAY SUMMARY

The MHRA granted GW Pharma Limited a Marketing Authorisation (licence) for the medicinal product Sativex Oromucosal Spray (PL 18024/0009) on 16th June 2010. This is a prescription-only medicine (POM) used to improve symptoms related to muscle stiffness (spasticity) in multiple sclerosis (MS). Health professionals sometimes talk about 'spasticity' when describing the muscle stiffness. Spasticity means there is an increase in 'muscle tone'. In other words, when the muscle is moved, there is more resistance to this movement than there normally would be. Muscles feel more rigid. Sativex is used when other medicines have not worked to relieve your muscle stiffness.

Sativex is a mouth spray which contains cannabis extracts containing compounds called cannabinoids.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Sativex Oromucosal Spray outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Information about the initial 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.
ATC Code	N02BG 10
Pharmaceutical form(s) and strength(s):	Oromucosal Spray
Reference Number for the Decentralised Procedure	UK/H/2462/001/DC
Reference Member State:	United Kingdom
Member States concerned:	Spain
Applicant (name and address)	GW Pharma Limited Porton Down Science Park, Salisbury, Wiltshire SP4 OJQ
Timetable	Day 210 – 17th May 2010

Module 2

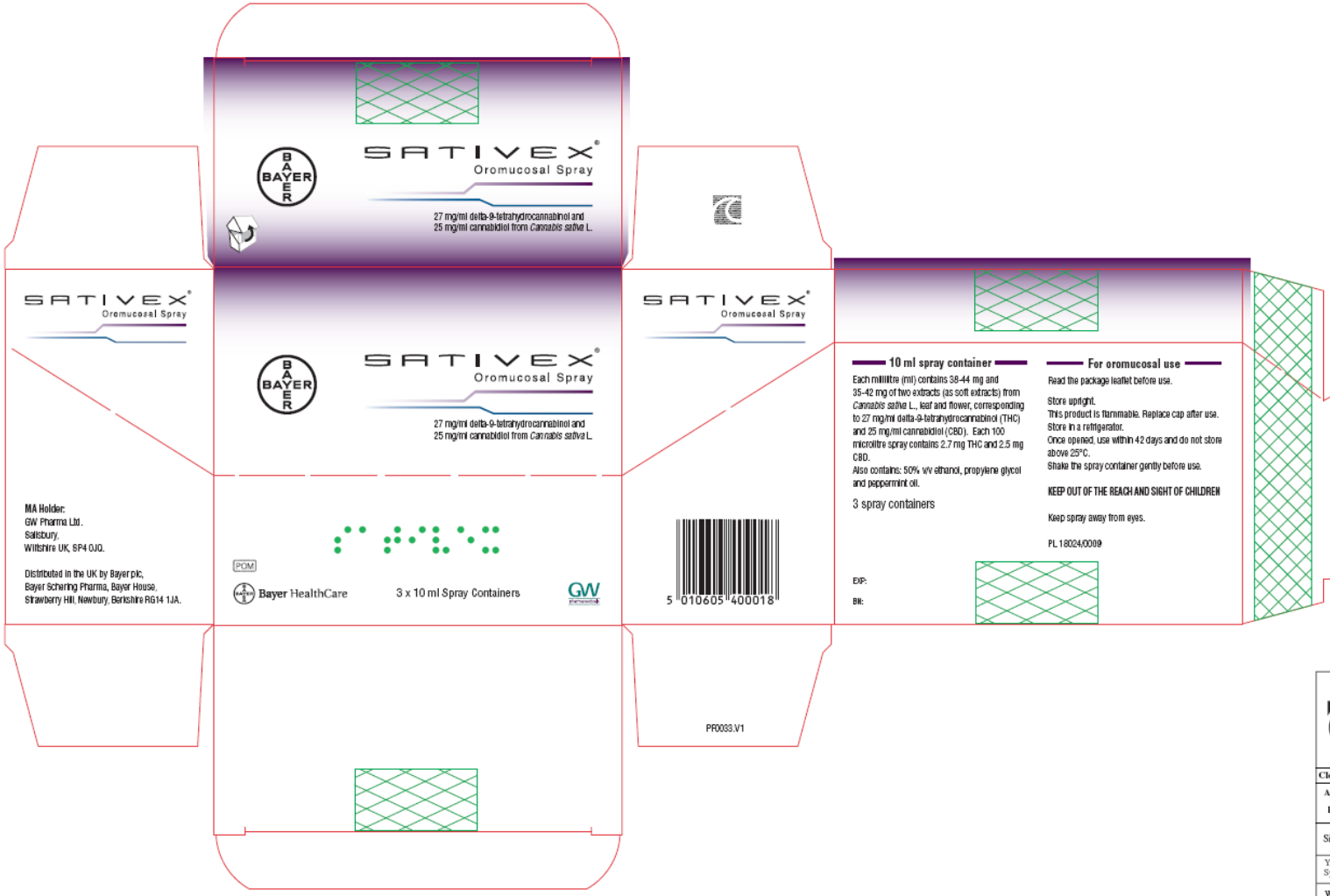
Summary of Product Characteristics

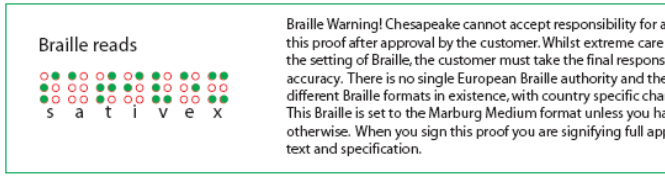
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at anational level are available on the MHRA website.

Module 4
Labelling





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Customer	GW Pharma
Description	Sativex UK 10ml 3 vial Carton
Code Ref	PF0033-V1
Cutter Ref	9422707_B
Size	100 x 52 x 87mm
Min. Point Size	7 pt
Page Numbers	2 of 2
Market	UK
Language	English
Proof By	Louise Heel
Proof No.	Five (AC Layer Added)
Date	23/04/2010
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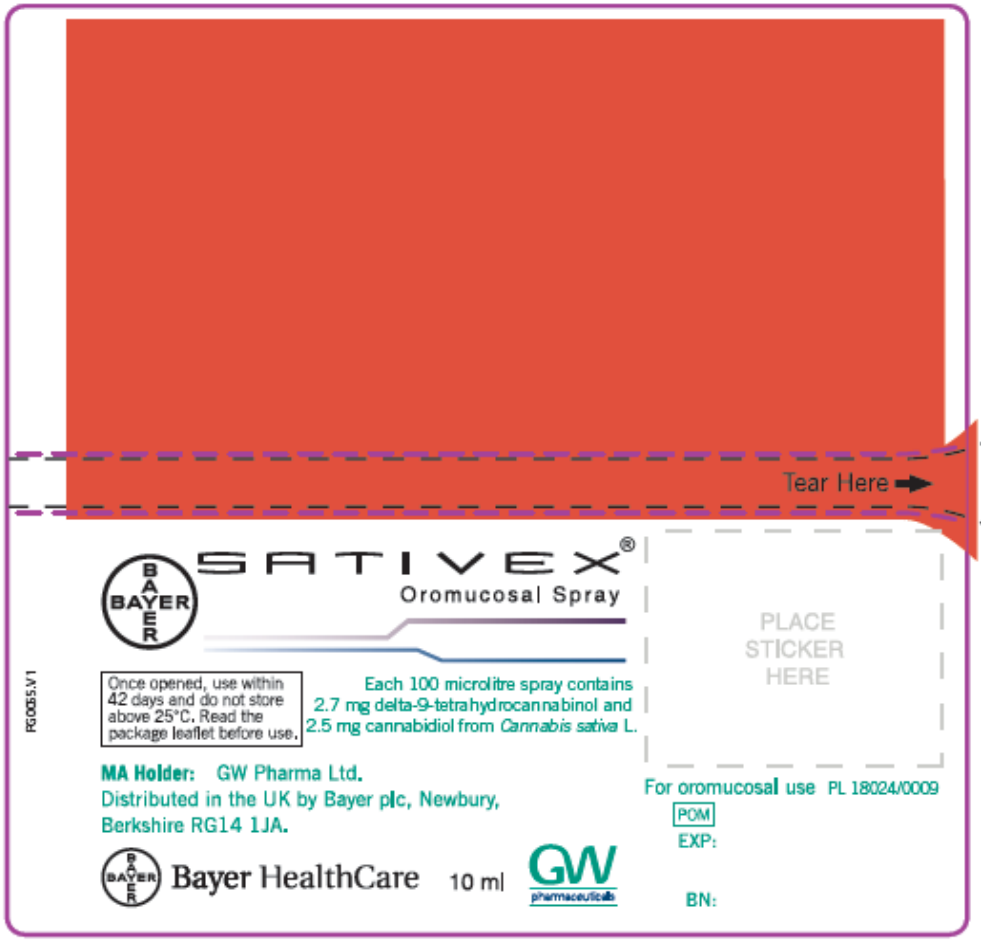


Bayer HealthCare

Sativex® Sticker Card

A sticker has been provided for each spray container.

Write the date that you open your spray on one of the stickers provided.
Stick the sticker on the spray so that you can check the date.

For each spray container:
Do not use the spray after it has been open for more than 6 weeks (42 days) and do not store above 25°C.

Once opened, use within 42 days Opening Date: DD / MM	Once opened, use within 42 days Opening Date: DD / MM	Once opened, use within 42 days Opening Date: DD / MM

PF0034.V1

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Sativex Oromucosal Spray (PL 18024/0009; UK/H/2462/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as reference member state (RMS) and Spain as concerned member state (CMS).

The product is a prescription-only medicine as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

These are applications made under the decentralised procedure (DCP), according to Article 8.3 of 2001/83/EC, as amended, for a new active substance Delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS) with Cannabidiol Botanical Drug Substance (CBD BDS).

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. Beneficial effects of cannabis on symptoms such as pain, urinary disturbance, tremor, spasm and spasiticity have also been claimed by individuals with multiple sclerosis (MS).

A previous application for this product was submitted in 2006 via the decentralised procedure (UK/H/961/01/DC). The Concerned Member States for this earlier procedure were DK, ES and NL. That application was withdrawn by the Applicant following the Day 180 Draft Assessment Report. At the time of the withdrawal of the application the RMS (UK) and CMSs unanimously considered that the application for Sativex Oromucosal Spray as add-on therapy, for symptomatic relief of spasticity in patients with multiple sclerosis (MS) was not approvable.

Further information on the previous application can be found in the Public Information Report at the following link which was published in December 2007.
http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033379.pdf

In the current application, filed in May 2009, the applicant has provided substantial new data to address issues relating to efficacy that were identified in the earlier decentralised procedure.

All non-clinical studies were conducted in accordance with current regulations.

All clinical studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 17th May 2010. After a subsequent national phase, the licences were granted in the UK on 16th June 2010.

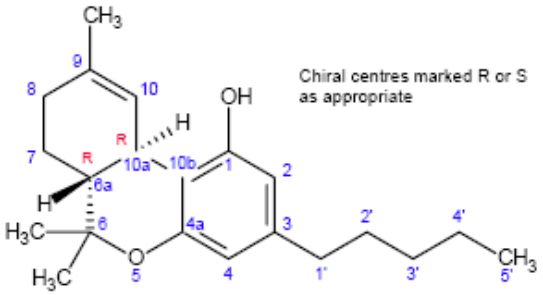
II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sativex Oromucosal Spray
Name(s) of the active substance(s) (INN)	Delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS) [Tetranabinex] and Cannabidiol Botanical Drug Substance (CBD BDS) [Nabidiolex], as extracts of *Cannabis sativa* L.
Pharmacotherapeutic classification (ATC code)	NO2BG 10
Pharmaceutical form and strength(s)	27mg/ml delta-9-tetrahydrocannabinol and 25mg/ml cannabidol
Reference numbers for the Mutual Recognition Procedure	UK/H/2462/001/DC
Reference Member State	United Kingdom
Member States concerned	Spain
Marketing Authorisation Number(s)	PL 18024/0009
Name and address of the authorisation holder	GW Pharma Limited, Porton Down Science Park, Salisbury, Wiltshire, SP4 OJQ

III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substances

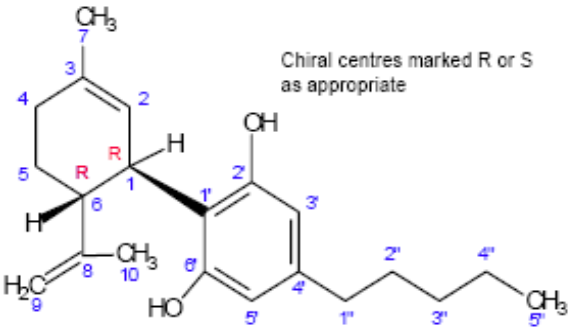
The two active substances are extracts from the leaves and flowers of the plant *Cannabis sativa* L., standardised to contain THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol), respectively.

Common Name: Delta-9-tetrahydrocannabinol
Chemical Name: (−)-(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol
Molecular Formula: $C_{21}H_{30}O_2$
Chemical Structure:



Molecular Weight: 314.45

Common Name: Cannabidiol
Chemical Name: 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol
Molecular Formula: $C_{21}H_{30}O_2$
Chemical Structure:



Molecular Weight: 314.46

Herbal substances

The plants are cultivated in line with Good Agricultural and Collection Practice (GACP). Two plant varieties are grown; one that contains higher levels of THC (delta-9-tetrahydrocannabinol) and one that contains higher levels of CBD (cannabidiol).

Satisfactory details have been provided describing the production of the herbal substances.

Appropriate specifications have been provided for both herbal substances. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Appropriate stability data have been provided and support the proposed retest period

Herbal preparations
Preparation of the extracts from the herbal substances has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate characterisation of the herbal preparations has been undertaken and appropriate specifications have been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

The specifications for the container-closures for both herbal preparations have been provided and are satisfactory. Declarations have been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been provided to support the retest periods for the herbal preparations, when stored in the proposed packaging. Suitable post approval stability commitments for the active substance have been provided.

P. Medicinal Product

The dosage form is a solution of the two cannabis extracts presented as an oromucosal spray.

Other Ingredients

Other ingredients consist of the pharmaceutical excipients ethanol anhydrous, propylene glycol and peppermint oil. All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient showing compliance with its respective monograph.

None of the excipients are sourced from animal or human origins. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The product is packaged in a Type I amber 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 microlitres per spray. Pack sizes are 5.5 millilitres (to deliver up to 48 actuations) and 10 millilitres (to deliver up to 90 actuations). The product is packaged in cartons with 1, 2, 3, 4, 5, 6, 10 or 12 glass sprays per carton.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to submitting mock-ups of any new pack sizes to the regulatory authorities before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the storage conditions "Store in a refrigerator (2 to 8^{o}C). Once the spray container is opened and in use, refrigerated storage is not necessary but do not store above 25^{o}C. Store upright. Keep away from heat and direct sunlight".

Suitable post approval stability commitments have been provided.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Follow-up measures and specific obligations
These include full implementation of the agreed Risk Management Plan as well as continuing work on the quality control of the product.

Conclusion
The grant of a marketing authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

Many of the non-clinical data are derived from published studies. Pivotal pharmacokinetic and toxicity studies have, however, been sponsored by the applicant.

At the conclusion of the earlier DC procedure for Sativex there were no outstanding non-clinical issues. The final report of the rat oncogenicity study was outstanding and the applicant was asked to conduct and submit definitive reproductive toxicology studies and additional genotoxicity studies. The applicant has complied with these requests.

Other new studies relating to primary pharmacodynamics, safety pharmacology, repeated-dose toxicity and local tolerance have also been submitted presumably to improve the quality of the dossier for future applications.

With the exception of the rat oncogenicity study on CBD BDS (cannabidiol botanical drug substance), all new studies have been conducted on the two active ingredients CBD BDS and THC BDS (delta-9-tetrahydrocannabinol botanical drug substance) in the same proportion as that proposed for clinical use (effectively 1:1) also known as GW-1000-02.

The likely overall safety of Sativex® has been adequately evaluated from both published reports and commissioned studies and potential adverse effects identified. In particular, there is low potential for genotoxicity, carcinogenicity and local toxicological effects with adequate/sufficient margin of safety estimated for the finished product. Clinically significant drug-drug interactions are unlikely. In addition, major organ toxicity at clinical doses is not expected.

Some potential for reproductive effects in terms of pup development and nursing behaviour has been observed. Overall, the available animal data suggest that Sativex® should not be used during pregnancy or during the period of breast-feeding.

New non-clinical mechanistic data were provided including published data and a new mouse pharmacodynamic study.

The Applicant has supplied details of a body literature of data confirming cannabinoids to relieve motor dysfunction and spasticity in accepted animal models.

A study in mice was conducted. In this study, the “stiffness” of spastic limbs was measured using a strain gauge, and assessed by the resistance force against hindlimb flexion.

Sativex BDSs administered at an intravenous dose of 5 $mg \cdot kg^{-1}$ THC + 5 $mg \cdot kg^{-1}$ CBD produced an approximate 20% peak reduction in hindlimb stiffness (spasticity).

Sativex BDSs administered at an intravenous dose of 10 $mg \cdot kg^{-1}$ THC +10 $mg \cdot kg^{-1}$ CBD produced an approximate 40% peak reduction in hindlimb stiffness (spasticity).

It was evident that the compounds within Sativex® have the potential to dose-dependently inhibit spasticity in an experimental mouse model of multiple sclerosis.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC and PIL are acceptable from a non-clinical point of view.

Expert report

The non-clinical expert report was written by an appropriately qualified person and is a suitable summary of the nonclinical dossier. The Applicant's responses to various issues identified during the assessment procedure were satisfactory.

Environmental Risk Assessment
The *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00) states in Section 2 (Scope and legal basis) that herbal medicinal products are exempted due to the nature of their constituents. Therefore an Environmental Risk Assessment was not required for Sativex.

Conclusion
The grant of a marketing authorisation is recommended.

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction
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 oromucosal 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. Additional studies are provided to characterize the PK profile of Sativex.

Biopharmaceutics and Drug Delivery Methods
The oromucosal route chosen for Sativex avoids the problem of the low and highly variable bioavailability (typically 6 to 20%) of orally administered cannabinoids due to first pass metabolism. CBD and THC are both are highly lipophilic and consequently are well absorbed following oromucosal (e.g. sub-lingual) administration. Possible alternative routes of administration that would minimize first pass metabolism include the pulmonary, nasal, and rectal routes. Each has significant disadvantages.

Study GWPKOlO9 was an open label, randomised, 5-way crossover design looking at the PK profiles following delivery of a 5 mg dose of cannabis-based medicine extracts (CBME) in a range of pump sizes (25, 50 and 100µl) with and without the addition of peppermint masking flavour. The mean pharmacokinetic parameters are shown in the clinical pharmacology summary. Addition of peppermint made no significant changes to the pharmacokinetic profile. Keeping the formulation constant but changing the pump size produced inconsistent changes in the pharmacokinetics. The C_{max} and AUC of both THC and CBD were greater with 25µl pump than with 50µl pump but there was no significant difference between the 25 µl pump and 100µl pumps.

Because cannabinoids are virtually insoluble in water the active ingredients of Sativex are solubilised in organic solvents - ethanol and propylene glycol. The clinical expert report states that ethanol has value in this type of formulation also because it acts as a penetration enhancer. The quantity of ethanol in the product is such that the recommended daily maximum of 12 sprays would result in the administration of 0.48 g of ethanol over a 24 hour period. As ethanol is an irritant the applicant carried out single and repeat dose local irritation toxicology in the standard model of the hamster cheek pouch in which Sativex did not provoke inflammation. The alcohol content is substantially below the recommended

maximum intake of ethanol within a medicine (of 1.5g) recommended even for paediatric use (EMEA/HMPC/85114/2008) and concludes that there is no serious concern about the repeated local application of such small quantities of ethanol.

Assessor's comment

The proposed formulation, route of administration and delivery system seem appropriate. The available data do not indicate any significant concerns surrounding the repeated local application of the small quantities of ethanol in each dose. However there have been recent published reports of an increased risk of oral and upper airway malignancy in association with alcohol containing mouthwashes, especially in smokers. It is known that most such malignancies occur in subjects who both smoke and drink alcohol, especially spirits and the mechanism is thought to involve ethanol acting as a penetration enhancer for the carcinogens in cigarette smoke. The applicant should comment on the risk and if necessary propose additional SPC advice. This should include a consideration of whether it might be advisable to rotate the site of dose application, bearing in mind what effect this might have on the intra-individual variability of the PK profile.

Absorption

The inhaled route results in a very different plasma concentration/time profile from that following oromucosal administration of Sativex. A rapid increase in plasma THC levels occurs when cannabis smoke is inhaled, in contrast to the T_{max} for Sativex of approximately 90 minutes. From the available published literature it can be demonstrated that the plasma levels of THC following smoked or vaporized THC BDS (mean dose: 6.65 mg, mean C_{max} = 118ng/mL, Study GWPK0114) are over ten times higher than those achieved with a cautious oromucosal administration with Sativex (mean dose: 10.4mg THC + 10mg CBD, mean C_{max} = 4.90ng/mL (THC), Study GWPK0215).

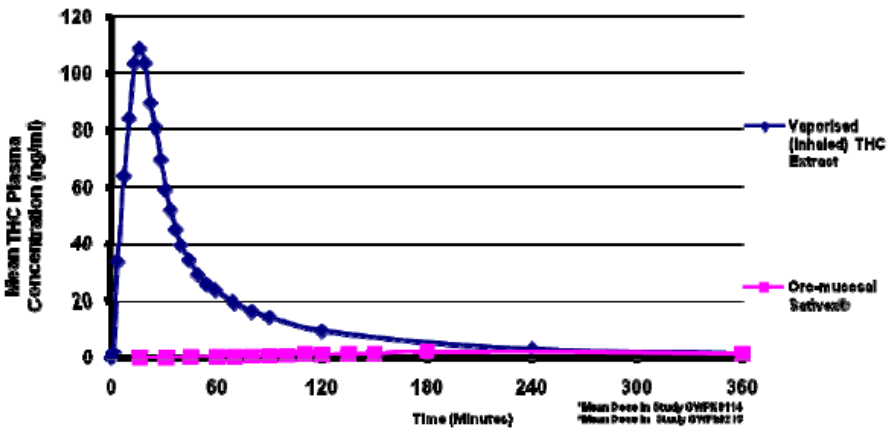


Figure 1. Plasma THC levels following administration of 6.65mg of vaporised THC extract or 4 sprays of Sativex® (10.8mg THC & 10mg CBD)

Analyte	Dose of THC administered (mg)	mean C_{max} (ng/ml)	T_{max} (mins)
Vaporised (inhaled) THC extract	6.65	103.52	13
Oromucosal Sativex (4 sprays)	10.4	2.72	60-90
Smoked Cannabis (8 inhalations)*	30.0	162.2	9

Table 1. C_{max} and T_{max} of THC after administration of vaporised THC, Sativex or smoked cannabis, showing that pulmonary administration of THC produces much higher plasma levels of THC, much faster than does Sativex.

*Huestis M (2005)

Single-dose pharmacokinetic studies using the proposed formulation of Sativex showed that sub-lingual administration resulted in similar plasma levels compared with administration to other parts of the oral mucosa. The choice of sub-lingual administration is appropriate and might be the most patient friendly of the transmucosal options. It is reassuring that the PK data support administration to other parts of the oral mucosa for example in the event of local irritation from repeated administration at the same site.

The rate and extent of absorption of Sativex showed very high inter and intra-subject variation in the PK studies. Within a group of volunteer subjects dosed equally, the C_{max} of THC and CBD may vary by ten times between one subject and another. Bioavailability of THC was consistently higher than that of CBD. This high variability in bioavailability is inevitable due to variability in the proportion of each dose which is swallowed and therefore subject to first pass metabolism, the extent of which is itself very variable. 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 proposed.

In practical terms, the effect of food and/or drink intake relates much more to its influence on the proportion of the Sativex dose that is swallowed before buccal absorption is complete than to its effect on G-I absorption. GW has not specifically investigated this; however there are a number of strands of evidence that provide reassurance:

- Patients participating in clinical trials with Sativex self-titrate until they find their optimum dose. This will also be the case for patients who receive Sativex on prescription. The self-titration approach allows for any variation with respect to the effect of food and drink (e.g. the relative timing of dosing and food intake adopted by individual patients).
- Between-patient PK variability is high, but within-patient PK variability is low. This suggests that the theoretical benefits of the self-titration approach are translated into practice.
- Once patients have titrated their dose, there is strong evidence to show that this dose remains stable.
- The pharmacokinetics of Sativex were assessed in patients with multiple sclerosis at 2 clinic visits 8 weeks apart (study GWMS0001EXT). The result showed a much higher degree of within-patient consistency than that seen between patients and across the group actual plasma concentrations achieved were relatively consistent (5-10 ng/ml).

Assessor's comment

The much more rapid increase in plasma levels and the associated higher C_{max} 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 dose related undesirable effects and for the possibility of patient unblinding to randomized treatment.

The UK assessor agrees that the oromucosal route of administration is appropriate. The SPC and PIL should advise against taking fluids shortly after dose administration as this could in principle substantially affect the proportion of an administered dose that is swallowed and therefore subject to first pass metabolism.

The proposal for a flexible individual patient dose titration regimen is well-justified.

Distribution

The 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 cannabinoids from vessel-poor fatty tissue.

Assessor's comment

This characteristic is advantageous as the aim of the product is to achieve relatively stable plasma and CNS levels without the peaks that would be associated with side effects. Long term accumulation of any drug in fatty tissues can potentially represent safety issues if plasma levels rise progressively or if there is a need to withdraw treatment suddenly. In the case of Sativex neither of these appears to be of concern (see below).

Elimination

The metabolism of THC and CBD following administration of Sativex has not been specifically studied on the grounds that the metabolism of these cannabinoids has been thoroughly described in the literature.

CBD is extensively metabolised and more than 33 metabolites have been identified. The major metabolic route was hydroxylation and oxidation at C-7. The major oxidised metabolite identified was CBD-7-oic acid.

THC on the other hand is metabolised very rapidly by live enzymes with 11-OH-THC being the main metabolite. After oral administration, the faecal excretion of THC metabolites was 48 - 53%. 11-OH-THC is excreted unchanged in faeces. After IV administration the urinary excretion of THC metabolites ranged from 13 - 17% and faecal excretion 25-30% of total dose.

The terminal elimination half life is at least 24 to 36 hours. PK 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 (, or of the primary metabolite of THC), as indicated in the table below. A similar range of C_{min} values after chronic dosing to those seen after single dose was seen.

Table NL C1-1: Trough levels of THC, CBD and 11-hydroxy THC at Visit A and Visit B, separated by 8 weeks, in patients dosed long-term with Sativex.

	Trough plasma levels (mean and range: ng/ml)					
	THC		CBD		11 OH THC	
	Visit A	Visit B	Visit A	Visit B	Visit A	Visit B
Mean	2.53	2.10	2.73	2.51	3.18	2.90
min	0.06	0.63	0.12	1.00	0.05	1.36
max	6.28	3.56	7.40	4.12	8.68	4.73

Assessor's comment

The data showing a lack of accumulation during chronic exposure is 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.

Dose proportionality

Conventional dose proportionality studies were not conducted on Sativex. The pharmacokinetic data taken from patients on different daily doses of Sativex in long-term treatment in the Phase III study GWMS0001 show that the dose-normalised trough levels are similar for patients taking widely differing daily doses of Sativex in chronic use, and that the range of trough levels seen is similar at Visit A and at and Visit B (after 8 weeks of continuing treatment) in chronic use. In addition, the dose-normalised C_{max} in these subjects shows much less variability than the daily dose, indicating reasonable dose linearity in chronic dosing, and is similar to the dose-normalised C_{max} seen in single dose studies.

The Applicant proposes that these data indicate a high degree of within patient consistency in pharmacokinetics in chronic dosing despite an acknowledged high degree of between subject variability in pharmacokinetics. It is also clear, both from the literature, from the single dose Phase 1 studies carried out by the Applicant that there is a substantial amount of between patient variability in the pharmacodynamics of Sativex.

This variability in within patient pharmacodynamic effects is also well demonstrated clinically, where the absence of a dose-response relationship in either safety or efficacy further confirms the within patient dose titration approach as being appropriate.

The Applicant argues that it is for these reason that a within patient dose titration approach by the patient is most appropriate.

Assessor's comment

This is satisfactory. The assessor agrees that in the context of the high variability of kinetics between patients and the lack of a clear dose response relationship in the occurrence of adverse events or efficacy there is sufficient information showing dose linearity.

Pharmacokinetic data with regard to maximum dose

The maximum proposed daily dose of Sativex is12 sprays per day. In the PK evaluation of Sativex in patients gaining long-term benefit (Study GWMS0001Ext) the mean interval between sprays varied, along with the number of sprays taken at each interval. The mean interval between administrations for Visit A was 3.26 hours and the mean interval for Visit B was 3.27 hours. Based on the observed intervals between doses during the PK sampling period, the calculated mean no. of sprays per day taken was 26.22 sprays per day.
Thus the conclusions from the PK data collected do reflect plasma data in patients who would have been taking high doses of Sativex (exceeding the maximum daily dose).

While there are no extensive exposure data in long-term use, there are several observations from the data provided by the Applicant that are reassuring on this point:

- the single dose pharmacokinetics are similar between patients and healthy subject volunteers
- there is no evidence of accumulation of THC, the psychoactive component of Sativex, in chronic dosing in patients with multiple sclerosis.
- there is an acknowledged between patient variability in pharmacokinetics and pharmacodynamics
- there is no dose response relationship in the occurrence of adverse events or efficacy.

These factors combine to make it unlikely that a maximum recommended daily dose could be justified by establishing a relationship between plasma exposure and tolerability.

Assessor's comment
There are sufficient data from patients exposed to the maximum dose recommended in the amended SPC.

Pharmacokinetics in target population
Pharmacokinetics were investigated in patients with multiple sclerosis and the data are presented in the clinical pharmacology summary. The kinetic profile was not substantially different from that observed in healthy volunteers.

Special populations
Pharmacokinetic studies in special populations have not been undertaken and appropriate warnings and contraindications included in the SPC are supported by the PK characteristics in these groups known from the published literature.

- **Impaired hepatic and renal function**

The SPC states: "*No specific studies have been carried out in patients with significant hepatic or renal impairment, therefore if Sativex is used by such patients, frequent review by a clinician is recommended.*"

Assessor's comment
This is not satisfactory. There is sufficient information available from the published literature to provide authoritative information and recommendations.

- **Elderly**

No specific studies were carried out in elderly patients, although patients up to 90 years of age were included in clinical trials. No differences in safety or efficacy were seen between elderly patients and those under 65 years of age. This information is provided in the SPC.

Assessor's comment
The company's approach is satisfactory.

- **Children**

Sativex was not investigated in the paediatric population. The SPC states that no studies have been conducted in adolescents or children less than 18 years of age, therefore, SATIVEX is not recommended in the paediatric population.

Assessor's comment
This is acceptable at the present time. However, MS with spasticity can occur in adolescents so the applicant should provide proposals for post-authorisation paediatric assessment.
A Pediatric Investigation Plan (PIP) for Sativex was published by the European Medicines Agency: EMEA/162839/2009 (P/41/2009). The PIP indication is "intractable spasticity due to cerebral palsy or traumatic CNS injury".

Interactions

- ***In vitro***

The effect of the cannabinoid extracts on activity of P450 (CYP450) is addressed by the applicant with *in vitro* studies with human hepatic microsome preparations. These indicate that Sativex has a very limited ability to inhibit CYP450 isoforms at concentrations substantially in excess of those reached by the therapeutic administration of Sativex.

The CYP450 inhibition and induction studies carried out by the Applicant confirm that there is not likely to be a clinically relevant interaction between cannabinoids and CYP450 isoforms. The

most potent interaction was between THC and testosterone 6 beta hydroxylation, a marker for 3A4 activity, with an IC_{50} of 7 micromolar. In a duplicate set of experiments, the IC_{50} of the CBD:THC 1:1 mixture was 10 micromolar. Again it is worth recalling that a 1 micromolar concentration of CBD is equivalent to a plasma concentration of 314 ng/ml. The maximum plasma concentration observed in chronic dosing at high levels of Sativex intake has been less than 14 ng/ml, which is less than 50nanomolar, and around 400 fold less than the IC50.

According to the literature, CBD significantly inhibits P-glycoprotein-mediated drug transport *in vitro*, suggesting CBD could potentially influence the absorption and disposition of other co-administered compounds that are P-gp substrates in vivo. Digoxin is a well known substrate for P-gp, which regulates oral absorption and renal clearance of this drug. As digoxin is a narrow therapeutic drug this represents a potentially important interaction.

CBD has an inhibitory effect on P-gp when it has been induced, at an IC_{50} of somewhere between 8 and 39 micromolar. This is quantitatively and qualitatively similar to that seen with curcumin (turmeric), and in some assays, is similar to that seen with verapamil. There is as yet no obvious mode of action for this observed effect, which is also seen with endogenous cannabinoids, but appears to be independent of the cannabinoid receptor.

When Sativex is administered to humans, the maximum observed plasma concentration of CBD seen in chronic dosing at high daily dose levels, has been less than 14 ng/ml, which is less than 50 nanomolar. This is almost two orders of magnitude lower than the concentrations of CBD which cause a 50% inhibition of induced p-glycoprotein.

As part of the integrated summary of safety, the Applicant has examined the adverse event profile of Sativex compared with placebo when it has been given concomitantly in patients with multiple sclerosis with amitriptyline (n=63), baclofen (n=197), benzodiazepines (n=76), gabapentin (n=42), strong opioids (n=78), and in patients with other chronic neurological conditions when it has been given concomitantly with amitriptyline (n=18), baclofen (n=27), benzodiazepines (n=30), gabapentin (n=53) and opioids (n=55). [The numbers given are for the subjects on Sativex – placebo numbers are similar].

There have been no clinically apparent drug-drug interactions in the clinical study experience with Sativex.

Finally, in the literature as it relates to smoked cannabis, there are no anecdotal reports which suggest adverse events consequent on a P-gp interaction. In this context, the plasma levels of THC, the principal cannabinoid present in smoked cannabis, reach in excess of 100ng/ml.
In conclusion, while there may be a very theoretical and preliminary basis for hypothesising a relevant interaction between very high levels of CBD and P-gp, there is no clinical evidence for this. The Applicant therefore does not propose conducting a formal drug-drug interaction study with digoxin.

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

- ***In vivo***

The applicant has not carried out any pharmacokinetic interaction studies as sufficient information is available from the published literature.

Assessor's comment

This is acceptable as the published data and the *in vitro* study indicate a low likelihood of interactions with Sativex. Additional *in vivo* studies are not required.

Assessor's overall conclusions on pharmacokinetics

The pharmacokinetic profile of Sativex has been well-described and discussed in the clinical pharmacology summary and clinical overview. No issues were identified and other than the lack of advice regarding hepatic or renal impairment, the SPC wording is adequately justified. As there is a high degree of intra- and inter-subject variability in pharmacokinetics (and the therapeutic dose is highly variable), titration to individual therapeutic response is appropriate. Long term accumulation of the drug in fatty tissues could represent a safety issue.

Pharmacodynamics

Introduction and mechanism of action

The following description of the mechanisms of action of the cannabinoids in Sativex is given in the summary of product characteristics:

Mechanism of action

As part of the human endocannabinoid system (ECS), cannabinoid receptors, CB_1 and CB_2 receptors are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. THC acts as a partial agonist at both CB_1 and CB_2 receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g. reduce effects of excitatory neurotransmitters such as glutamate).

In animal models of MS and spasticity CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. These effects are prevented by CB antagonists, and CB1 knockout mice show more severe spasticity. In the CREAE (chronic relapsing experimental autoimmune encephalomyelitis) mouse model, Sativex produced a dose-related reduction in the hind limb stiffness.

Clinical experience

Sativex has been studied at doses of up to 48 sprays/day in controlled clinical trials of up to 19 weeks duration in more than 1500 patients with MS. In the pivotal trials to assess the efficacy and safety of Sativex for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) the primary efficacy measure was a 0 to 10 point Numeric Rating Scale (NRS) on which patients indicated the average level of their spasticity related symptoms over the last 24 hours where 0 is no spasticity and 10 is the worst possible spasticity.

In a first Phase 3 placebo controlled trial over a 6-week treatment period the difference from placebo reached statistical significance but the difference between treatments of 0.5 to 0.6 points on the 0-10 point NRS was of questionable clinical relevance. In a responder analysis 40% Sativex and 22% placebo responded to treatment using the criterion of greater than a 30% reduction in NRS score. A trend in favour of Sativex was seen on secondary efficacy measures, including the Modified Ashworth Score, but none reached statistical significance.

A second 14 week Phase 3 study failed to show a significant treatment effect although the majority of endpoints showed a trend in favour of Sativex. The difference from placebo on the NRS score was 0.2 points.

It was postulated that a clinically important treatment effect in some patients was being partly masked by data from non-responders in the analyses of mean changes. In analyses comparing NRS scores with patient global impression of change (PGI), a 19% NRS response was estimated to represent a clinically relevant improvement on the PGI and a response of 28% "much improved" on the PGI. In post hoc exploratory combined analyses of the above two studies, a 4-week trial period using a 20% NRS response threshold was found to be a good predictor of eventual response defined as a 30% reduction.

A third Phase 3 trial incorporated a formalised 4-week therapeutic trial period prior to randomisation. The aim of the trial was to assess the benefit of continued treatment for patients who achieve an initial response to treatment. 572 patients with MS and refractory spasticity all received single blind Sativex for four weeks. After four weeks on active treatment 241 met the entry criterion of a reduction of at least 20% on the spasticity symptom NRS, with a mean change from the start of treatment of -3.0 points. These patients were then randomised to either continue to receive active or switch to placebo for the 12 week double-blind phase, for a total of 16 weeks treatment overall.

During the double-blind phase the patients receiving Sativex generally retained the improvement in symptoms obtained over the initial 4-week treatment period (mean change from randomisation in NRS score -0.19), while the patients switched to placebo began to decline back towards pre-treatment levels (mean change in NRS score +0.64). The difference* between treatment groups was 0.84 (95% CI -1.29, -0.40).
* Difference adjusted for centre, baseline NRS and ambulatory status

Of those patients who had a 20% reduction from screening in NRS score at week 4 and continued in the trial to receive randomised treatment, 74% (Sativex) and 51% (placebo) achieved a 30% reduction at week 16.

The results over the 12-week randomised phase are shown below for the secondary endpoints. The majority of secondary endpoints showed a similar pattern to the NRS score, with patients who continued to receive Sativex maintaining the improvement seen from the initial 4-week treatment period, while patients switching to placebo begin to decline back to pre-treatment levels. :

Modified Ashworth Score:	Sativex -0.1 ; Placebo +1.8 ; Adjusted Difference -1.75 (95% CI -3.80, 0.30)
Spasm frequency (per day):	Sativex -0.05 ; Placebo +2.41 Adjusted Difference -2.53 (95% CI -4.27, -0.79)
Sleep disruption by spasticity: (0 to 10 NRS)	Sativex -0.25 ; Placebo +0.59 ; Adjusted Difference -0.88 (95% CI -1.25, -0.51)
Timed 10 metre walk (seconds):	Sativex -2.3; Placebo +2.0; Adjusted Difference -3.34 (95% CI -6.96, 0.26)
Motricity index (arm and leg):	No differences between treatment groups were seen.
Barthel Activities of Daily Living:	Odds ratio for improvement : 2.04

Subject global impression of change (OR=1.71), carer global impression of change (OR=2.40) and physician global impression of change (OR=1.96) all showed highly statistically significant superiority of Sativex over placebo.

The benefit of continued treatment in the long-term was shown in a placebo controlled, parallel group, randomised withdrawal study in subjects taking long-term Sativex. There were 36 patients recruited with a mean duration of Sativex use prior to the trial of 3.6 years. Patients were randomised to either continue with Sativex treatment or switch to placebo for 28 days. The primary endpoint was time to treatment failure, defined as the time from the first day of randomised treatment to a 20% increase in NRS or premature withdrawal from randomised treatment. Treatment failure was experienced by 44% of Sativex patients, and 94% of placebo patients, and the hazard ratio was 0.335 (95% CI 0.16, 0.69) representing a 65% reduction in risk with continued treatment.

In a study designed to identify its abuse potential, Sativex at a dose of 4 sprays taken at one time did not differ significantly from placebo. Higher doses of Sativex of 8 to 16 sprays taken at one time did show abuse potential comparable to equivalent doses of dronabinol, a synthetic cannabinoid. Cognitive performance (short-term memory, choice reaction time and divided attention) was not shown to be impaired by Sativex at the doses tested in this study. In a QTc study a dose of Sativex 4 sprays over 20 minutes twice daily was well-tolerated, but a substantially supratherapeutic dose of 18 sprays over 20 minutes twice daily resulted in significant psychoactivity and cognitive impairment.

Primary pharmacology

A comprehensive review of the published literature on the CNS pharmacology of cannabinoids is provided in the preclinical summary. The clinical pharmacology provides a review of neuropsychiatric, cognitive and neuromotor aspects in humans.

There have been a number of reports of the evaluation of THC and of cannabis extracts in animal models of spasticity but none evaluating CBD alone. These data have been considered by the preclinical assessor.

There are no human studies reported investigating a pharmacodynamic effect of THC or CBD on the physiologic phenomenon of spasticity, other than a number of clinical studies using measures such as the Ashworth scale, which generally failed to show an effect.

The first Phase I study and its extension investigated some aspects of the pharmacology of Sativex.

GWPD9901: A single centre, placebo-controlled, four period, crossover, tolerability study assessing, pharmacodynamic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of Cannabis Based Medicine Extract (CBME).

Three preparations (High THC 20mg, High CBD 20mg and THC + CBD 20mg + 20mg) of CBME were studied. The primary objective was to evaluate the tolerability of the three preparations compared to placebo. The secondary objectives were to assess cognitive effects, plasma pharmacokinetics and PD effects over a 12-hour period. The greatest mean change, compared to baseline, in feeling of well being, wakefulness and mood were reported three hours following the CBD + THC sublingual drops. Effects on muscle tone were not studied.

GWPD9901Ext: A two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a Cannabis Based Medicine Extract given via two administration routes.

An extension of study GWPD9901, single doses of a CBME given via pressurised aerosol and nebuliser were studied. The mean incidence of unpleasant effects was greatest and reported earlier following administration of the nebuliser test treatment. A questionnaire analysis revealed that the sublingual test treatments were best liked and the nebuliser test treatment least liked. Effects on muscle tone were not studied.

Assessor's comment

This first in man study (with GW formulated CBME product) and its extension does not provide any substantial new information on the pharmacodynamic activity of THC and CBD. In particular it provides no information on effects on muscle tone or spasticity.

The review of the published data (preclinical data in particular) provided some 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. However there is no robust confirmation of these concepts by studies measuring the effect of cannabinoids on muscle tone or spasticity.

In the dossier as a whole there is a lack of information on the effect of THC and CBD on muscle tone or spasticity, either in normal subjects or in patients with spasticity. For the purpose of the current application this is the primary pharmacodynamic activity of the

product. The theoretical basis described in the literature for a potential effect of cannabinoids in treating the specific symptom of spasticity in patients with MS is no substitute for hard data demonstrating such a pharmacodynamic effect.

The argument that "there is no bio-marker for spasticity" is not fully accepted. Although it is true that spasticity has no single defining feature and has various elements including hyper-reflexia, increased tone (resistance to passive movement), spasms, weakness and fatiguability, the key elements are potentially amenable to measurement.

Secondary pharmacology

The secondary pharmacology of THC and CBD, based on published literature, is comprehensively described in the clinical pharmacology summary. This information is mostly well known and aspects not of particular relevance to Sativex, with implications for safety or efficacy in the proposed indication, are not re-presented here.

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 6.65mg dose of vaporised THC extract resulted in a mean C_{max} of more than 100ng/ml, reached within minutes of administration and producing significant psychoactivity. In contrast a 10mg dose of Sativex administered sub-lingually achieved a mean C_{max} of around 3ng/ml and a T_{max} 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.

Study GWPK0110

This study investigated the effects of CBME on sleep in healthy volunteers. The company concluded that the effects of THC and CBD on sleep were unlikely to prejudice any improvement in sleep brought about by an anticipated effects of the treatment in alleviating pain and discomfort. However, although 15 mg THC is free of adverse effects of clinical significance on the sleep process, its activity is associated with residual effects. In this context the co-administration of THC and CBD has advantages beyond the therapeutic benefits that both drugs may bring individually. An equal dose of CBD appears to counteract the residual effects of THC on daytime sleep latencies and memory, even though the subjects may still report sleepiness.

Assessor's comment

The information provided on the secondary pharmacology of THC and CBD seems adequate. There are no particular concerns arising that would require the company to conduct further studies on secondary PD characteristics.

Relationship between plasma concentration and effect

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.

Assessor's comment
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.

Pharmacodynamic interactions with other medicinal products or substances
Clearly 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.

Assessor's comment
The lack of pharmacodynamic interaction studies could be considered a moderate deficiency. It would be of value to know for example how Sativex might interact with muscle relaxing agents such as baclofen and benzodiazepines in terms of maintaining muscle power and appropriate tone to avoid falls.

Genetic differences in PD response
This has not been investigated.

Assessor's comment
In the context of this application this is acceptable

Assessor's overall conclusions on pharmacodynamics
Much of the information regarding the main pharmacological effects of the principal cannabinoids present in Sativex comes is well-established in the published literature. However the actions of cannabinoids that are claimed to confer efficacy in the treatment of spasticity are much less well-described.

The principal weakness of the pharmacodynamic data is a lack of information on the effect of THC and CBD on muscle tone or spasticity, either in normal subjects or in patients with spasticity. Preclinical data might suffice in principle as spasticity is not readily measurable with precision in humans. In response to this issue, a study in mice was conducted by the Applicant. In this study, the "stiffness" of spastic limbs was measured using a strain gauge, and assessed by the resistance force against hindlimb flexion.

Sativex BDSs administered at an intravenous dose of 5 mg·kg-1 THC + 5 mg·kg-1 CBD produced an approximate 20% peak reduction in hindlimb stiffness (spasticity).

Sativex BDSs administered at an intravenous dose of 10 mg·kg-1 THC + 10 mg·kg-1 CBD produced an approximate 40% peak reduction in hindlimb stiffness (spasticity).

It was concluded that the compounds within Sativex® have the potential to dose-dependently inhibit spasticity in an experimental mouse model of multiple sclerosis.

The secondary pharmacodynamic effects of cannabinoids have been shown to be highly variable between subjects.

Overall the Phase I studies performed by the company, supported by the information presented from the published literature on the pharmacological effects of the principal cannabinoids present in Sativex, and the data from the pre-clinical model are considered adequate.

CLINICAL EFFICACY

Introduction

Two Phase II and four Phase III short-term placebo-controlled studies 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). In addition there are two open label extension studies and one Phase III randomised withdrawal study in patients treated long term with Sativex.

Full study reports for the Phase II studies, three of the four Phase III studies and the open-label extension studies were submitted for the previous application for this product via the decentralised procedure (UK/H/961/01/DC).

The assessments of the Phase III short term placebo controlled study GWSP0604 and the randomised withdrawal study GWSP0702 are new. In addition the applicant has provided substantial new data to address issues relating to efficacy that were identified in the earlier decentralised procedure. The sections of this report concerning these issues and the data addressing them are also new.

Phase II / dose-response studies

There are two Phase II clinical trials as summarised in the table.

Study Number	Description	Phase
GWN19902 n= 25	A preliminary double-blind, randomised crossover placebo-controlled investigation of the therapeutic profile of three cannabis-based medicine extracts in patients with multiple sclerosis, spinal cord conditions, peripheral nerve injury, or central nervous system damage associated with vascular, traumatic, infective, genetic, neoplastic and metabolic disease; any of which has resulted in pain and/or spasticity. The duration of the study was 10 weeks in total, two weeks open label run in, followed by four crossover periods of two weeks each.	Phase II controlled study
GWN19904 n= 29	A preliminary placebo-controlled investigation of the therapeutic profile of three cannabis-based medicine extracts in patients with multiple sclerosis and other neurological conditions resulting in pain and/or spasticity, or arthritic conditions. Maximum duration of two weeks open label therapy followed by a maximum of four weeks blinded crossover therapy per study section.	Phase II controlled study

Study GWN19902:

This was a single centre, placebo-controlled, double blind, randomised, "N of 1" crossover study of the therapeutic profile of three cannabis based medicine extracts in patients with chronic refractory pain and/or defect of neurological function due to a range of CNS pathologies. Patients with chronic pain and/or defects of neurological function due to MS, spinal cord injury, peripheral nerve or central nervous system damage for which other therapy had been unsuitable were eligible to enrol into the study.

Each patient had a baseline period of two weeks followed by an open dose escalation/familiarisation period during which Sativex was administered for two weeks. Patients self titrated to symptom relief or maximum tolerated dose. This was followed by

the treatment phase of the study in which each of which 4 study medications were administered in a randomised and double blind fashion for two weeks. The four medications were given in a random order. The four study medications were GW-1000 (Sativex 25mg/ml THC + 25mg/ml CBD), GW-2000 (25mg/ml THC), GW-3000 (25mglml CBD) and placebo. There was no washout between the treatment periods.
In the protocol it states that this study intended to enrol a maximum of 30 patients with MS, 30 patients with spinal cord injury and 30 patients with peripheral nerve injury. Study procedures were to be reviewed after the first 6 patients had completed the study and when 30 patients had done so.

A number of statistical analyses have been presented in the study report. The Least Squares Means from these analyses are summarised in the table below.

Symptom	*GW-3000*	*GW-2000*	*Sativex*	*Placebo*	*p-value for treatment contrast*
Pain	*55.8*	*54.6*	*50.1*	*44.6*	*0.019*
Spasm	*54.4*	*58.5*	*55.8*	*47.4*	*0.052*
Spasticity	*46.3*	*57.0*	*45.1*	*42.9*	*0.096*
Urinary	*59.9*	*57.2*	*55.5*	*54.9*	*0.84*
Co-ordination	*37.9*	*43.0*	*40.4*	*40.8*	*0.81*
Other	*51.6*	*50.2*	*46.7*	*46.7*	*0.79*
Overall	*51.8*	*52.9*	*49.5*	*46.0*	*0.091*

Comment: No allowance for multiple significance testing has been made. Given the 7 comparisons made here none of the symptom scores would receive statistical significance if a Bonferonni correction were applied. Again the statistical analysis of this study was not pre-specified in the protocol. Even so GW-2000 and GW-3000 appears to have a beneficial effect on pain and GW-2000 a beneficial effect on spasm.

Study GWN19904:
This study did not provide evidence to support the efficacy of Sativex in the treatment of spasticity. As a proof of concept study it suggested that Sativex may have some activity in improving symptom scores in patients suffering from neuropathic pain who cannot tolerate other therapies.

Assessors' conclusion on phase II trials
As discussed the use of N of 1 studies in phase II of drug development is controversial. Of particular concern is the lack of a prespecified total sample size. Hence it is possible that the results of the studies have been analysed after each patient completes the study. No adjustment for the multiplicity has been made in analyses of study endpoints. Some of the protocols of the N of 1 studies specifically stated that no analyses would be performed. Study reports have included analyses that of course were not prespecified. Such post hoc analyses do not provide robust evidence of efficacy. Another concern is the N of 1 studies had an open label run in period. Hence patients had used Sativex before entering the double blind treatment phase. It is possible that the run-in period could have improved the efficacy of Sativex during the double blind phase. Therefore the results in the double blind phase may not be a true reflect of the short-term efficacy of Sativex.

However, even with all of these concerns the N of 1 studies can at least be used as "demonstration (if not proof) of concept" for Sativex. No conventional dose finding studies have been performed. Also as these trials were short-term self-titrating trials it is not clear whether efficacy is prolonged and also how the efficacy compares with fixed dose or forced titration.

Phase III short-term efficacy studies

Overview

Four short-term Phase III placebo controlled studies 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).

The first study, GWMS0001, studied a range of MS symptoms and only 39 of 160 patients identified spasticity as their most troublesome symptom. As such it is considered to be an exploratory study and not pivotal for the specific claimed indication for spasticity. Studies GWMS0106 and GWCL0403 were presented as pivotal for the earlier application. They were similar in design and were designed specifically to study the effect of Sativex on spasticity in MS patients. All patients reported spasticity as their primary symptom.

Study GWSP0604 differed as it was designed to test the efficacy of Sativex in a specific new population, reflecting the amended proposed indicated patient population, which would exclude patients who failed to respond in an initial 4 week therapeutic trial.

The patient populations studied in studies GWMS0106, GWCL0403 and GWSP0604 were similar as shown below. All subjects had tried anti-spasticity medication and failed to gain an adequate response. They were kept on a stable regimen of existing anti-spasticity medication, most commonly including baclofen. Patients generally had somewhat advanced disease with moderate to severe spasticity at baseline

	GWMS0001	**GWMS0106**	**GWCL0403**	**GWSP0604**
Mean age (yrs)	51	49	48	49
M/F (%)	38/62	40/60	39/61	40/60
Weight (kg)	73	74	72	72
Baseline severity	6.9*	5.5	6.6	7.0
Duration of MS (yrs)	16.3	12.6	15.2	12.6

Phase 3 studies investigating the efficacy and safety of Sativex in the treatment of spasticity in patients with Multiple Sclerosis

Study Number	Description	Primary endpoint	Treatment Duration
GWMS0001 n = 160 Primary spasticity group n = 39 All patients with spasticity n = 140	A double blind, randomised, parallel group, placebo-controlled trial of a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) 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: 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 Cannabis Based Medicine Extract (CBME) 1:1 THC:CBD compared with 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
GWSP0604 n=572 (Phase A) n=241 (Phase B)	A two-phase Phase 3 study of the safety and efficacy of Sativex®, in the symptomatic relief of spasticity in subjects with spasticity due to multiple sclerosis: Phase A – single blind response assessment; Phase B - double blind, randomised, placebo controlled, parallel group study.	Mean daily severity of spasticity assessed with a 0-10 Numeric Rating Scale	4 weeks (Phase A) 12 weeks (Phase B)

Primary efficacy measure for the Phase III studies

All of the three short-term and one long-term Phase III studies that are considered pivotal for this application used a 0 to 10 point Numeric Rating Scale (NRS) as the primary efficacy measure. The lack of adequate validation of the NRS as a reliable measure specifically of spasticity in the proposed patient population was an outstanding major issue at the conclusion of the previous decentralized procedure:

> *"The validity of the NRS as a measure specifically of spasticity appears unclear. The proposed indication is specifically for spasticity. The applicant should discuss 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."*

Historically the most widely used measure of spasticity has been the Ashworth Scale, which was recorded as a secondary measure in the pivotal trials for the 2006 application. The clinical expert argues that the reliability and validity of the Ashworth Scale and the modified Ashworth Scale are lacking and provides references in support.

Score	Ashworth Scale[12]	Modified Ashworth Scale[13]
0	No increase in tone	No increase in muscle tone
1	Slight increase in tone giving a catch when the limb was moved in flexion or extension	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+		Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)
2	More marked increase in tone but limb easily flexed	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in tone, passive movement difficult	Considerable increase in muscle tone, passive movement difficult
4	Limb rigid in flexion or extension	Affected part(s) rigid in flexion or extension

The Ashworth Scale and its modified variant are of value in the context of this application as they are objective measures specifically of spasticity, or at least of resistance to passive movement. The assessor agrees however with the applicant that they have been shown to be rather blunt tools for measuring spasticity in patients with advanced MS and are insensitive to change. Patients can experience a significant improvement in their spasticity associated symptoms without necessarily moving from one Ashworth category to another. There also appears to be a troublesome degree of inter-rater variability and the correlation of Ashworth scores with associated symptoms and clinically relevant outcome (such as discomfort or function) is not clear. This view seems to prevail widely in the literature.

Another commonly used measure of spasticity, the Tardieu scale, possesses some theoretical advantage over the Ashworth Scale as it takes the velocity of muscle stretch into account when the observer makes an assessment of the resistance to passive stretch. It is otherwise similar to the Ashworth Scale.

It is, therefore, reasonable to attempt to develop an alternative assessment tool for the measurement of efficacy.

The applicant believes the 11-point Numerical Rating Scale (NRS) has the following advantages as a primary efficacy measure for this application:

1. It reflects the patient's daily experience of spasticity
2. By taking the mean of the spasticity severity over an extended period it allows for the day to day fluctuations in severity (which are characteristic of spasticity)
3. It correlates well with other useful assessments of spasticity such as the spasm severity and Patient Global Impression of Change
4. It is easy for patients to use accurately, even in the presence of some cognitive impairment
5. It allows for an assessment of clinical relevance

Items 1, 2 and 5 are agreed by the assessor and are advantageous in comparison with physician assessments at infrequent time points. Item 3 relates to the question of whether the NRS is valid as a measure specifically of the symptoms of spasticity, or whether it might be confounded by other symptoms such as pain or fatigue.

The applicant addresses this critical question in two ways. Firstly, by addressing the validity and reliability of the NRS as a measurement tool of spasticity, and secondly by analyses of

the extent to which patients are able to identify interventions that affect their spasticity as opposed to their pain, fatigue or any other symptom.

The validity of the Numerical Rating Scale (NRS) as a measurement tool for the assessment of spasticity in MS – analysis of data from clinical studies GWMS0106 and GWCL0403

The applicant provided analyses of data from clinical studies GWMS0106 and GWCL0403 assessing the NRS as a measure of spasticity, based on published criteria for a valid measurement tool. This was supported by a published paper (Farrar *et al*.) which was based on some of the same data. In addition the applicant provided a published longitudinal validation study (Anwar and Barnes, 2009) addressing whether the NRS is measuring the same phenomenon as is being assessed by the observer-based measurement tools of the Ashworth Scale and the Tardieu Scale.

The validation analyses of studies GWMS0106 and GWCL0403 for the the validity, reliability of the 0-10 NRS as an assessment tool in spasticity assessed the NRS against the following criteria proposed by Bland and Altman (2002) for validation of a new instrument:

- Face and Content Validity
- Construct Validity
- Internal Consistency and Reliability
- Responsiveness
- Clinical Usefulness
- Feasible to use in the Clinical Setting

Face and Content Validity
A targeted question was asked in the daily diaries completed by the patients referring specifically to the symptom of spasticity (defined to the patients as muscle-stiffness), its severity ("level") and the patient's experience of that severity over the previous 24 hours.

Assessor s comment
The question asked of patients was: "On a scale of 0-10 please indicate your level of spasticity over the last 24 hours" (where 0= No spasticity and 10 = Worst ever spasticity). Patients were told that spasticity was defined as "muscle stiffness". The face and content validity are satisfactory.

Construct Validity
Construct validity was investigated by assessing the degree of association between the primary outcome measure (spasticity NRS), and other measures of spasticity-related outcome measures such as the Ashworth scores, spasm frequency scores and SGIC. The stronger the association between the variables, the greater the construct validity.

In Study GWMS0106, there was a significant correlation between the spasticity NRS and change in the spasm frequency scale ($r = 0.63$, $p < 0.001$). There was also a significant correlation between % change in spasticity NRS and the SGIC ($r = 0.515$, $p < 0.0001$) and the association with the Ashworth Scale approached significance ($p = 0.06$). In Study GWCL0403, there was also a significant correlation between spasticity NRS and the CGIC ($r = 0.515$, $p < 0.0001$).

Assessor's comment

The key issue is whether the NRS is truly a measure of spasticity as opposed to other symptoms that patients might complain of, and general well being. Of most interest in the construct validity analyses are the comparisons between the NRS and the objective measures reflecting spasticity. These were the Ashworth Scale and the spasm frequency scale (spasms and spasticity are closely related in this context). The correlation with the Ashworth scale was weak. To some extent this may reflect the unreliability of the Ashworth scale (see below). On the other hand the NRS correlated well with the spasm frequency scale (see graphical illustration above).

These data provide only modest evidence that the NRS is a reliable measure of spasticity. However, in response to this, the Applicant has re-presented data from the NRS validation exercise carried out on the data from studies GWMS0106 and GWCL0403, which did include an assessment of the correlation between change in the NRS and change in the Ashworth Scale score. Correlation was generally modest (but highly statistically significant). The applicant argues that the most likely explanation that there is not a stronger correlation between the NRS and the Ashworth scale lies in the recognised lack of sensitivity of the latter scale- it is simply not very good at measuring change.

The assessor agrees that the key problem with showing the sensitivity of the NRS scale to detect change against a physical measure of spasticity (Ashworth scale) is that the Ashworth scale itself lacks of sensitivity to detect change. Even a very highly sensitive test will not show good correlation with a reference method if the latter is itself poor at detecting change.

The NRS is a symptomatic scale and its sensitivity to detect change in severity of symptoms of spasticity has been clearly correlated with and validated against other well established symptomatic measures.

The assessor considers that company has adequately demonstrated the validity of the NRS as a measure of symptoms related to spasticity for the purpose of supporting an indication for symptomatic treatment in this patient population.

Internal Consistency and Reliability

Test/re-test reliability may be evaluated by testing the performance measure under investigation over time. The test/re-test reliability of the NRS Spasticity Scores and Ashworth scores over the baseline period in Study GWMS0106 is presented below. Mean values at the end of the baseline period are plotted against mean values at the beginning of the baseline period. There was no clinical intervention over this period and patients were supposed to have stable symptoms and concomitant treatment.

Figure 1 - The Test/Re-Test Reliability of the NRS Spasticity Scores (Study GWMS0106) – Mean of 4 Baseline NRS Scores Repeatability

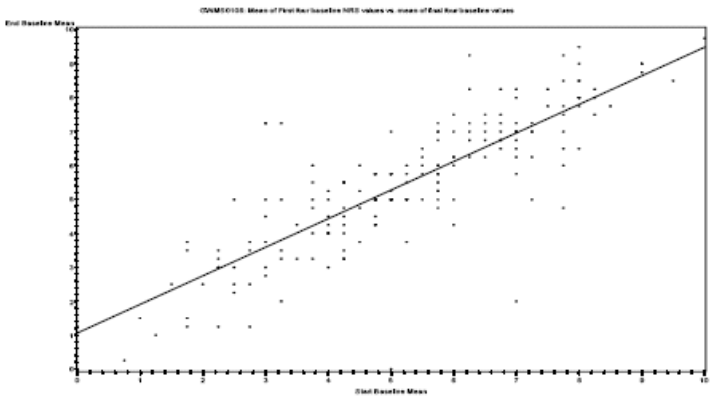


Figure 16 - The Test/Re-Test Reliability of the Ashworth Spasticity Scores (Study GWMS0106)

There was a highly statistically significant association (correlation coefficient: 0.828, $p<0.0001$) between the spasticity NRS scores produced at Visit 1 (Study Screening) and those recorded at Visit 2 (Baseline). The correlation coefficient was >0.8, reflecting a high degree of association of the scores between visits.

The equivalent analysis for the Ashworth Scale (all patients in these analyses had a mean Ashworth score of at least 2 on the second visit) shows substantially less correlation between the scores recorded at two baseline visits (correlation coefficient: 0.58, $p<0.0001$) reflecting lower test/re-test reliability.

Assessor's comment

The test/re-test reliability of the NRS was very good, and clearly substantially superior to that of the Ashworth Scale. However this does not contribute to the argument of whether it is a valid measure of spasticity.

Responsiveness to Change
Responsiveness/sensitivity to change (which may be defined as "ability of the instrument to detect changes in the clinical status") has been demonstrated in the sense that it was consistent during baseline but was subsequently able to show a clear difference between active treatment and placebo. However the sensitivity to change specifically in spasticity as measured by an objective measure has not been demonstrated.

Assessor's conclusion
The face and content validity, internal consistency and reliability and responsiveness to change of the spasticity NRS have been well demonstrated. The test/re-test reliability of the NRS was very good, and clearly substantially superior to that of the Ashworth Scale. The sensitivity to change specifically in spasticity as measured by an objective measure has not been demonstrated. There is only weak evidence from these analyses that the NRS is a reliable measure of spasticity.

Clinical correlation with clinician scored measures of spasticity (Anwar and Barnes, 2009)
The applicant has provided a report of a study entitled "Spasticity Validation: A pilot study of a comparison between a patient scored numeric rating scale and clinician scored measures of spasticity in multiple sclerosis". The authors are the clinical expert, Professor M P Barnes, and an associate.

This study was conducted following the conclusion of the previous unsuccessful decentralised procedure and was independent of the clinical studies. It was completely independent of the pivotal clinical trials supporting this application and its objective was to investigate the relationship between the patient recorded spasticity NRS and observer assessments of spasticity severity.

Patients with stable spasticity due to MS and stable anti-spasticity medication were asked to make a diary NRS assessment of their spasticity over 7 days prior to a clinic assessment of their spasticity. Assessments were made at two consecutive clinic visits, 6-8 weeks apart (visits 2 and 3). At each clinic visit the following physician-based assessments were made; Modified Ashworth Score, Tardieu Scale score, Motricity Index and a Timed 10m Walk. The first two are specific measures of spasticity while the others are measures of strength and function respectively.

Results
The results of most interest are the construct validity analyses comparing the spasticity NRS against the five physician-based assessments of motor function using Pearson's Correlation Coefficient, as presented in the following table.

Table 11: Summary of correlation coefficients between mean NRS diary scores and other assessments

Assessment Performed		n	Correlation coefficient	p-value
Modified Ashworth Scale	*Visit 2*	35	0.459	0.0056
	Visit 3	32	0.446	0.0106
	Change	32	0.230	0.2060
Tardieu Scale	*Visit 2*	34	0.429	0.0113
	Visit 3	32	0.407	0.0209
	Change	31	0.051	0.7856
Motricity Index	*Visit 2*	35	-0.566	0.0004
	Visit 3	31	-0.341	0.0602
	Change	31	-0.090	0.6297
Timed 10 metre walk	*Visit 2*	14	0.267	0.3569
	Visit 3	14	0.326	0.2559
	Change	14	0.223	0.4431

The level of correlation between the spasticity NRS and the specific measures of spasticity (Modified Ashworth Score and Tardieu Scale score) are of pivotal interest. These showed quite good correlation with very similar results at the two visits.

The correlation with these specific measures of spasticity was greater than with the timed walk but less than with the Motricity Index. The authors provide the following comments:

As would be expected, the correlation of the 0-10 spasticity NRS with assessments of functional improvement (10m walk time) were not as robust, as the NRS measures the patient's daily experience of their spasticity as opposed to functional improvement in ambulatory ability.

Although the Motricity Index does not measure spasticity per se, it is a validated measurement tool for the assessment of voluntary motor power. The fact that it negatively correlates with the spasticity NRS, indicates that as patients spasticity improves, their motor control and muscle power also seems to improve. This is important in that it may reflect patients' ability to help themselves if their spasticity is relieved in response to anti-spasticity medication or other interventions.

The authors concluded that when a subject assesses their spasticity using a NRS, they are indeed assessing spasticity and not, for example, general well-being.

Assessor's comment

The internal consistency of the spasticity NRS was again well-demonstrated. The study shows a moderate to good correlation of the NRS with objective physician-based specific measures of spasticity. The fact that the correlation is not stronger might reflect the high degree of variability of the Modified Ashworth and Tardieu Scales as much as any issues with the specificity of the NRS. There is reasonable but not compelling evidence from these analyses that the NRS is a reliable measure of spasticity.

Are subjects with multiple sclerosis able to distinguish spasticity from other symptoms?
The applicant provides the following arguments in response to this question.

In each of the clinical studies subjects have been asked to assess the severity of various symptoms of MS. It has been questioned whether subjects with MS are able to distinguish their spasticity from other symptoms, in particular those that may reflect a general sense of lack of well-being.

In the absence of a gold standard measurement, or accepted biomarker for each symptom, this is a question that can not have a definitive answer. There are similarities here with the assessment of pain. In general, we accept that in a patient who claims their migraine headache has improved, that it has actually improved. However, several observations from the clinical studies provide evidence that subjects with spasticity are indeed readily able to distinguish one symptom from another. The simple observation is that there was a different response seen for different symptoms.

- The subjects included in these studies had all suffered from spasticity for a considerable period of time and were all responding inadequately to currently available medication. Therefore these subjects were likely to be well-acquainted with spasticity symptoms and able to assess/record them accurately.
- A large population based survey carried out among MS patients in the US shows a very high degree of correlation between patients' self-reported spasticity severity and a basket of independent assessments of its severity (Rizzo et al., 2004).
- The meaning of "spasticity" is clarified as "muscle stiffness" in the subject information leaflets for each of the pivotal studies.
- Similarly, spasticity is equated to muscle stiffness at the protocol level in each of the pivotal studies.
- Symptoms that might potentially be confused with spasticity were also assessed during the pivotal studies. For example, pain, fatigue, sleep quality and severity of tremor were assessed at baseline and at study visits, also using a NRS scale. Each of these symptoms might be expected to change in parallel with spasticity if the subjects were simply expressing an improved sense of well-being. They did not – spasticity improved, yet fatigue was worse on drug than on placebo. This confirms not only that subjects are able to distinguish one symptom from another, but also that the Global Impression of Change response refers to spasticity (which improved) rather than pain, tremor or fatigue. This phenomenon has been seen in each of the Phase 3 studies where multiple symptoms have been assessed the Phase 3 studies described in this summary.

In study GWMS0001, subjects were also asked to assess the impact of treatment (Sativex vs. placebo) on a basket of symptoms, including fatigue, pain and sleep. Again, there was a clear separation of response according to the symptom being assessed, with pain and fatigue being unaffected by Sativex. This demonstrates again that subjects are able to distinguish one symptom from another.

- It is probable that a marked general improvement in well-being would have been communicated by the subject to the doctor and recorded as an adverse event most likely within the general or psychiatric body systems and would have been coded to a preferred term such as euphoria. This was not the case; in particular, euphoria was reported equally frequently on placebo as it was on Sativex.
- While it is not possible to confirm that patients never confuse one symptom with another, there is no evidence that they do.

- The personal communication from Professor Lynne Turner-Stokes (2005), Dunhill Professor of Rehabilitation at King's College, London, Member of the steering group that participated in the implementation of the NICE guidance for Multiple Sclerosis (MS), and Deputy Chair for the National Service Framework (NSF) for Long Term Conditions indicates the expert clinical opinion that the NRS is an entirely appropriate way to assess the patient's experience of their spasticity.

Assessor's comment
The description of spasticity as "muscle stiffness" in the subject information leaflets for each of the pivotal studies seems likely to be well understood. Not all of the applicant's arguments are fully accepted (e.g. "that a marked general improvement in well-being would have been communicated by the subject to the doctor and recorded as an adverse event") but overall it seems that patients are able to report a spasticity measure with a sufficient degree of specificity. It is reassuring that other symptoms that were assessed using a NRS and would not be expected to respond favourably to Sativex (including fatigue, sleep quality and tremor) did indeed in general not show a response.

Assessor's overall conclusions on the validity of the NRS
It is agreed that the NRS has a number of clear advantages over physician based assessments of spasticity such as the Ashworth or Tardieu scales. It measures the severity of spasticity over an extended period of time to take account of day to day fluctuations and fulfils the requirement to demonstrate clinically relevant benefit in terms of patients' daily experience of spasticity. However any subjective patient reported assessment measure has its own potential problems, especially if as in this case a degree of patient unblinding to treatment allocation seems a possibility.

A variety of published data indicate that the reliability and validity of the Ashworth Scale (including the modified version) and Tardieu scales are lacking. Data provided by the applicant appear to confirm this as the test/re-test reliability of the NRS was very good and substantially superior to that of the Ashworth Scale. However the Ashworth Scale has long been considered to be standard tool for measuring spasticity and superiority to placebo on this scale has been demonstrated for certain well established anti-spasticity medicines.

Any new scale needs to be shown to be a valid measure of outcome. The applicant argues that patient reported assessment measures such as the NRS and VAS are well established and validated in recording symptoms such as chronic pain. However the difference in this case is that the only observer that can reliably measure pain is the individual experiencing it. It is possible for a trained external observer to make an objective assessment of the physiological phenomenon of spasticity which is not possible in the measurement of pain. There are far more potentially confounding factors in the spasticity / MS clinical situation than in pain models.

A key issue for this application is the validity of the NRS as a measure specifically of spasticity as this is the specific proposed indication. The effectiveness of Sativex on this specific aspect must be clearly shown. It is necessary to establish 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 and its clinical manifestations, as opposed to other symptoms that a patient might complain of and their general well being.

The NRS scale in spasticity correlated well with the Patient's Global Impression of Change (PGIC). However this provides no information on the validity of the NRS as a measure specifically of spasticity. The secondary analyses of the correlation between the patient reported NRS score and more objective measures of spasticity in the original Phase III studies provided only modest evidence that the NRS is a reliable measure of spasticity. Much better evidence is provided by the new study from the clinical expert, Professor M P Barnes, and an associate (Anwar & Barnes, NeuroRehabilitation 2009). This study showed quite a good degree of correlation between the NRS and Ashworth scores in patients with stable symptoms but did not provide data on the sensitivity of the NRS to change in spasticity as measured by the Ashworth scale.

In addressing the issue of the sensitivity of the NRS to detect a change in spasticity in response to therapeutic intervention it would have been helpful to have data on the ability of the NRS and Ashworth scale to detect a change in spasticity severity induced by a known anti-spasticity agent, as in a trial of intrathecal baclofen.

It has been reasonably well-demonstrated that patients with multiple sclerosis are able to distinguish spasticity from their other symptoms when providing spasticity NRS scores. It seems inevitable that there is likely to be some influence of other symptoms in the scores reported by patients for the spasticity NRS. However the data provided in response to this issue since the previous application may be considered to provide sufficient reassurance that the patient assessments of their spasticity on the NRS are a sufficiently specific measure of their symptoms related to their spasticity as opposed, for example, to general well-being. Correlation between the NRS and Ashworth scores has been shown in patients with stable symptoms but not on the sensitivity of the NRS to detect a change in spasticity in response to therapeutic intervention. The assessor agrees that the key problem with showing the sensitivity of the NRS scale to detect change against a physical measure of spasticity (Ashworth scale) is that the Ashworth scale itself lacks of sensitivity to detect change. Even a very highly sensitive test will not show good correlation with a reference method if the latter is itself poor at detecting change. Otherwise the assessor considers that the company has provided reasonable demonstration of the validity of the NRS as a measure of symptoms related to spasticity for the purpose of supporting an indication for the symptomatic treatment of spasticity in this patient population. Taken as a whole these data are considered sufficient to demonstrate conclusively an objective effect of cannabinoids in general and Sativex in particular on the physiological phenomenon of spasticity.

<u>Secondary efficacy measures for Phase III studies</u>
Although the primary efficacy measures must be a specific measure of the symptoms of spasticity as this is the specific requested indication, it is important also to show benefit in terms of a functional improvement. This is of importance in considering the clinical relevance of the observed effect. At least some such measures should clearly relate specifically to spasticity rather than more general functioning or wellbeing.

In the two pivotal short term efficacy studies presented with the previous application the secondary efficacy measures were as follows:
GWMS0106:

- Ashworth Scale.
- Daily five point ordinal scale score of spasm frequency
- Motricity Index.
- Patient's perception of change in their condition using the Patients Global Impression of Change (PGIC).

GWCL0403

- Modified Ashworth Scale.
- MS symptom/intoxication NRSs
- Timed 10 metre Walk (if ambulatory)
- Barthel Activities of Daily Living (Barthel ADL)
- Expanded Disability Status Scale (EDSS)
- EQ-5D (a standardised measure of health outcome)
- MS Quality of Life-54 (UK only)
- Carer global impression of change (CGIC)
- Investigator blinding assessment

The secondary efficacy measures in the third pivotal short term efficacy study GWSP 0604 included a number of additional objective measures of motor function including spasticity as follows:

GWSP 0604

- Modified Ashworth Scale.
- Spasm frequency
- Motricity Index
- Timed 10 metre Walk (if ambulatory)
- Barthel Activities of Daily Living (Barthel ADL)
- Expanded Disability Status Scale (EDSS)
- EQ-5D (a standardised measure of health outcome)
- SF 36 (a multi-purpose, short-form health survey)
- Physician global impression of change (PGIC)
- Carer global impression of change (CGIC)
- Subject global impression of change (SGIC)

Study GWMS0001

This was a Phase III, double-blind, randomised, parallel-group, placebo-controlled study. The trial compared a development formulation containing delta-9- tetrahydrocannabinol (THC-25mglml) and cannabidiol (CBD-25mg/ml) with placebo, in patients with multiple sclerosis and symptoms of pain, spasticity, muscle spasm, bladder problems or tremor

Study medication was administered as 100µl metered sprays to the oromucosal surface. The maximum permitted dose was eight actuations (20mg THC. 20mg CBD) within three hours and 48 actuations (120mg THC, 120mg CBD) in 24 hours.

Following a 1- to 2-week baseline period patients self titrated study medication to symptom resolution or maximum tolerated dose over a six week double blind period. Although it was planned to enrol 130 patients, 160 patients (80 per group) were randomised and analysed.

Patients completed 100mm VAS severity scores for their most severe MS symptom (primary impairment) in one of the five qualifying categories; pain (non-rnusculoskeletal), muscle spasm, spasticity, bladder problems or tremor. The primary efficacy endpoint was the change from baseline in the individually identified primary symptom VAS score at the end of the parallel group period. Analyses of all five individual impairments were secondary endpoints. Of the 160 patients 39 (20 Sativex, 19 placebo) reported spasticity as their primary impairment.

Primary analysis:
There was no statistically significant difference between treatments for the primary endpoint. The mean change from baseline at 6 weeks in VAS rating for the composite score of five target symptoms was -25.29 in the Sativex group compared to -19.35 in the placebo group. The difference between the means in the two groups was -5.93 (p = 0.l24, 95% CI -13.52, 1.65).

Summary of the statistical analysis of the individual impairment VAS score, ITT population (taken from table 9.1.2..1, page 135, vol 1/10, GWMS0001)

Change from baseline in	Adjusted mean GW-1000-02	Adjusted mean Placebo	95% CI		p-value
			Lower	Upper	
Pain	-15.25	-13.36	-12.73	8.96	0.731
Spasm	-24.25	- 20.95	-11.82	5.21	0.443
Spasticity	-23.27	- 16.17	-14.56	0.37	**0.062**
Tremor	-21.98	- 15.12	-20.31	6.60	0.311
Bladder problem	-27.98	- 21.72	-14.90	2.38	0.154

Summary of the statistical analysis of the individual impairment VAS scores identified as Primary, ITT population (taken from table 9.1.2..1, page 136, vol 1/10, GWMS0001)

Change from baseline in	Adjusted mean GW-1000-02	Adjusted mean Placebo	95% CI		p-value
			Lower	Upper	
Pain	-11.44	-20.17	- 10.39	27.84	0.360
Spasm	- 26.50	- 21.20	- 19.81	9.22	0.464
Spasticity	- 31.20	- 8.40	- 35.52	-10.07	**0.001**
Tremor	- 21.42	- 25.17	- 30.17	37.68	0.810
Bladder problem	- 34.32	- 26.34	- 27.44	11.48	0.408

Assessor's comment
This was a failed study. The Statistical Analysis Plan, in common with standard clinical trial interpretation methodology, clearly states that secondary analyses are only supportive to the primary analysis. The failure of the primary analysis to produce a significant result cannot be rescued by results on secondary endpoints.

Nevertheless efficacy for the spasticity impairment domain is of relevance for this application. Although the analysis for spasticity as a whole did not produce a p-value less than 0.05, the analysis of the individual impairment VAS scores identified as primary did reveal a p-value of 0.001 for spasticity (39 patients) although this value was not adjusted for multiplicity (there were 10 comparisons in the key secondary analyses). The estimated treatment difference was large and would be clearly clinically significant if confirmed (-22.79mm, 95% Cl -35.52, -10.07).

These encouraging results for spasticity in the limited number of patients in this study whose primary impairment was spasticity are viewed as hypothesis generating. Pivotal evidence of efficacy in the proposed indication depends on the results of subsequent studies which are specifically designed to address this endpoint.

Study GWMS0106:

This was a double blind, randomised placebo controlled, parallel group study to assess the efficacy and safety of Sativex for the treatment of spasticity in patients with MS over a 6-week treatment period. Patients were randomised into the trial in a 2:1 ratio of active to placebo. Patients had stable MS (for at least three months) with spasticity unrelieved - or incompletely relieved - by current therapy. Subjects were required to have significant spasticity in at least two muscle groups, defined as a score of two or more on the Ashworth Scale. The patients were not to have used cannabinoids for at least seven days before visit 1 and were required to abstain from any use of cannabis during the study. Patients continued on stable doses of medication for relief of spasticity during the study.

	Visit	**Day relative to treatment**
Visit 1	Screening	
Visit 2	Baseline	Day 1
Visit 3	Week 2	Day 15
Visit 4	Week 6 / End of study	Day 43

Patients continued on stable doses of medication for relief of spasticity during the study. Hence study treatment represented add-on therapy in patients with MS who did not respond adequately to other anti-spasticity medication, which reflects the proposed indication.

The maximum permitted dose was eight 100µl actuations in any three hour period and 48 actuations (THC 130mg, CBD 120 mg) in 24 hours. Duration of treatment was six weeks. 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 primary efficacy measure was the 1- - to 10 NRS (Numerical Rating Scale). The Ashworth Scale was originally specified in the protocol as the primary endpoint, but was replaced by the NRS while the study was ongoing, ., in response to the results from the published CAMS study which had failed to show improvement in Ashworth Score, and the Cochrane Review, published around the same time, which highlighted the shortcomings of the Ashworth Scale. This is satisfactory as it was done but before the blind was broken.

The primary endpoint was the change from baseline to the end of treatment in the NRS spasticity score. The end of treatment score was the mean score recorded over the last 7 days in the study (the last day being defined as the last day with diary card spasticity data that occurred on or before the last day on study medication). The baseline score was the average recorded over the last 7 days of the baseline period.

The change from baseline in NRS spasticity scores was compared between treatments using analysis of covariance, with terms for treatment, centre and baseline spasticity score.

Patient accountability:
A total of 226 patients were screened, of which 189 were randomised and received treatment. In all 174 patients completed the study and only 15 withdrew. There was a higher proportion of withdrawals on the Sativex arm, mainly because of adverse events.

	Sativex	**Placebo**
Randomised	124	65
Completed study	112 (90%)	62 (95%)
Withdrawn (before or at Visit 3)	7 (6%)	1 (2%)
Withdrawn (after Visit 3)	5 (4%)	2 (3%)
Primary reason for withdrawal:		
Adverse event	6 (5%)	1 (2%)
Non-compliance	1 (1%)	0
Withdrew consent	4 (3%)	0
Administrative decision	0	1 (2%)
Significant protocol deviation	0	1 (2%)
Lost to follow-up	1 (1%)	0
Duration of exposure (days)		
Mean (sd)	40.0 (11.5)	41.1 (7.3)
Median	42.0	42.0

Study medication:
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.

Analysis populations:
The ITT population was defined as all randomised subjects who received at least one dose of study medication and had on-treatment efficacy data. All 124 subjects provided on-treatment efficacy data. For the analysis of the primary endpoint there were 3 patients (2 on Sativex and 1 on placebo) who did not record baseline data for the primary efficacy endpoint. As such they were not included in the primary analysis of change from baseline, and this is acceptable. However two further Sativex patients were omitted from the primary analysis, presumably for not having any post-treatment data for this particular endpoint. These patients should have been included as treatment failures.

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 (from the company's perspective). Analyses are presented with and without this outlier. This patient had a baseline NRS spasticity score of 7.9 and an end of treatment score of 0.2, giving a change from baseline of -7.7, the largest change from baseline in the trial, although the baseline score was not the highest seen. The assessor considers that the analyses including the outlier must be considered to be main analysis by which efficacy should be judged. However the presentation of analyses excluding the outlier is not entirely without merit as it is clear that the patient failed to meet the inclusion/exclusion criteria and there is reasonable clinical justification that the apparent response to placebo was due instead to their earlier treatment with interferon.

Results:

Summary of NRS spasticity by time - ITT population:

Timepoint	Sativex			Placebo		
	n	Mean (sd)	Median	n	Mean (sd)	Median
Baseline	122	5.49 (1.91)	5.43	64	5.39 (1.91)	5.57
Week 1	120	4.57 (1.97)	4.64	65	4.77 (2.02)	4.43
Week 2	118	4.50 (2.11)	4.54	65	4.65 (2.15)	4.71
Week 3	116	4.24 (2.18)	4.14	63	4.68 (2.16)	5.00
Week 4	113	4.20 (2.19)	4.00	61	4.78 (2.24)	5.00
Week 5	113	4.19 (2.23)	4.14	61	4.73 (2.18)	4.57
Week 6	110	4.34 (2.26)	4.14	59	4.65 (2.20)	4.86
Last 7 days	122	4.31 (2.25)	4.14	65	4.75 (2.26)	4.86
Change from baseline						
Week 1	119	-0.93 (1.35)	-0.64	64	-0.60 (1.04)	-0.30
Week 2	116	-0.97 (1.74)	-0.86	64	-0.73 (1.31)	-0.43
Week 3	114	-1.23 (1.69)	-1.14	62	-0.71 (1.48)	-0.43
Week 4	111	-1.25 (1.77)	-1.14	60	-0.63 (1.64)	-0.36
Week 5	111	-1.26 (1.75)	-1.00	60	-0.65 (1.46)	-0.36
Week 6	108	-1.13 (1.77)	-0.96	58	-0.73 (1.57)	-0.57
Last 7 days	120	-1.18 (1.83)	-1.00	64	-0.63 (1.62)	-0.23

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

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 the 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).

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 was also questioned.

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

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:
The adjusted mean change in Ashworth Scale score from baseline to Visit 4 was 0.11 points in favour of the GW-1000-02 treatment. This was not statistically significant (p=0.218, 95% CI: -0.29, 0.07), and would be of questionable clinical relevance.
The treatment difference between the groups for Spasm Frequency Score, Motricity Index and Patient's global impression of change were also not statistically or clinically significant.

Assessors' Conclusions
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. 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).

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 which could be of clinical relevance. 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 may 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.

There were no significant findings in any of the secondary endpoints, weakening the internal validity of the trial. The positive evidence seems almost completely restricted to the primary endpoint, with at best small trends of questionable clinical relevance seen in the supportive endpoints.

Therefore, it is concluded that this trial provides weak evidence of efficacy.

Study GWCL0403
This was a randomised, double-blind, placebo-controlled study of Sativex in the treatment of patients with symptoms of spasticity due to multiple sclerosis. Subjects had any disease sub-type of MS, of at least six months duration, and at least a three-month history of spasticity due to MS, which was not wholly relieved with current therapy. Patients were maintained on anti-spasticity medication for the duration of the study and hence Sativex was compared with placebo as add-on therapy to other anti-spasticity agents. The randomised treatment period was 14 weeks.

The primary endpoint was the 11 point numeric rating scale (NRS) with scores ranging from 0 (no spasticity) to 10 (worst ever spasticity). To be included in the trial, the sum of the last 6 assessments during the 7 day baseline period had to be at least 24 (an average of 4). This inclusion criterion is satisfactory as it represents a population with a degree of spasticity that is of at least moderate severity and likely to be disabling despite conventional treatment and for whom there is therefore an unmet clinical need.

Patients self-titrated to their optimal dose based upon efficacy and tolerability up to a maximum of 24 sprays per 24 hours, with up to 8 actuations allowed in a 3 hour period.

A total of 388 subjects were screened, of which 337 were randomised and received treatment. TThe majority of patients completed the study with around 10% withdrawing in both groups.

Study medication:
The mean (sd) number of doses per day was 8.5 (4.76) for Sativex compared to 15.4 (6.15) for placebo. The median was 7.4 for Sativex and 16.8 for placebo. This result is difficult to interpret. It could represent lack of efficacy for placebo, with patients feeling the need to take extra medication. However it could equally well suggest a tolerability issue for Sativex with patients being unwilling to take additional doses.

Analysis populations
The full analysis set was defined as all randomised subjects who received at least one dose of study medication and have on-treatment efficacy data. There were two subjects who did not provide on-treatment efficacy data and so were excluded from the full analysis set.

This does not match the definition in the protocol, where the intention-to-treat population was defined as all subjects who are randomised and receive study medication. This is the definition advocated in ICH E9 and would have been preferred. However with only two patients falling into this category, it is not an important problem.

Primary efficacy assessment:
The primary endpoint was the change from baseline to the end of the evaluable period in the 11 point NRS scale. The end of evaluable period score was the average daily score recorded over the last 14 days of the evaluable period (end of treatment). The baseline score was the average recorded over days 2-7 of the 7 day baseline period. (For patients whose evaluable period ended before day 50, the end of treatment value was the mean of the last 7 days of the evaluable period. For patients where the evaluable period ended before day 7 the mean of all available data was used.)

The initial model used for the analysis of the primary endpoint was to be an analysis of covariance (ANCOVA) with baseline spasticity as a covariate and treatment group, centre group, ambulatory status at baseline and previous use of cannabis as main effects. Interactions between treatment group and each of centre group, ambulatory status and previous cannabis use were to be investigated in this initial model. If these interactions were not significant at the 10% level then they were to be dropped from the model. The main effect of previous cannabis use was then to be investigated and if this was not significant at the 5% level then it too was to be dropped from the model. The final model was then to include terms for treatment group, centre group, ambulatory status and baseline spasticity.

This stepwise approach to variable selection, selecting covariates based upon the data observed in the study, is not generally considered an acceptable approach for a phase III clinical study. In such a study it is expected that the model to be used is fully specified in advance. However in this case it does not seem to have been a completely open variable selection procedure as the anticipated final model was fairly clearly stated in the analysis plan, with most of the covariates specified for inclusion regardless of the results of significance tests.

Results:

1. Primary endpoint

Summary of NRS spasticity by time – (LOCF)

Full analysis set, evaluable period

Timepoint	Sativex (n=166)		Placebo (n=169)	
	Mean (sd)	Median	Mean (sd)	Median
Baseline	6.77 (1.33)	6.83	6.48 (1.32)	6.50
Day 1-14	6.14 (1.58)	6.29	5.94 (1.38)	5.86
Day 15-28	5.80 (1.79)	6.07	5.74 (1.62)	5.93
Day 29-42	5.66 (1.94)	5.79	5.65 (1.82)	5.71
Day 43-56	5.62 (1.97)	5.71	5.67 (1.83)	5.86
Day 57-70	5.50 (2.04)	5.46	5.69 (1.87)	5.93
Day 71-84	5.52 (2.04)	5.64	5.58 (1.93)	5.57
Day 85-98	5.55 (2.02)	5.54	5.58 (1.98)	5.69
Last 14 days	5.55 (2.03)	5.54	5.57 (1.98)	5.64
Change from baseline				
Day 1-14	-0.62 (1.11)	-0.38	-0.54 (0.96)	-0.36
Day 15-28	-0.97 (1.41)	-0.67	-0.75 (1.30)	-0.67
Day 29-42	-1.11 (1.61)	-0.68	-0.84 (1.57)	-0.60
Day 43-56	-1.15 (1.69)	-0.76	-0.81 (1.57)	-0.60
Day 57-70	-1.27 (1.77)	-0.79	-0.79 (1.58)	-0.67
Day 71-84	-1.25 (1.80)	-0.90	-0.90 (1.66)	-0.69
Day 85-98	-1.22 (1.76)	-0.88	-0.91 (1.72)	-0.67
Last 14 days	-1.22 (1.76)	-0.85	-0.91 (1.72)	-0.67

It is interesting to note that the average NRS spasticity scores at the end of the treatment period are very similar for the two treatments. The difference in change from baseline comes from differences at baseline rather then differences at the end of treatment.

Analysis of change from baseline – full analysis set

	Sativex	Placebo	Difference	95% CI	p-value
Adjusted mean (evaluable period)	-1.05	-0.82	-0.23	-0.59, 0.14	p=0.2195
Adjusted mean (complete period)	-1.01	-0.84	-0.17	-0.53, 0.19	p=0.3592

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

Sativex did not show statistically significant superiority over placebo on the spasticity NRS score. The results were consistent across the analyses conducted using the evaluable period and the complete period.

2. Responder analysis

The applicant expressed a concern that as patients in the studies were treatment resistant, the average change from baseline may appear small even though the treatment may provide a useful benefit for many patients. This would certainly be the case if there was a dichotomous population with a substantial group of patients who could expect no response, but another group who gain substantial benefit from treatment. This situation does appear clinically plausible. The solution proposed by the applicant was to focus on the per-protocol population, but this is not considered to be appropriate (see below for further details). However an analysis of responder rates may help to address this point.

Percentage of patients with a response at endpoint

	Sativex (n=166)	**Placebo (n=169)**	**Difference (95% CI)**	
30% response (evaluable period)	51 (31%)	42 (25%)	6% (-4, 15)	p=0.2310
30% response (complete period)	47 (28%)	40 (24%)	5% (-5, 14)	p=0.3331
50% response (evaluable period)	21 (13%)	18 (11%)	2% (-5, 9)	p=0.5689
50% response (complete period)	20 (12%)	16 (9%)	3% (-4, 9)	p=0.4464

Response: At least a 30% (50%) reduction from baseline in spasticity MRS

There was no evidence from these data of a large group of patients gaining benefit from treatment. The 30% reduction responder rate was only 4-6% greater on Sativex, while for a 50% reduction the difference was only 2-3%. Even if these differences were real (and the confidence intervals are wide, so they may not be) this would lead to a large number of patients receiving an ineffective treatment in order to benefit only a few.

3. Per-protocol population

Spasticity NRS score – per-protocol population

	Sativex (n=122)	**Placebo (n=143)**
Baseline	6.84 (1.35)	6.49 (1.26)
Endpoint (evaluable period)	5.38 (2.11)	5.58 (1.96)
Change from baseline (evaluable period)	-1.46 (1.84)	-0.91 (1.65)

Analysis of change from baseline – per protocol population

	Sativex	**Placebo**	**Difference (95% CI)**	**p-value**
Adjusted mean (evaluable period)	-1.30	-0.84	-0.46 (-0.88,-0.03)	p=0.0348

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

Responder analysis

	Sativex (n=122)	**Placebo (n=143)**	**Difference (95% CI)**	
30% response (evaluable period)	44 (36%)	35 (24%)	12% (0.5, 23)	p=0.0402
50% response (evaluable period)	20 (16%)	15 (10%)	6% (-2, 14)	p=0.5689

Response: At least a 30% (50%) reduction from baseline in spasticity MRS

The applicant places some emphasis on the per-protocol population; 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.

This seems a plausible explanation for the per-protocol results we are seeing here, as:

- The Sativex group has a high percentage of patients who discontinue treatment prematurely, possibly because of adverse events combined with lack of efficacy.
- Only 3/44 (7%) of Sativex patients excluded from the per-protocol population were responders, compared to 7/26 (27%) on placebo.
- The mean change from baseline for the excluded patients was -0.52 on Sativex compared to -1.04 for placebo.

It is clear that in some scenarios, even if there truly is no difference in efficacy between treatments, analysis of the per-protocol population can produce a difference. Hence it is

considered that for this study, analyses using the per-protocol population are not helpful, and could be misleading.

4. Other efficacy endpoints
At baseline and at all subsequent clinic visits patients were asked to assess their symptoms. The question asked was "On a scale of '0 to 10' please indicate the average level of your *[symptom]* yesterday". The symptoms assessed were spasticity, spasm severity, pain, fatigue, tremor, bladder symptoms and sleep quality.

There was no statistically significant difference seen in any of the symptoms. The majority of symptoms had a small trend in favour of Sativex, but the differences were not close to achieving statistical significance or being of a clinically relevant magnitude.

The results for the secondary efficacy endpoints, including Modified Ashworth score, 10 metre walk time, Barthel index and Carer's global impression were all consistent with the findings of the primary endpoint. There were no significant differences between the treatments. The trends (such as they were) favoured Sativex, but in general the treatment differences were smaller than the differences seen at baseline.

Blinding assessment:
At the end of treatment visit (visit 6) the investigator was asked the following question: "Which treatment do you think the subject was taking during the study?" The results are shown by treatment group in the table below.

	Sativex (n=167)	Placebo (n=170)
Placebo	22 (13%)	84 (49%)
Sativex	106 (63%)	60 (35%)
Do not know	34 (20%)	22 (13%)
Not recorded	5 (3%)	4 (2%)

The investigators only guessed the treatment allocation correctly for 56% of patients. Given that complete guesswork would result in a 50% rate this is not strikingly high.

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. The trends (such as they were) were 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.

Given that the claim is being made for efficacy in spasticity it creates further concern that the effect on spasticity was not the largest effect seen of all the symptoms assessed in the clinic. Hence there was some concern that the ordering of the symptoms in hypothesis generating study GWMS0001 where spasticity showed the largest effect, could have been by chance.

The results from this study taken in isolation would also create concern that even if there was a benefit in a sub-population of responders, a large number of patients would need to be treated to benefit only a few, and that it would not be possible to detect responders quickly

and thus limit exposure for non-responders. The risks to a large number of patients of a prolonged therapeutic trial might not be outweighed by a potential benefit in a small number of patients that do turn out to respond favourably to treatment.

Combined analyses of short term efficacy pivotal for UK/H/24621/001/DC

The pivotal efficacy studies for the previous submission for Sativex were the 6-week study GWMS0106 and the 14-week study GWCL0403. Other than their duration the studies were of similar design, employed the same primary efficacy endpoint and studied similar patient populations. It was considered valid to combine them in a meta-analysis. Study GWMS0001 was not included as it was considered exploratory. The combined analyses of the two pivotal studies formed the basis of the applicant's new pivotal trial design employing a therapeutic trial to identify responders to Sativex who would continue to receive treatment. This section therefore does not consider the new short term pivotal trial, which could not in any case be combined with studies GWMS0106 and GWCL0403 because of its substantially different design.

The overall result for the primary endpoint of the two pivotal studies GWMS0106 and GWCL0403 and a meta-analysis of them showed a modest mean treatment effect of questionable clinical significance:

Change from baseline in NRS spasticity score

Study	Sativex		Placebo		Difference	95% CI	p-value
	n		n				
GWMS0106	120	-1.11	64	-0.59	-0.52	-1.03, -0.004	p=0.048
GWCL0403	166	-1.05	169	-0.82	-0.23		p=0.22
Overall	286	-1.21	233	-0.87	-0.34	-0.64, -0.04	p=0.027

Responder rates in comparison with placebo, which can be a useful way of assessing the clinical relevance of a difference in means observed on a scale, were more encouraging:

Percentage of patients with a 30% improvement from baseline in spasticity

Study	Sativex	Placebo	Difference	Odds ratio	95% CI	p-value
GWMS0106	48/120 (40%)	14/64 (22%)	18%	2.38	1.19, 4.78	
GWCL0403	51/166 (31%)	42/169 (25%)	6%	1.34	0.83, 2.17	
Overall	99/286 (35%)	56/233 (24%)	11%	1.63*	1.10, 2.41*	p=0.015

* From Cochrane-Mantel-Haenszel test adjusting for study

The difference of around 10% was 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 pretty consistent. An alternative analysis of patients achieving certain absolute reductions in NRS score yielded similar results.

The applicant proposed that an important treatment effect in a substantial minority of patients might be being masked to some extent by the data "noise" from a larger number of non-responders in the analyses of mean changes. This seems plausible from a clinical point of view considering the patient population being studied. The assessor agreed that if it can be shown that it is possible reliably to identify non-responders without exposing them to ineffective treatment for a prolonged period, then a therapeutic trial to identify responders could be a reasonable approach, as no patient characteristic has been identified that accurately predicts response to Sativex treatment.

In this situation responder analyses are of value in identifying a clinically relevant treatment effect in a proportion of patients. The additional 11% of patients (over placebo) experiencing a response as suggested in the responder meta-analysis could reasonably be considered to be of clinical relevance. 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.

Excluding non-responders at 4 weeks from the treated patient population analyses will be expected to increase the mean treatment effect in the remaining patients who will continue to receive treatment in the medium to long term. It is reasonable to suppose that the efficacy obtained by responders in the two pivotal trails should be greater than the overall mean treatment difference of 0.34 points, and could be clinically significant. However the available data did not permit a reliable estimate to be made of the magnitude of the clinical effect in these patients.

A key consideration will be the proportion of patients that will fail a therapeutic trial and discontinue treatment. The data indicated that approximately 57% of patients would fail to achieve a 15-20% improvement in spasticity score by week 4, which corresponds to the magnitude of response that the company has concluded represents the minimum clinically relevant improvement (19% response). According to the company's proposals these patients should discontinue treatment but it is not clear whether this would be the case in practice. If in the real world patients would tend to continue treatment regardless, then the above assumptions might be invalid.

Justification of a four-week duration of therapeutic trial

Analyses of the predictive value of response levels during the first 4 weeks of Sativex treatment as an indicator of ultimate response achieved are presented below.

The primary endpoint of study GWMS0106 occurred at 6 weeks (only 2 weeks after the collection of the 4-week data presented in Table UK C2-1 above). There is, therefore, a strong argument for focusing on the 14 weeks follow-up study GWCL0403 in which the interval between the end of the first 4 weeks treatment and the primary endpoint was 10 weeks.

Table UK C2-1: Response to first 4 weeks treatment in patients who ultimately achieve at least a 30% improvement on Sativex at the end of study

Study	Proportion of ultimate 30% responders achieving a 20% response at any time during the first 4 weeks of Sativex treatment (%)	Proportion of ultimate 30% responders achieving a 30% response at any time during the first 4 weeks of Sativex treatment (%)
GWMS0106	100	92
GWCL0403	94	73
Meta-analysis	97	82

Source: Additional Efficacy Tables for GWMS0106 and GWCL0403 (Module 5.3.5.3)

A 19% response was found to be the mean level associated by patients with significant clinical improvement and a 29% response represented "very much improved" (justified in the paper by Farrar et al). The corresponding analysis for ultimate response at the 20% level are presented below.

Table UK C2-2: Ability of a four-week therapeutic trial of Sativex to correctly predict patient outcomes (responder defined as 20% improvement from baseline).

	Therapeutic trial and primary endpoint outcomes	GWMS0106 (n=120)	GWCL0403 (n=166)	Pooled-analysis (n=286)
Four-week therapeutic trial correctly predicts result.	Responder in trial; responder at primary endpoint	60 (50%)	57 (34%)	117 (41%)
	Non-responder in trial; non-responder at primary endpoint	39 (33%)	81 (49%)	120 (42%)
Total		99 (83%)	138 (83%)	237 (83%)
Four-week therapeutic trial incorrectly predicts result	Responder in trial; non-responder at primary endpoint	19 (16%)	15 (9%)	34 (12%)
	Non-responder in trial; responder at primary endpoint	2 (2%)	13 (8%)	15 (5%)
Total		21 (18%)	28 (17%)	49 (17%)

Source: "Additional Efficacy Tables for GWMS0106 and GWCL0403" (Module 5.3.5.3), pages 16-18. Absolute numbers are available in these tables. Percentage data are recalculated specifically for Table UK C2-2.

The table below shows the percentage of patients in study GWCL0403 that achieved a 20% response in the first 4 weeks and whether they achieved a 20% response at endpoint.

	Endpoint		
	Responder	**Non-responder**	
Responder	57 (34%)	15 (9%)	72 (43%)
Non-responder	13 (8%)	81 (49%)	94 (57%)
	70 (42%)	96 (58%)	

The results were very similar for both pivotal studies and for the meta-analysis.

Assessor's comment
The conclusions from the investigation carried out by Farrar et al (2007) that a 19% response represents the minimum clinically relevant improvement, and a response of 29% represents "much improved", seems reasonable. However the data relating to an objective measure of spasticity are lacking. Restriction of the key analyses to study GWCL0403 in which the primary endpoint was at 14 weeks is appropriate as the 6 week duration of GWMS0106 is too short for this purpose.

The sensitivity of a trial period using a 20% threshold at 4-weeks to detect patients ultimately achieving a 30% response was 57/70 (81%). As indicated above the sensitivity for detecting an ultimate 30% response is higher (94%). If the trial criterion was increased to achieving a 30% response at some time during the first 4 weeks, the percentage of 30% responses that were captured was only 73%. Applying this criterion would appear therefore to exclude too many patients from further treatment.

Using the 20% threshold at 4-weeks, if a patient ultimately failed to achieve a 30% response the trial predicted this in 81 out of 96 cases (84%).

These figures are fairly high and suggested that a 4 week therapeutic trial might be a way to allow responders access to treatment without subjecting non-responders to long-term treatment. The 20% threshold for response at 4 weeks appeared to achieve a reasonable balance between sensitivity and specificity.

This exercise in designing a rule to be used for a therapeutic trial generated a possibly useful hypothesis from an unplanned post-hoc analysis that required confirmation in a prospective controlled trial.

Study GWSP 0604
Statistical assessment:
The applicant then proposed a 'therapeutic trial' approach to the use of Sativex. It was proposed that patients are exposed to treatment for 4 weeks, and only those who achieve a 20% improvement from baseline at that time-point will be considered suitable for further treatment.

The four-week duration and 20% improvement criteria for the therapeutic trial was selected based upon data from the previously conducted studies GWMS0106 and GWCL0403 as discussed in the previous section.

Study GWSP0604 was specifically designed to prospectively test the benefits of this approach to treatment. The study was designed taking account of Scientific Advice from the MHRA and from AEMPS, the Spanish Competent Authority

1. Study design
This was a randomised, double-blind, placebo-controlled study of Sativex in patients with symptoms of spasticity due to multiple sclerosis who had been identified as having a capacity to respond to Sativex.

The trial consisted of a 7-day screening period, a single-blind 4-week treatment period (phase A), a 12 week double-blind, placebo-controlled treatment period (phase B) and a 14 day follow-up period.

Patients were screened (Visit 1, day A1) and then entered the 7 day baseline period. At the end of this period, eligible patients were randomised into the study (Visit 2, day A8) and a four week single-blind course of treatment with Sativex was started.

At the end of this period (Visit 3, day A36) their response to Sativex was assessed. Eligible subjects (those who demonstrated a capacity to respond to Sativex) were randomised into the 12-week double-blind, placebo-controlled treatment phase. Study visits were scheduled at 28 day intervals.

Subjects were not made aware of which study medication they were receiving in the single-blind phase and were not informed that their study medication may be changed at visit 3. From the subject perspective there was a continuous 16 week treatment period.

	Visit	**Study day**
Visit 1	Screening	A1
Visit 2	Initiate single blind treatment	A8
Visit 3	Initiate double blind treatment	Day A36/B1
Visit 4		Day B29
Visit 5		Day B57
Visit 6	End of double-blind treatment	Day B85
Visit 7	Follow-up visit	Day B99 (or 14 days after end of treatment)

The primary endpoint was a numerical rating score (NRS) measuring spasticity on an 11 point scale, scores ranging from 0 (no spasticity) to 10 (worst possible spasticity). Subjects were asked "*On a scale of '0 to 10' please indicate the average level of your spasticity over the last 24 hours*".

To be included in the single-blind phase of the trial the subject had to have at least moderate spasticity at visit 2 – the sum of the last 6 assessments during the 7 day baseline period had to be at least 24 (an average of 4).

To be included in the double-blind phase of the trial the subject had to have demonstrated a capacity to respond to Sativex – must have had at least a 20% reduction from week 1 (baseline) to week 5 (week 4 of the single-blind period) in their mean NRS score. The subject must also have not received any new anti-spasticity or disease modifying treatments in that period, complied with study procedures including completion of the NRS score during week 5, and in the opinion of the investigator must be unaware of which study medication they had received.

Patients were randomised into the double-blind phase of the trial in a 1:1 ratio using a computer generated randomisation list consisting of permuted blocks allocated to each centre.

Study medication (Sativex or placebo) was delivered using a pump action oromucosal spray. Each actuation of Sativex delivered 2.7 mg THC and 2.5 mg CBD. Subjects self-titrated to their optimal dose based upon efficacy, tolerability and maximum permitted dose. Patients were limited to a maximum of 12 actuations in a 24 hour period. In the randomised phase subjects were to maintain a stable dose as established in the single-blind phase.

2. Patient accountability

A total of 660 subjects were screened, of which 572 were enrolled in the single-blind treatment phase. Of these 538 (94%) completed the 4-weeks of single-blind treatment and 241 (42%) met the entry criteria and were randomised into the double-blind placebo-controlled phase.

	Sativex	Placebo
Enrolled in single-blind phase	572	
Completed single-blind phase	538 (94%)	
Reason for non-completion		
Adverse event	19	
Withdrew consent	6	
Disease progression	1	
Did not meet entry criteria	4	
Other	4	
Randomised	241 (42%)	
Completed but not randomised	297 (52%)	
Reason not randomised		
Did not meet entry criteria	274	
Adverse event	10	
Withdrew consent	4	
Lack of efficacy	5	
Disease progression	1	
Lost to follow-up	1	
Not recorded	1	
Other	1	
Randomised	124	117
Completed study double-blind phase	109 (88%)	115 (98%)
Withdrawn	15 (12%)	2 (2%)
Reason for withdrawal:		
Adverse event	8 (6%)	0
Disease progression	1 (1%)	0
Withdrew consent	3 (2%)	2 (2%)
Pregnancy	1 (1%)	0
Other (holiday abroad)	2 (2%)	0

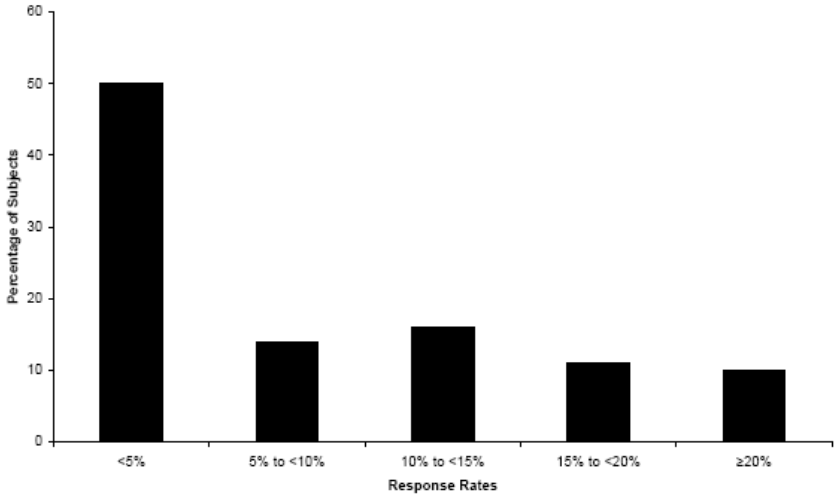
The vast majority of patients completed the single-blind treatment phase. Of all the patients treated there were 42% who completed treatment and satisfactorily demonstrated a capacity to respond to Sativex and were randomised into the double-blind phase.

There were an additional 32 subjects who did achieve a 20% improvement but were not randomised for various reasons (mainly lack of compliance with completing the NRS score), and one patient who was randomised who didn't achieve the required improvement. So therefore 272 (48%) achieved a 20% reduction. The pooled results from GWMS0106 and GWCL0403 show 46% of patients achieving a 20% improvement from baseline, so the figure of 48% seen here is very consistent with that.

It is also interesting to look at the response achieved in the rest of the subjects who were not randomised (see figure 8.4-13). Around 50% of these subjects achieved less than 5% improvement, supporting the idea that there is a group refractory to treatment, while others can achieve large benefits.

The majority of randomised patients completed the double-blind phase. There were more withdrawals in the Sativex group, though the proportion of withdrawals was low even in that group. These withdrawals were mainly because of adverse events.

Figure 8.4-13 Level of NRS Spasticity Response for Subjects Non-Randomised to Double-Blind Phase (Phase B) (N=331)



3. Analysis populations
The single-blind set included all subjects who received at least one dose of Sativex in phase A.

The double-blind ITT analysis set included all subjects who were randomised and received at least one dose of randomised study medication. This was the primary analysis set for efficacy and is considered by the assessor to be appropriate.

The double-blind per-protocol set was defined as all subjects in the double-blind ITT analysis set who completed phase B with no protocol violations deemed to compromise the analysis of efficacy.

The double-blind safety set was identical to the double-blind ITT analysis set, with the exception that any patients receiving the incorrect treatment were analysed according to the treatment received.

Population	**Sativex**	**Placebo**
Single-blind set	572	
Randomised	241	
Double-blind safety set	124 (100%)	117 (100%)
Double-blind ITT analysis set	124 (100%)	117 (100%)
Double blind per-protocol set	117 (94%)	108 (92%)

There were only 16 patients excluded from the per-protocol analysis set.

Deviation leading to exclusion*	**Sativex**	**Placebo**
Patients excluded from per-protocol population	7 (6%)	9 (8%)
Changed anti-spasticity or disease modifying meds during study	1 (1%)	3 (3%)
Did not use study medication for at least 4 out of 7 days in primary period	2 (2%)	0
Sativex subject with negative THC test within 5 days of final dose	3 (2%)	0
Placebo subject with positive THC test	0	4 (3%)
Did not achieve 20% improvement at end of single-blind phase	0	1 (1%)
Unstable dosing during last 7 days of baseline compared to last 7 days of double-blind phase	1 (1%)	1 (1%)

** Patients can have more than one deviation*

There was one additional patient on the Sativex group who changed their anti-spasticity or disease modifying meds during study but was not excluded from the per-protocol population.

4. Primary efficacy assessment
The primary endpoint was the change from double-blind baseline to the end of the evaluable period in the 11 point NRS scale. The end of evaluable period score was the average daily score recorded over the last 7 days of the evaluable period. The baseline score was the average recorded over the last 7 days of single-blind phase A treatment.

Anti-spasticity and disease modifying medications used during the study were to be maintained at a stable dose. However, if they were changed then there was a potential to affect the primary endpoint independently of the study medication and this needed to be considered in the analysis. Hence the primary efficacy analysis was conducted using only data from the 'evaluable period'. The evaluable period was defined as starting on the first day the subject took randomised treatment in phase B and ending on the earliest of (i) day B85; (ii) the last day in which randomised study medication was taken; (iii) the last day with relevant efficacy data available; or (iv) the day before a relevant change in prohibited anti-spasticity or disease modifying medication was made during phase B.

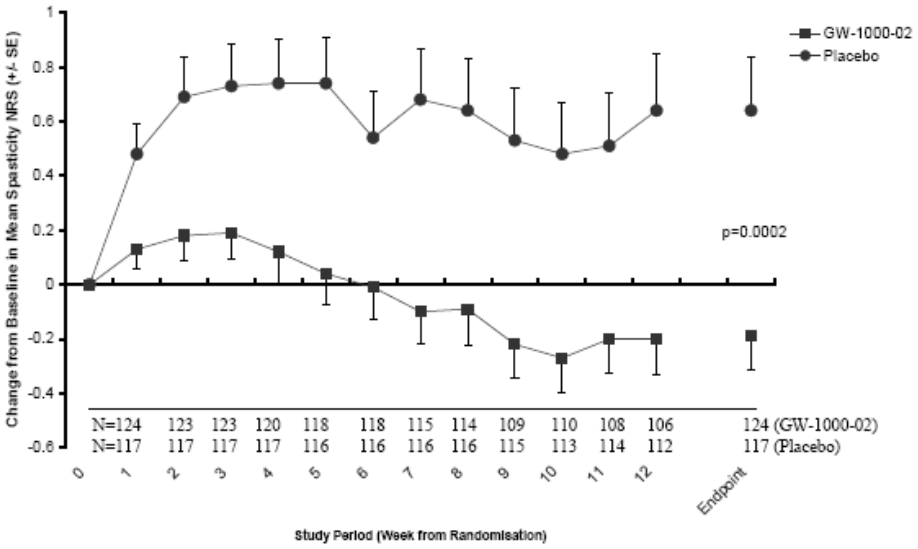
The change from double-blind baseline to end of study was analysed using ANCOVA with the baseline value as a covariate and treatment, country and ambulatory status at baseline as factors.

The main secondary endpoints were responder rates. Two responder rates were investigated which examined the improvement from screening (rather than randomised baseline).

Results:
5. Primary endpoint
Summary of NRS spasticity Double-blind ITT analysis set, evaluable period
Screening – mean (se) for randomised subjects = 6.91 (1.25)

Timepoint	**Sativex**			**Placebo**		
	n	Mean (sd)	Median	n	Mean (sd)	Median
DB Baseline	124	3.87 (1.49)	4.00	117	3.92 (1.55)	4.00
Day B1-7	124	4.00 (1.56)	4.14	117	4.40 (1.81)	4.43
Day B8-14	123	4.05 (1.62)	4.00	117	4.61 (2.08)	4.71
Day B15-21	123	4.07 (1.69)	4.00	117	4.65 (2.08)	5.00
Day B22-28	120	3.99 (1.83)	4.00	117	4.66 (2.10)	4.83
Day B29-35	118	3.92 (1.83)	3.79	116	4.64 (2.11)	4.73
Day B36-42	118	3.87 (1.80)	3.93	116	4.45 (2.19)	4.63
Day B43-49	115	3.79 (1.78)	3.86	116	4.59 (2.26)	4.79
Day B50-56	114	3.75 (1.85)	3.66	116	4.55 (2.29)	4.71
Day B57-63	109	3.65 (1.76)	3.43	115	4.45 (2.31)	4.00
Day B64-70	110	3.58 (1.81)	3.43	113	4.43 (2.35)	4.00
Day B71-77	108	3.67 (1.76)	3.50	114	4.43 (2.35)	4.21
Day B78-84	106	3.67 (1.86)	3.71	112	4.57 (2.30)	4.36
Last 7 days	124	3.68 (1.83)	3.71	117	4.56 (2.31)	4.29
Change from baseline						
Day B1-7	124	0.13 (0.80)	0.00	117	0.48 (1.17)	0.29
Day B8-14	123	0.18 (1.00)	0.00	117	0.69 (1.61)	0.48
Day B15-21	123	0.19 (1.10)	0.00	117	0.73 (1.66)	0.57
Day B22-28	120	0.12 (1.26)	0.00	117	0.74 (1.74)	0.43
Day B29-35	118	0.04 (1.23)	0.00	116	0.74 (1.79)	0.71
Day B36-42	118	-0.01 (1.27)	0.00	116	0.54 (1.82)	0.54
Day B43-49	115	-0.10 (1.29)	0.00	116	0.68 (1.98)	0.71
Day B50-56	114	-0.09 (1.40)	-0.14	116	0.64 (2.04)	0.64
Day B57-63	109	-0.22 (1.32)	0.00	115	0.53 (2.09)	0.29
Day B64-70	110	-0.27 (1.31)	-0.14	113	0.48 (2.03)	0.14
Day B71-77	108	-0.20 (1.29)	-0.07	114	0.51 (2.09)	0.27
Day B78-84	106	-0.20 (1.34)	-0.21	112	0.64 (2.18)	0.29
Last 7 days	124	-0.19 (1.35)	-0.21	117	0.64 (2.14)	0.29

Figure 8.4-1 Change from Baseline in Mean IVRS Spasticity NRS by Time – (Double-Blind [Phase B])



Analysis of change from baseline – DB ITT analysis set

	Sativex	Placebo	Difference	95% CI	p-value
Adjusted mean	-0.04	0.81	-0.84	-1.29, -0.40	p=0.0002

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

Sativex showed statistically significant superiority over placebo on the spasticity NRS score.

When the study was being powered the difference of clinical interest was considered to be 0.75 points. The observed difference of 0.84 points is of a similar magnitude.

As there was some suggestion of a skew in the data, a Wilcoxon rank-sum test was performed (p=0.0007), Hodges-Lehmann 95% CI (-1.14, -0.29). This was consistent with the findings of the primary analysis and demonstrates the robustness of the results.

6. Responder analysis

Analysis of responders – improvement from screening

	Sativex (n=166)	Placebo (n=169)	Difference (95% CI)	Odds ratio (95% CI)	
30% response	92 (74%)	60 (51%)	23% (11, 35)	2.73 (1.59, 4.69)	p=0.0003
50% response	56 (45%)	39 (33%)	12% (-0, 24)	1.63 (0.98, 2.78)	p=0.0612

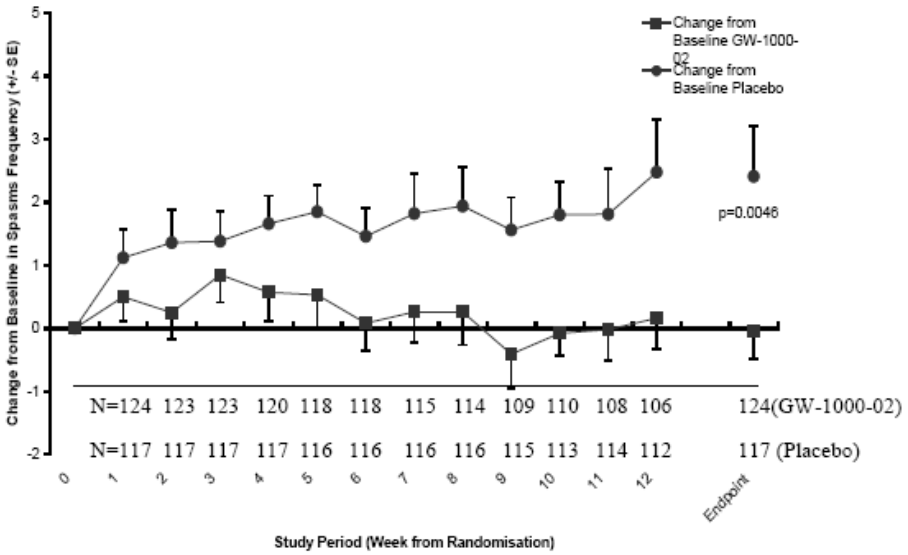
Response: At least a 30% (50%) reduction from baseline in spasticity MRS (from single-blind baseline)

The raw response rates need to be interpreted with care as they represent the proportion of subjects with a 20% response at week 4 who go on to achieve a 30% (50%) response by week 16 (not simply the proportion of patients who respond at week 16). But the statistically significant difference shows that responders at week 4 are more likely to improve that response with continued treatment.

7. Spasm frequency

Spasm frequency simply measured the number of spasms per day.

Figure 8.4-3 Change from Baseline in Spasm Frequency by Time – (Double-Blind [Phase B])



Analysis of change from baseline – DB ITT analysis set

Screening – mean (se) for randomised subjects = 10.73 (13.40)

	Sativex	Placebo	Difference	95% CI	p-value
DB baseline					
mean	5.61	5.29			
median	3.14	3.14			
Change to last 7 days	-0.25	0.59			
mean	-0.05	2.41			
median	0.00	0.29			
Adjusted mean	0.03	2.56	-2.53	-4.27, -0.79	p-0.0046

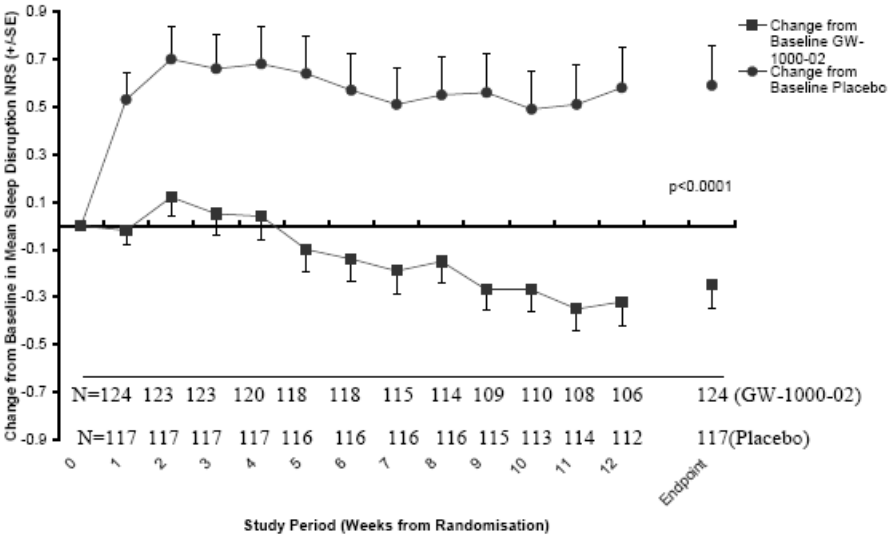
Analysis from ANOVA with terms for treatment, centre, baseline spasm frequency, and ambulatory status

There was a statistically significant difference in spasm frequency, although the analysis of means is questionable as the distribution appears to be skewed, with a big difference between the mean and median values. The company also noted this, and so performed a Wilcoxon rank-sum test to check the robustness of the primary analysis. This in fact resulted in a more extreme statistical result (p=0.0023), though the Hodges-Lehmann confidence interval suggested a slightly smaller treatment effect (-1.29, -0.286).

8. Sleep disruption

Sleep disruption was measured using an NRS: 0= no sleep disruption, 10= worst possible sleep disruption

Figure 8.4-4 Change from Baseline in Sleep Disruption NRS by Time – (Double-Blind [Phase B])



Analysis of change from baseline – DB ITT analysis set

Screening – mean (se) for randomised subjects = 4.40 (2.34)

	Sativex	Placebo	Difference	95% CI	p-value
DB baseline					
mean	1.96	2.07			
median	1.50	1.86			
Change to last 7 days					
mean	-0.25	0.59			
median	0.00	0.29			
Adjusted mean	-0.13	0.75	-0.88	-1.25, -0.51	p<0.0001

Analysis from ANOVA with terms for treatment, centre, baseline sleep disruption, and ambulatory status

There was a highly statistically significant difference in sleep disruption.

Again because of the skewed data the Wilcoxon rank-sum test was performed: p<0.0001, 95% CI (-0.86, -0.29). This confirms that there is strong evidence of a treatment difference, however the size of difference is probably exaggerated by the original analysis.

9. Other endpoints

Modified Ashworth score

Screening – mean (se) for randomised subjects = 28.0 (14.8)

	Sativex		Placebo		Difference	95% CI	p-value
DB baseline	n		n				
mean	121	22.1	113	20.8			
median		19.0		19.0			
Change to end of treatment							
mean	119	-0.1	112	1.8			
median		0.0		0.0			
Adjusted mean	119	0.08	112	1.83	-1.75	-3.80, 0.30	p=0.0939

Analysis from ANOVA with terms for treatment, centre, baseline score, and ambulatory status

Statistical significance was not seen for this score, though the trend favoured the Sativex group.

Motricity index arm

Screening – mean (se) for randomised subjects = 77.7 (18.85)

	Sativex		Placebo		Diff	95% CI	p-value
DB baseline	n		n				
mean	22	74.8	18	85.5			
median		82.3		84.5			
Change to end of treatment							
mean	19	0.6	15	0.7			
median		0.0		0.0			
Adjusted mean	19	-10.50	112	-8.58	-1.92	-10.02, 6.18	p=0.6302

An increase in score indicates an improvement in condition
Analysis from ANOVA with terms for treatment, centre, baseline score, and ambulatory status

Motricity index leg

Screening – mean (se) for randomised subjects = 58.7 (22.42)

	Sativex		Placebo		Difference	95% CI	p-value
DB baseline	n		n				
mean	90	63.6	91	64.4			
median		67.0		67.0			
Change to end of treatment							
mean	79	-1.4	81	-1.9			
median		0.0		0.0			
Adjusted mean	79	-3.24	81	-4.21	0.97	-1.49, 3.42	p=0.4391

An increase in score indicates an improvement in condition
Analysis from ANOVA with terms for treatment, centre, baseline score, and ambulatory status

There were no statistically significant differences seen for the motricity index.

The adjusted means were vastly different to the observed mean changes, which requires some explanation.

Timed 10 metre walk (seconds)

Screening – mean (se) for randomised subjects = 27.9 (33.08)

	Sativex		Placebo		Difference	95% CI	p-value
DB baseline	n		n				
mean	87	24.5	86	25.3			
median		15.0		15.0			
Change to end of treatment							
mean	82	-2.3	80	2.0			
median		0.0		0.0			
Adjusted mean	82	-0.13	80	3.22	-3.34	-6.96, 0.26	p=0.0687

A decrease in time indicates an improvement in condition
Analysis from ANOVA with terms for treatment, centre, and baseline walk time

Statistical significance was again not seen for this secondary endpoint, though there was a strong trend favouring the Sativex group.

Again the adjusted means did not seem to reflect well the observed mean changes. The choice of ANOVA for the analysis method is questioned as the data appear to be skewed. The applicant noted this. Because of the large number of ties the Wilcoxon test was felt to be inappropriate and various approaches were tried. The Cochran-Mantel-Haenszel test achieved statistical significance (p=0.029), use of rank scores did not (p=0.36), logistic regression to compare the odds of worsening also did not (OR=1.506 (0.796, 2.869), p=0.210.
The overall conclusion regarding this endpoint can only be that a trend was observed in favour of Sativex that may be real, but the findings are not conclusive.

In addition the walk time was only assessed for subjects who completed the 10 metre walk, so is not a clean comparison of randomised groups.

Barthel index

Screening – mean (se) for randomised subjects = 74.0 (24.23)

	Sativex		**Placebo**		**Difference**	**95% CI**	**p-value**
DB baseline	n		n				
mean	122	73.8	116	78.1			
median		85.0		85.0			
Change to end of treatment							
mean	120	0.0	116	-1.9			
median		0.0		0.0			
Adjusted mean	120	-0.53	116	-2.37	1.84	0.02, 3.66	p=0.0479

An increase in score indicates an improvement in condition
Analysis from ANOVA with terms for treatment, centre, and baseline walk time

There was a marginal statistically significant difference seen here. Again the data seem to be skewed, and the Barthel Index can only take 10 distinct values, so the choice of analysis was questionable. The applicant also observed this, and performed an alternative analysis based on proportions. From this re-analysis it is clear that there are many more patients who improved in the Sativex group, fewer who worsened and a highly statistically significant result is seen.

Barthel index change from baseline

	Sativex (n=124)	**Placebo (n=117)**
30	2 (2%)	0
15	2 (2%)	0
10	6 (5%)	5 (4%)
5	20 (17%)	7 (6%)
0	69 (58%)	73 (63%)
-5	8 (7%)	19 (16%)
-10	4 (3%)	4 (3%)
-15	4 (3%)	1 (1%)
-20	4 (3%)	5 (4%)
-25	1 (1%)	2 (2%)
Not observed	4	1
Odds ratio	2.040	
p-value	p=0.0067	

Generally the secondary endpoints were less sensitive than the primary scale, but apart from the motricity index (arm), which had a very small sample size, the trends all favoured Sativex, and for the barthel index, modified ashworth score and time 10 metre walk test either just achieved statistical significance or just missed it. The more appropriate re-analysis of the barthel index produced a highly significant result.

The large discrepancy between the adjusted means and observed means for some endpoints should be addressed, but overall these endpoints provide good supportive evidence of efficacy.

10. Global impressions of change

Subject global impression of change (end of DB treatment)

	Sativex (n=124)	**Placebo (n=117)**
Very much better	14 (12%)	10 (9%)
Much better	40 (33%)	28 (24%)
Minimally better	39 (32%)	33 (28%)
No change	17 (14%)	35 (30%)
Minimally worse	4 (3%)	7 (6%)
Much worse	6 (5%)	1 (1%)
Very much worse	1 (1%)	3 (3%)
Not recorded	3	0
Odds ratio	1.708	
p-value	p=0.0234	

Carer global impression of change (end of DB treatment)

	Sativex (n=124)	**Placebo (n=117)**
Very much better	2 (3%)	0
Much better	15 (21%)	11 (16%)
Minimally better	31 (44%)	19 (28%)
No change	16 (23%)	24 (35%)
Minimally worse	4 (6%)	8 (12%)
Much worse	2 (3%)	5 (7%)
Very much worse	1 (1%)	2 (3%)
Not recorded	53*	48*
Odds ratio	2.400	
p-value	p=0.0053	

** Not all subjects had a carer to make this assessment*

Physician global impression of change (end of DB treatment)

	Sativex (n=124)	Placebo (n=117)
Very much better	6 (5%)	8 (7%)
Much better	44 (36%)	29 (25%)
Minimally better	45 (37%)	26 (22%)
No change	17 (14%)	37 (32%)
Minimally worse	4 (3%)	13 (11%)
Much worse	6 (5%)	4 (3%)
Very much worse	0	0
Not recorded	2	0
Odds ratio	1.958	
p-value	p=0.0045	

Analysis from ordinal logistic regression using proportional odds model.

The global impression of change was statistically significantly better for the Sativex group compared to placebo for all three groups of scorers.

11. Statistical and clinical assessors' overall summary of efficacy for study GWSP 0604
Enrichment designs can over-estimate the magnitude of the mean treatment effect and are therefore discouraged in most situations. However in this case the enrichment design reflects proposed clinical practice, which is that only patients with an initial response to Sativex will receive treatment beyond the trial period. Only these patients are randomised and the ITT population is defined at the point of randomisation at the end of the 4 week trial period, not at the beginning of it. Hence the difference between active and placebo should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium to long term.

The study design with a 4-week therapeutic trial period was intended to reflect clinical practice as far as possible. However in order to ensure the internal validity of the trial patients were blinded to treatment in the 4-week trial period, which would not happen in clinical practice. There are advantages and disadvantages to this approach. Responses are more likely to be genuine if patients are blinded to treatment. However there are issues regarding the external validity of the study if the 4 week run in is blinded, as the patient population entering the randomised period might not be a true reflection of the clinical situation, where there would be no blinding. On balance the assessors agree that blinding of the 4 week run in period is the preferred approach. Because of the desire of many patients with severe intractable disability to take a treatment that might offer them any degree of benefit, in normal clinical practice the proportion of patients deemed to have achieved a response in the 4-week therapeutic trial is likely to be higher than the 48% that achieved a 20% NRS score reduction in this study. Prescribers need to be aware of the need to confirm a true treatment response before continuing with long term treatment in order to ensure that the risk-benefit is positive in the individual patient.

The data for many of the endpoints were clearly not normally distributed. The company noted this and performed non-parametric analysis, which confirmed the statistical significance of the findings, but in some cases reduced the size of the estimated treatment effect. When presenting results in the SPC, it is considered that the results from the non-parametric Wilcoxon test may be more appropriate than the ANOVA results.

The results of this trial support the 'therapeutic trial' approach to the use of Sativex. Analysis of past trials generated the hypothesis that a 4-week trial with Sativex could be used to identify those subjects likely to benefit from continued treatment.

The results of this trial show that patients who achieve a 20% response in that first 4 weeks derive benefit from continued treatment with Sativex. On average, patients continuing with Sativex treatment see further improvement, while those who discontinue treatment experienced a loss of efficacy, though they did not fall back to screening levels.

As with any measure on a visual analogue or numeric rating scale, different patients grade their perceptions very differently and the interpretation of a given change from baseline can therefore be very difficult to interpret. The value of a 28% change from baseline (including the placebo response) proposed as representing a "definition of clinically important improvement" proposed in a well known paper by Farrar et al (Pain, 2001) is widely quoted. For those randomised, the overall improvement from the original baseline was 3.01 units from a baseline of 6.91 (44%) and patients in the Sativex group showed further improvement in their NRS score. The observed difference therefore meets the Farrar 30% criterion in those patients showing an initial treatment response at 4 weeks. Secondary endpoints provide further information on clinical significance.

Long-term studies

Two open-label extension studies and one Phase III randomised withdrawal study in patients treated long-term with Sativex are provided as summarized below.

GWSP0702 n= 36	A placebo controlled, parallel group, randomised withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex. Duration of treatment was four weeks and one week baseline.	Phase III random-ised withdrawal study
GWMS0001 (EXT) n= 137	A long-term open label safety and tolerability study as an extension of study GWMS0001. A combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) was administered to patients with multiple sclerosis. The median duration of treatment was 735 days with a minimum of one and a maximum of 1149 days.	Phase III extension study
GWEXT0102 n= 507	A long–term, open label, safety and tolerability study of cannabis based medicine extract (CBME) in patients who have participated in a GW clinical study using CBME. The mean duration of treatment was 360 days, with a minimum of one and a maximum of 1051 days.	Phase III extension study

Randomised withdrawal long-term efficacy study GWSP0702

Study GWSP0702 was designed to assess the benefit of long-term treatment with Sativex. It was a placebo controlled, parallel group, randomised withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex. It was intended to address the objection raised for the previous application that since MS is a chronic disorder, there was a lack of evidence of maintenance of efficacy with long-term treatment.

1. Study design

This was a placebo-controlled, parallel group randomised, double-blind, withdrawal study of Sativex in subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term treatment with Sativex. The objective was to evaluate the maintenance of effect of Sativex compared with placebo in patients who had received long-term benefit from Sativex.

Subjects were recruited who had been diagnosed with multiple sclerosis and had been receiving Sativex for the relief of spasticity for at least 12 weeks prior to screening and had been judged to have been receiving benefit from and showing tolerability to the treatment in the subject and investigator's opinion.

The trial consisted of a 7-day baseline period and a 4-week randomised treatment period.

For ethical reasons patients discontinued from randomised treatment once they experienced treatment failure (the primary endpoint).

Following informed consent and screening, eligible subjects entered the study (Visit 1, day A1) and then entered the 7-day baseline period. At the end of this period, eligible patients were randomised into the study (Visit 2, day 1). They ceased treatment with their open-label Sativex and were randomised to receive either Sativex or placebo for 4 weeks. Subjects returned for an end of study visit at week 4 (Visit 3, day 28) or earlier if they withdrew from treatment.

Subjects administered the study medication at the same dosage at which they had been receiving treatment prior to the study.

2. Patient accountability and baseline characteristics
A total of 37 subjects were screened, of which 36 were randomised into the trial phase.

	Sativex	**Placebo**
Randomised	18	18
Completed 28 days of treatment	15 (83%)	2 (11%)
Did not complete	3 (17%)	16 (89%)
Reason for non-completion:		
Adverse event†	1 (6%)	8 (44%)
Withdrew consent	0	1 (6%)
Other*	2 (11%)	7 (39%)

† Placebo: muscle spasticity (2)
* Sativex: lack of efficacy (1), increase in spasticity (1); Placebo: increased spasticity (5), lack of efficacy (1), worsening of spasticity (1)

The majority of Sativex patients completed the double-blind treatment phase. Only two placebo patients completed the treatment phase. Nine of those withdrawals were directly attributable to loss of efficacy.

The mean duration of Sativex use prior to the trial was 3.62 years. Patients used a mean of 8.25 sprays per day.

	Sativex	**Placebo**
Duration of prior Sativex use	18	18
mean (sd)	4.22 (2.03)	3.03 (1.91)
median	4.33	3.16
Number of sprays per day		
mean (sd)	7.33 (3.12)	9.17 (9.00)
median	6.50	6.00
2	0	1
3	1	1
4	3	0
5	3	4
6	2	6
7	1	0
8	2	0
10	2	2
11	1	0
12	3	1
14	0	1
16	0	1
42	0	1

3. Analysis populations
The randomised-withdrawal analysis set included all subjects who were randomised and received at least one actuation of randomised study medication. This was the primary analysis set for efficacy.

This is the appropriate choice for the primary efficacy population.

Population	**Sativex**	**Placebo**
Randomised	18	18
Randomised withdrawal analysis set	18 (100%)	18 (100%)

4. Primary efficacy assessment
The primary efficacy variable was the spasticity NRS (11 point scale with 0 = 'no spasticity' and 10 = 'worst possible spasticity').

Treatment failure was defined as any of the following:

- Cessation of the randomised treatment before Visit 3 (i.e. subjects who withdrew from the study without completing the 28 day randomised treatment period). Subjects who completed the study but for administrative/practical reasons had a slightly shortened treatment period (25, 26, or 27 days instead of 28 days) or subjects who withdrew from the study on Day 28 or later were not considered to be treatment failures.
- A worsening of spasticity (defined as an increase in the mean spasticity NRS over the last seven days of the treatment period of at least 20% and at least 1 unit from the treatment baseline).
- A clinically relevant increase in anti-spasticity medication or disease modifying medication after randomisation; the relevance of any such changes to the levels of spasticity during the last seven days of the treatment period was assessed during the blinded review meeting.

The baseline score was defined as the mean of the NRS scores over the last 7 available days prior to randomisation.

The primary efficacy measure was the time to treatment failure. This was calculated as the number of days from the first day of randomised treatment up to the first day of treatment failure. The first day of treatment failure was the earliest of:

- The day of premature cessation of randomised study medication.
- The first day of the longest period, ending on the last day of treatment, where the mean spasticity NRS had increased by at least 20% and at least 1 unit from the treatment baseline i.e. the start of the longest period for which NRS assessed treatment failure had occurred.
- The day of a clinically relevant increase in anti-spasticity or disease modifying medication.

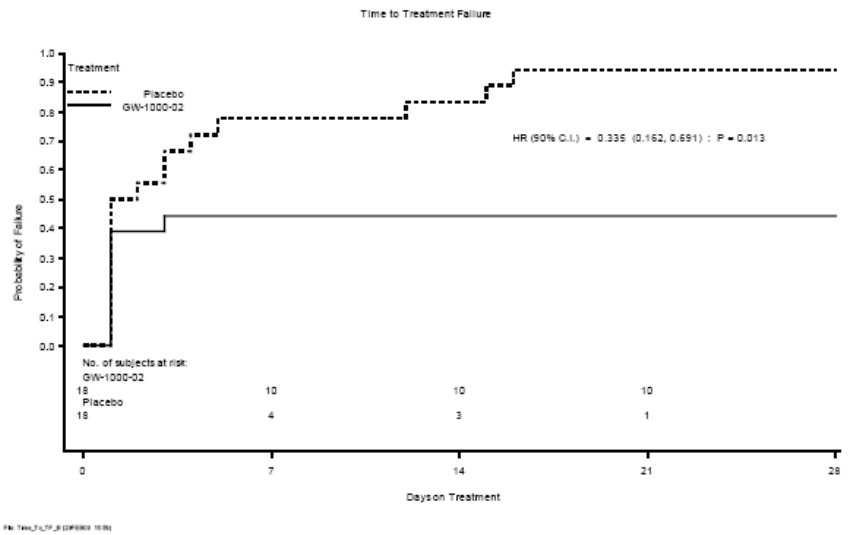
The time to treatment failure was analysed using Kaplan-Meier survival analysis methodology and proportional hazards regression with treatment group as the only covariate.

Results:
5. Primary endpoint

Summary of time to treatment failure

	Sativex (n=18)	**Placebo (n=18)**
Number of failures	8 (44%)	17 (94%)
Reason for failure		
≥20% increase in spasticity	8	11
Cessation of randomised medication	0	6
Hazard ratio (95% CI)	0.335 (0.16, 0.69)	
p-value*	0.013	

Figure 8.4-1 Treatment Failure by Time



There was a highly statistically significant difference in the time to treatment failure, with the risk of failure being reduced by around 65% in the Sativex group. This provides evidence of the benefit of patients benefitting from Sativex continuing to receive it in the long-term.

There were six subjects in the placebo group who were treatment failures because of cessation of randomised study medication before visit 3. For five of the patients the reason was related to increased spasticity. The other was increased MS related pain. All six seem to represent treatment failure, but given the indication being sought it is additionally reassuring that almost all of them relate to spasticity.

Secondary endpoints:

This trial was specifically designed to assess time to treatment failure, and not these change from baseline endpoints.

Given that subjects discontinued the trial after experiencing treatment failure results from, these endpoints are difficult to interpret. Both groups generally experience a worsening over time on average, (as would be expected, as subjects know there is a possibility they have been removed from treatment and the best result possible for an individual subject really is no change) but the comparisons between treatments are unfair, as the treatment groups were generally followed for different durations – it is possible that the placebo patients may have declined further if followed up for the same duration as the Sativex patients were.

In addition, the patient numbers, while adequate for the primary endpoint, do not allow conclusions to be drawn on most of these secondary scales.

6. Summary of NRS spasticity by time

Timepoint	Sativex			Placebo		
	n	Mean (sd)	Median	n	Mean (sd)	Median
Baseline	18	3.60 (1.67)	3.29	18	4.13 (2.23)	4.43
Day 1-7	17	4.04 (1.46)	3.71	13	4.94 (2.01)	5.71
Day 8-14	15	4.38 (1.60)	4.29	5	5.06 (2.77)	5.14
Day 15-21	15	4.40 (1.75)	4.43	3	6.90 (1.25)	6.57
Day 22-28	15	4.50 (1.95)	4.14	2	6.00 (0.61)	6.00
Last 7 days	18	4.71 (1.99)	4.50	18	5.24 (2.17)	5.62
Change from baseline						
Day 1-7	17	0.31 (1.00)	0.29	13	0.52 (1.49)	0.71
Day 8-14	15	0.60 (1.55)	0.57	5	-0.29 (1.93)	0.14
Day 15-21	15	0.62 (1.57)	0.71	3	0.95 (1.01)	1.14
Day 22-28	15	0.72 (1.65)	0.43	2	0.64 (1.52)	0.64
Last 7 days	18	1.11 (1.92)	0.79	18	1.10 (1.91)	1.20

Analysis of change from baseline

	Sativex	Placebo	Difference	95% CI	p-value
Adjusted mean	1.00	1.21	-0.21	-1.22, 0.79	p=0.7204

Analysis from ANOVA with terms for treatment and baseline spasticity

The cautions expressed above about differential follow-up apply here, so the lack of a difference between the treatments is not greatly concerning, as it would be expected to a certain extent. In addition the mean and median results differ, suggesting a non-normal distribution, questioning an ANOVA analysis based on means. The difference in median change from baseline does seem larger.

7. Sleep disruption

Sleep disruption was measured using an NRS: 0= no sleep disruption, 10= completely disrupted

Analysis of change from baseline

	Sativex	Placebo	Difference	95% CI	p-value
Baseline					
mean	2.31	2.11			
median	1.93	2.00			
Change to last 7 days					
mean	0.29	0.90			
median	0.00	0.66			
Adjusted mean	0.60	1.24	-0.64	-1.60, 0.33	p=0.271

Analysis from ANOVA with terms for treatment, baseline sleep disruption

8. Modified Ashworth score, 10 metre walk, motricity index

The sample sizes were very small for all these endpoints, meaning conclusions cannot be drawn. This was principally because many patients re-started their open-label medication before the end of study visit (visit 3).

Available sample size

Endpoint	Sativex	Placebo
Modified Ashworth score	17	8
10 metre walk	11	4
Motricity index – arms	4	1
Motricity index - legs	16	7

9. Global impressions of change

Subject global impression of change

	Sativex (n=18)	Placebo (n=18)
Very much better	0	0
Much better	0	0
Minimally better	0	0
No change	6 (33%)	1 (6%)
Minimally worse	6 (33%)	5 (28%)
Much worse	5 (28%)	9 (50%)
Very much worse	1 (6%)	3 (17%)
Not recorded	0	0
Odds ratio	4.552	
p-value	p=0.0172	

Carer global impression of change – functional ability

	Sativex (n=18)	Placebo (n=18)
Very much better	0	0
Much better	0	0
Minimally better	0	0
No change	3 (30%	0
Minimally worse	5 (50%)	3 (21%)
Much worse	2 (20%)	9 (64%)
Very much worse	0	2 (14%)
Not recorded	8	4
Odds ratio	18.550	
p-value	p=0.0011	

** Not all subjects had a carer to make this assessment*

Carer global impression of change – ease of transfer

	Sativex (n=18)	Placebo (n=18)
Very much better	0	0
Much better	0	0
Minimally better	0	0
No change	3 (30%	2 (14%)
Minimally worse	5 (50%)	5 (36%)
Much worse	2 (20%)	6 (43%)
Very much worse	0	1 (7%)
Not recorded	8	4
Odds ratio	3.444	
p-value	p=0.1151	

** Not all subjects had a carer to make this assessment*

The global impression of change was better for the Sativex group compared to placebo.

10. Overall summary of efficacy for study GWSP0702

The results of this trial provide evidence that continued long-term treatment with Sativex is beneficial for patients who are already benefitting from treatment.

The primary endpoint showed that the risk of treatment failure is reduced by around 65% with continued treatment as opposed to stopping treatment. While the majority of treatment failures were because of worsening spasticity there were 6 placebo treatment failures where the reason was given as “cessation of randomised medication before visit 3”. It would be useful to know the reasons for cessation of medication for these 6 patients.

Because of the trial design (which allowed open-label treatment to be initiated after treatment failure, rather than after a fixed period of time, appropriate for a trial of this kind) the majority of secondary endpoints were hard to interpret. However there were strong supporting data, particularly from the subject and carer global impression of change.

GWMS000l EXT

This was the open label extension phase of study GWMS0001. The primary objectives were to assess long term safety and tolerability of a development formulation and assessment of efficacy (monitored throughout the study by VAS scores) was a secondary objective. With no reference treatment or placebo control it is not possible to conclude that the apparent maintenance of efficacy measures is due to continuing efficacy of Sativex in this study and it cannot provide robust evidence of long-term maintenance of efficacy. It should be noted that patients would not be likely to stay in this study if they did not perceive a clinical benefit, and there were substantial numbers of dropouts. The effect of changes to the patient population due to efficacy related withdrawals would tend to bias these data towards showing apparent maintenance of efficacy. Any trends or notable features of the efficacy summaries 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. It is worth noting that the mean daily dose (8 sprays / 24h at the end of the study) did not increase with time.

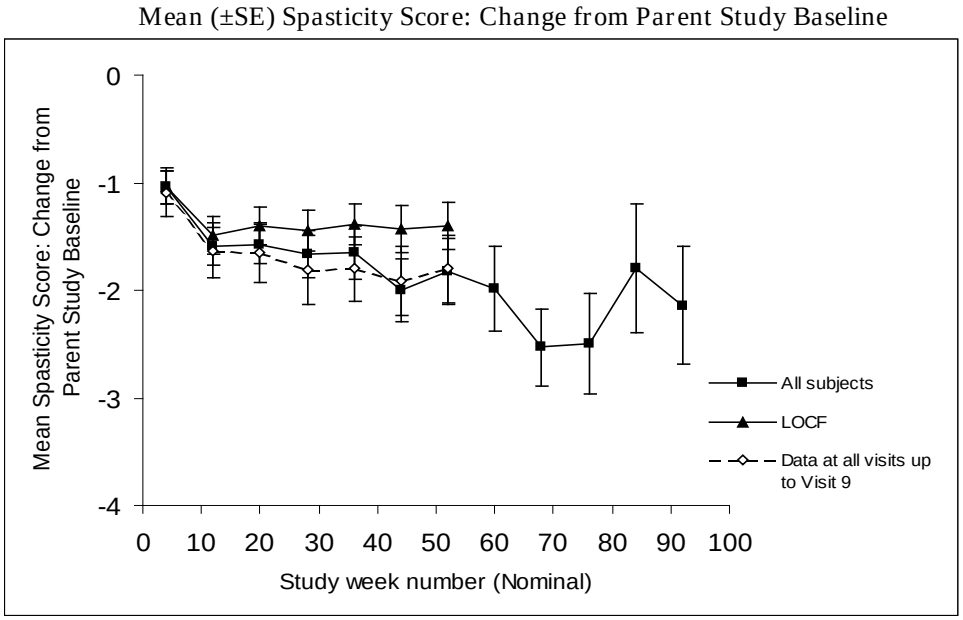
GWEXT0102

The primary objective of this open label study was also to assess the safety and tolerability of long-term therapy with Sativex. The secondary objectives were to determine whether there is any evidence of tolerance with long-term open label Sativex therapy, by assessing ratings of primary efficacy and overall condition scores and to assess the dosing profile of long-term use of Sativex. Patients had a wide variety of conditions including multiple sclerosis, spinal cord conditions, peripheral nerve injury and central nervous system damage associated with vascular, traumatic, infective, genetic or metabolic disease. Only a subgroup of the patient population is therefore of any relevance in terms of efficacy and dosing for this application.

A total of 507 patients were recruited of whom 262 (52%) withdrew from the study. 123 of these patients had MS with unrelieved spasticity and were recruited as an extension to GWMS0106. This is the sub-population of relevance to this application. Of these 87 patients were still contributing efficacy after 1 year and 67 were contributing efficacy data after 92 weeks.

Results

Since this was a non-comparative study, no formal hypothesis testing was performed.



The comments made in respect of GWMS001 EXT above apply also to this study. With no reference treatment or placebo control it is not possible to conclude that the apparent maintenance of efficacy measures is due to continuing efficacy of Sativex and this study cannot provide robust evidence of long-term maintenance of efficacy.

Assessors' overall conclusions on long term efficacy

The open label extension studies GWMS001 EXT and GWEXT 0102 do not provide robust evidence of long-term maintenance of efficacy, although they are not suggestive of a lack of efficacy either. The evidence of maintenance of efficacy of Sativex in MS patients therefore relies on the controlled randomised withdrawal trial GWSP0702. The results of this trial provided evidence that continued long-term treatment with Sativex is beneficial for patients who are already benefitting from treatment. It is considered that the efficacy of long-term treatment with Sativex has been satisfactorily demonstrated.

Maintenance of Blinding to Treatment Allocation

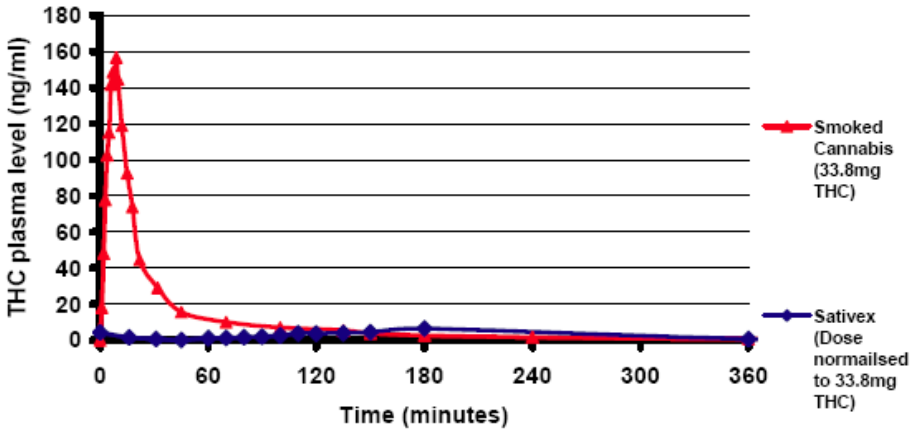
Given the substantial observed differences from placebo in side effects such as dizziness, there are concerns that if a significant proportion of patients became unblinded to treatment allocation there could be a potential for measurement bias, especially since the primary efficacy endpoint of the pivotal clinical trials is patient reported and subjective. The fact that a substantial proportion of patients had previously taken illicit cannabis as self medication potentially 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.

However patient unblinding might not be as widespread as one might intuitively imagine. It is clear that smoking cannabis results in obvious psychoactivity, but the PK profile of Sativex is very different from that of smoked cannabis as can be seen in the table and graphical illustration below. It does not produce the rapid rise in plasma levels and high C_{max} achieved by the inhaled route. Instead plasma levels are relatively stable, especially with maintenance treatment when the substantial reservoirs of drug in body fat are likely to further stabilise plasma levels.

Table NL C4-1: C_{max} & T_{max} of Vaporised THC & Sativex

Analyte	Dose of THC administered (mg)	C_{max} (ng/ml)	T_{max} (mins)
Oromucosal Sativex [2]	10.4	2.72	180
Oromucosal Sativex (Dose normalised) [2]	33.8	8.84	180
Smoked Cannabis (8 inhalations)*	33.8	162.2	9

Source: Table 4 Study GWPK0215 CSR[2] and * Huestis *et al.* (1992)[3]



In the pivotal placebo-controlled studies the mean daily dose of Sativex was 9 sprays, so the dosing interval was typically less than the T_{max} of a single dose. This pattern of drug administration would produce relatively modest peak-trough fluctuation. Plasma levels during treatment with Sativex are an order of magnitude lower than those obtained by smoking cannabis.

The Applicant commissioned an analysis of the relationship between the occurrence of CNS adverse events, prior experience of cannabis, and effectiveness of Sativex in relieving spasticity. This report indicated that efficacy measures did not differ between patients with and without prior experience of cannabis. This goes some way towards dispelling the concern that MS patients who had self medicated with cannabis would recognise whether they were on active treatment and that their efficacy assessments would be biased by their expectations. The report also found no correlation between efficacy measures and the most common AEs that might cause unblinding (such as dizziness and somnolence). It concluded that "there is no evidence to suggest that the blinding has been seriously compromised" and that "if any subjects did become unblinded then there is no evidence of any bias in the assessment of the treatment difference between Sativex and Placebo for efficacy, adverse events or study drug dosing".

The clinical expert argues that the following additional circumstantial evidence from the pivotal studies indicates that the blinding was not seriously compromised:

- The applicant asked investigators in trial GWCL0403 which treatment they believed each of the patients was taking. Even though this question was asked at the end of the trial when a combination of efficacy and adverse events would maximise the chance of the blind being broken, there wasn't a clear signal that this had happened.
- In GWSP0604, subjects were first exposed blind to Sativex and after 4 weeks those who had responded were randomised to continue on Sativex or switch to placebo. If there had been widespread awareness of the change in treatment there would likely have been a number of withdrawals from study in those who switched over to placebo, especially in those subjects who had responded to Sativex during the 4

week period. There was no such phenomenon. Furthermore the observed placebo response (in subjects who had all responded to blinded Sativex) would not have occurred if there had been widespread unblinding.

- In Study GWSP0702, patient with more than 3 years continuous exposure to Sativex were randomised to continue on Sativex, at the same dose, or to switch to placebo. Had the subjects who remained on Sativex been able to determine that they remained on the same medicine, then it is virtually inconceivable that only 5 of 18 would have indicated that their condition remained unchanged - the remainder indicating that their condition had deteriorated.

The clinical expert concludes that the available data show no evidence of unblinding to treatment allocation.

Assessor's comment

The pattern of CNS side effects such as sedation is highly suggestive that some unblinding is possible. The PK data do however provide reassurance that it might not be widespread as the rapid rise in plasma drug levels and high C_{max} seen with recreational use are largely absent with Sativex. The presented analysis does not suggest that efficacy measures differed in patients depending on whether or not they reported CNS side effects. However it is not clear that patients who experienced some psychoactivity due to active treatment would necessarily report this as an adverse event.

The power of the interaction tests is low, and in an application where the main effect of treatment has not been large, detecting an interaction between treatment and another factor is not an easy task. Hence the possibility that patients unblinded by the psychoactivity of Sativex tended to report higher efficacy measures cannot be excluded by this analysis, although it does provide a level of reassurance that any effect is not huge. 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 the possibility of unblinding might not represent a major concern.

Dose – response

The Applicant has not carried out any formal dose-ranging studies. Instead, all studies have adopted a within-patient dose titration regimen, where the dose is increased according to individual response and tolerability. The applicant makes the following justification:

In each of the placebo-controlled studies the maximum permitted daily dose varied from 48 sprays (in GWMS0106) to 24 sprays (in GWCL0403) to 12 sprays (GWSP0604). In each study the patient was permitted to find their own optimum dose up to that permitted daily maximum. In each study the final dosing pattern was very similar as shown in the table below.

Dosing in the three studies GWMS0106, GWCL0403 and GWSP0604.

	GWCL0403	GWMS0106	GWSP0604
n	167	124	241
Mean daily Sprays	8.5	9.4	8.3
SD	4.8	6.4	2.4
Median Daily Sprays	7.4	6.8	8.6
Inter-Quartile Range	5, 11	5, 13	6, 10
Min, Max	1, 22	2, 34	4, 12

In long-term open-label use, dosing was monitored by reviewing patient diaries. The applicant states that "dosing was found to be very stable over a prolonged period of time. Thus prolonged efficacy was achieved without the need for dose escalation. This shows firstly that dosing is fairly predictable in both short and long-term use, and secondly that there is no evidence of tolerance to the beneficial effects of Sativex."

The Sativex clinical development programme was designed to give patients the opportunity to titrate their dose to the level required to provide symptom relief. The resulting data show that the dose required to achieve this relief varies considerably between patients, i.e. the dose response curve is flat. This is widely considered to be normal in a situation involving self-titration to obtain symptom relief.

The pharmacokinetics of Sativex and the pharmacodynamic response to cannabinoids are known to be highly variable between subjects. This would undoubtedly have confounded attempts to investigate the dose-response relationship. Furthermore, the use of mean NRS data would be unproductive because the "noise" generated by non-responders would obscure any "signal" from responders.

All these issues are relevant to the retrospective analysis of dose vs. response obtained in the completed clinical trials. *A priori* therefore, there are multiple reasons leading to the expectation that such analyses will fail to yield convincing evidence of a dose response.

The following conclusions can be drawn:

- A flat dose-response is normal for this therapeutic scenario and for this style of clinical development plan.
- Attempts to investigate dose response using conventional study designs would have been confounded by pharmacokinetic variability.
- Retrospective analysis of NRS data is not useful because of the low signal to noise ratio.
- Retrospective responder analysis is not useful because assessment time points are inappropriate for this aim.

In conclusion, it is neither appropriate nor feasible to look for a dose response relationship from the efficacy perspective.

In general, the adverse event safety profile does not vary according to dose, but noteworthy increases in adverse event frequency do occur at higher doses for vertigo, diarrhoea, nausea, vomiting, urinary tract infection, muscle spasms and dysgeusia.

RMS comment

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 is difficult, not least because of the high inter-individual variability. It is likely to be more feasible to study within-patient dose-response an enriched patient population of clear "responders" with stable symptoms taking a number of doses of Sativex in a crossover design. The possibility of carryover might be problematic however.

Assessor's summary and overall conclusions on clinical efficacy

Spasticity has a variety of clinical manifestations including hyper-reflexia, resistance to passive movement, muscle weakness, loss of dexterity and leads to abnormal posture, fatigue, pain and muscle spasms. It is accepted that currently available treatment for spasticity is limited, that spasticity continues to be responsible for substantial disability in MS patients with troublesome spasticity, despite maximal conventional treatment, and that there is therefore a clear unmet clinical need in these patients. Preclinical data submitted on the effect of Sativex on spasticity are discussed in the preclinical assessment.

Spasticity is difficult to measure. The Ashworth Scale has long been considered the standard tool for measuring spasticity but there are substantial problems associated with it, in particular poor reproducibility and insensitivity to change. The applicant has chosen instead to employ a patient reported measure of symptoms related to spasticity, the 0 to 10 point Numeric Rating Scale (NRS) and has provided extensive data attempting to validate this measure. There are some weaknesses in these data including a lack of data showing the sensitivity to of the NRS to detect a confirmed objective change in spasticity in response to therapeutic intervention. Otherwise the assessor considers that company has provided reasonable demonstration of the validity of the NRS as a measure of symptoms related to spasticity for the purpose of supporting an indication for symptomatic treatment in this patient population.

The first large study, GWMS0001, was negative overall, but was encouraging for spasticity as a secondary endpoint. This has to be viewed as hypothesis generating, so any conclusions regarding efficacy in spasticity depend entirely on the results of the pivotal studies GWMS0106, GWCL0403 and GWSP 0604, which were designed to address this endpoint.

The 6-week Study 0106 showed some evidence of efficacy in the spasticity indication. The difference from placebo reached a modest level of statistical significance and the difference between treatments of around 0.5 to 0.6 points on a scale ranging from 0-10 was of questionable clinical relevance. The 14-week study GWCL0403 was negative, although the majority of endpoints showed a trend in favour of Sativex.

A meta-analysis of studies GWMS0106 and GWCL0403 was presented and was considered statistically valid. The overall result for the primary endpoint of the two pivotal studies GWMS0106 and GWCL0403 and a meta-analysis of them showed a modest mean treatment effect of questionable clinical significance (-0.34 points on the 10 point NRS). Responder rates in comparison with placebo, which can be a useful way of assessing the clinical relevance of a difference in means observed on a scale, were more encouraging, with a mean response rate (30% improvement) of 35% for Sativex compared with 24% for placebo.

In response to these findings, the applicant proposed a 'therapeutic trial' approach to the use of Sativex. The notion of a dichotomy of patients some of whom will show no response and some of whom may show a good response seems plausible as does the argument that an

important treatment effect in some patients might be masked by the data "noise" from a large number of non- responders in an analysis of mean changes. It was agreed that in a situation where only a minority of patients might be expected to respond to a treatment, a therapeutic trial to identify the responders could in principle be justified provided that non-responders can be identified quickly and the risk to them of the therapeutic trial is low.

The applicant conducted a variety of post hoc analyses in an attempt to identify a sub-population of patients that would ultimately respond well. Earlier analyses, comparing NRS scores with patient global impression of change, had indicated that a 19% response represented a clinically relevant improvement and a response of 28% represents "much improved". This is very much in line with published data on pain VAS scores. On this basis, the applicant chose 30% improvement from baseline as the threshold for the magnitude of clinical response that the therapeutic trial was intended to predict.

The sensitivity and specificity of alternative durations for the trial period and alternative responder criteria at the end of it were explored. The applicant considered that the optimal results were obtained with 4 week trial period using a 20% threshold. This had a sensitivity of 94% i.e. 94% of patients that ultimately achieved a 30% response achieved a 20% response by 4 weeks. The sensitivity to detect ultimate 30% responders with 4 week trial period using a higher 30% threshold fell to 73%. This was felt to be unsatisfactory as applying this criterion would be expected to exclude substantially more patients that would ultimately have benefitted from further treatment (approximately a quarter).

These figures suggested that a 4-week therapeutic trial might be a way to allow responders access to treatment without subjecting non-responders to long-term treatment. The 20% threshold for response at 4 weeks appeared to achieve a reasonable balance between sensitivity and specificity for predicting ultimate response at the 30% level.

The pivotal study GWSP0604 was specifically designed to prospectively test the benefits of this approach to treatment. It was unusual in that it was an enrichment design which is normally discouraged in most situations as it can over-estimate the magnitude of the mean treatment effect. However in this case the enrichment design reflects proposed clinical practice and in principle the difference between active and placebo should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium to long term.

GWSP0604 showed that patients who achieve a 20% response in that first 4 weeks derived benefit from continued treatment with Sativex as measured on the NRS. On average, patients continuing with Sativex treatment saw further improvement, while those who discontinue treatment experienced a loss of efficacy. It is difficult to assess to what extent the observed difference of 0.84 points on the 0-10 point NRS from a double-blind baseline of 3.9 is of clinical significance. The differences from placebo in responder rates and in the range of other efficacy measures are therefore of considerable value in making this judgement. Highly significant superiority to placebo was seen in the global impression of change for subjects, carers and physician, and for a number of other measures. The most important of these are the objective measures that either measure spasticity or are a direct manifestation of spasticity. Conventional statistical significance was not seen for the modified Ashworth score, though there was a strong trend favouring the Sativex group (95% CI -3.80, 0.30 and p-value 0.094). There was however a statistically significant difference in spasm frequency (number of spasms per day) which is closely related to the phenomenon of spasticity. There was a significant treatment effect on sleep disruption and barthel index and borderline significant effect on timed 10 metre walk test. Motricity index

(a measure of effective strength) for upper and lower limb showed no difference from placebo.

The open-label extension studies GWMS001 EXT and GWEXT 0102 do not provide robust evidence of long-term maintenance of efficacy, although they are not suggestive of a lack of efficacy either. Robust evidence of long-term efficacy of Sativex in the relief of spasticity in MS patients , which was lacking in the previous application, is provided by the new placebo controlled, parallel group, randomised withdrawal study GWSP0702. There was a highly statistically significant difference in primary efficacy endpoint of the time to treatment failure, with the risk of failure being reduced by around 65% in the Sativex group. The results of this trial are considered to provide adequate evidence of the benefit of continued long-term treatment with Sativex for patients who are already benefiting from treatment.

In conclusion, there is clear evidence of a substantial treatment-effect of Sativex on the primary efficacy measure, the patient-reported spasticity symptom Numeric Rating Scale (NRS).

In response to the question concerning the potential effect on the self-reported NRS scores of a beneficial effect on mood and other CNS effects associated with cannabinoids, good evidence is provided in particular from those studies where validated rating scales for anxiety and depression were employed (for the purpose of safety evaluations rather than efficacy). These data do not show differences between active and placebo and do not correlate with efficacy measures. The failure of four actuations of Sativex, taken all at once, to be recognised by drug users as desirable in the abuse potential study is also very reassuring that a significant mood-elevating effect is not likely. This is half of the median maintenance dose in the pivotal trial and 1/3 the maximum daily dose and so would be expected to achieve plasma levels substantially greater than would be the case with therapeutic Sativex. The assessor agrees that Sativex is very different from illicit cannabis in pharmacokinetic and central nervous system effect profile and that there is no evidence of confounding of efficacy measures by central nervous system effects unrelated to spasticity.

The clinical relevance of the findings on the NRS scale was addressed. The question of the clinical relevance of a given difference on an efficacy rating scale that does not obviously translate into an estimate of patient benefit is a familiar problem. For example, in psychiatry trials differences from placebo often seem very small in comparison with the total range of the scale employed (less than 10%) and are typically smaller than the magnitude of the placebo response.

In these situations the clinical relevance of the measured treatment effect is generally assessed by looking at the results for responder analyses and results on key secondary efficacy endpoints that are of more clear clinical relevance (but less suitable as a primary efficacy measure). Where available comparisons with an active comparator are also very helpful in showing clinical relevance although no suitable comparator of established efficacy in the spasticity add on indication is available.

The results presented by the applicant for the responder analyses and key secondary efficacy endpoints are persuasive that the measured superiority to placebo on the NRS primary endpoint is of clear clinical significance in this very difficult to treat patient population.

CLINICAL SAFETY

Introduction

The safety dossier includes all available data to March 2009 from 42 GW sponsored studies and from post-marketing experience. It is specifically for Sativex (also described in parts of the dossier as GW-1000 or GW-1000-02 or THC:CBD 1:1) and does not include comprehensive information on other cannabis-based medicines (CBM). The clinical safety summary is comprehensive and thorough.

Sativex has been studied both in people with MS and in other conditions, in both short term placebo-controlled studies, and in long term open-label non-comparative studies. The other indications studied have largely comprised subjects with cancer and chronic neuropathic pain of various origins. This is useful insofar as it allows for a comparison of the AE profile across populations. The safety data has been integrated into three main populations. These are the MS sub-population referred to hereafter as “MS population”; the non-MS sub-population “Non-MS population” and the cancer sub-population “Cancer population”.

Patient exposure

The integrated safety populations are presented for the placebo controlled populations and non-comparative study populations. The cancer sub-population (60 subjects with advanced cancer exposed to Sativex) is presented separately because of the very different AE profile in these patients.

In the comparative integrated MS population 805 subjects were exposed to Sativex; and in non-comparative integrated MS population 1016 subjects received Sativex (see table below). Within the 1016 non-comparative MS subjects exposed to Sativex, 572 subjects were from a 4 week non-comparative Sativex phase of a pivotal study. In the Non-MS comparative integrated population 425 subjects have been exposed to Sativex; and in the non-comparative integrated Non-MS population there have been 598 exposed to Sativex.

In addition, only SAE data from other studies not included in the integrated populations, including phase one and some phase II studies and SAEs from the IIT studies are referred to as “Other population” which included approximately 668 subjects.

Sativex has also been available as a prescription medicine in Canada (for the treatment of neuropathic pain in patients with MS, and for the relief of pain in patients with advanced cancer), and has been fairly widely used in the UK as an unlicensed medicine. Spontaneous reports from this ‘real-world’ experience with Sativex allow for a comparison of clinical trial results with results seen post-marketing. There is 5500 patient years of post-marketing and Named Patient use of Sativex, including more than 2000 patients prescribed Sativex in the UK as an unlicensed medicine and 172 in Spain.

The extent of exposure to Sativex in clinical studies included in the integrated sub-populations is discussed and tabulated below. This table shows the integrated population of subjects with MS, the integrated population with Non-MS subjects and also the cancer subjects.

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)	1016	598	805	425	740	419	60	59
Mean Exposure (Days)	215	240	67	60	71	66	14	14
Total Exposure (Subject Years)	598	393	148	70	144	76	2	2

In the MS population from comparative studies, the mean duration of treatment exposure was 67 days compared with 60 days in the Non-MS population. In the cancer study the mean duration of treatment was 14 days. In the non-comparative studies the mean duration of exposure was 215 days in the MS population compared with 240 in the Non-MS population.

Exposure (Days) to Sativex in Phase III Integrated Comparative and non-comparative studies

	Comparative Studies		Non-comparative Studies	
	MS Sub-sub-population	Non-MS Sub-sub-population	MS Sub-sub-population	Non-MS Sub-sub-population
No of subjects	N=805	N=425	N=1016	N=598
1-14 days	33	45	35	42
15-28 days	61	75	204	30
29-42 days	128	80	390	22
43-84 days	262	35	23	58
85-182 days	321	188	58	84
183-364 days			75	280
365-729 days			106	49
>=730 days			125	33

This table shows that more than 660 subjects have more than six months exposure, and approximately 310 of these subjects have more than a year of exposure to Sativex. Over 300 subjects with MS have more than six months exposure, and 231 subjects with MS have been exposed to Sativex for over one year.

In the MS population approximately two thirds of the participants were female in both active and placebo groups. By contrast in the Non-MS and cancer populations, there was a small excess of males. The gender ratio difference between populations reflects the gender difference in the prevalence of multiple sclerosis.

There were no subjects in any study under the age of 18 years, as the inclusion criteria specified that subjects had to be over 18 year of age. This is acceptable. In the MS population the mean age for subjects receiving active medication was 49 years (range 19-77) and slightly older in the non-MS population at 56 years (range 20-90). All subjects in

the non-comparative studies were recruited from the comparative studies, hence the age distribution in the non-comparative studies is similar. In the cancer population, the mean age was higher (60 years) with a range of 25-88 years.

Many subjects were taking concomitant medications during both the comparative and non-comparative studies in all indications. The table below shows the distribution of some of the common concomitant medications seen in the MS and Non-MS populations taking Sativex, during the comparative studies. The common concomitant medications used were baclofen (for spasticity), amitriptyline (as an antidepressant and/or for neuropathic pain), gabapentin (for neuropathic pain and for spasticity in subjects with MS), benzodiazepines (for spasticity and/or anxiolysis) and opioids (for pain).

Concomitant Medications for Subjects on Sativex During Comparative Studies

MS Population (n=805)		**Non-MS Population (n=425)**
Amitriptyline	98 (12 %)	70 (16%)
Baclofen	326 (41 %)	28 (7%)
Benzodiazepines	127 (16 %)	70 (16%)
Gabapentin	124 (15 %)	123 (29%)
Opioids	156 (19%)	188 (44%)
Strong Opioids	73 (9 %)	87 (20%)

In all studies, a within-subject dose titration regimen according to individual response and tolerability was used. The permitted daily maximum number of sprays was initially 48, but this was gradually reduced during the clinical development of Sativex to 12 sprays. Over all studies, in the MS population, the Sativex subjects used a mean 9.1 (SD 5.07) sprays per day compared with 13.7 (SD 7.49) for the placebo treated subjects. The inter-quartile range for number of sprays per day was 11.3 to 5.7. In the non-comparative MS studies, the mean number of sprays per day was 7.2 (SD 4.3). The profile of study medication administration was similar in the Non-MS and cancer populations.

Assessor's comment

The size of the safety database is acceptable in principle. Much is known about the safety profile of cannabis from the published literature although some important safety issues, in particular the potential for psychiatric adverse events, are still not clearly defined. The key points that the Sativex safety database will need 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.

Listings of Adverse Events

The tables below shows the number of adverse events for Sativex and placebo in the short-term placebo controlled parallel group phase III comparative studies and the long-term open label Sativex extension studies. Details are also provided for those AEs classified as severe. Serious AEs are presented separately below.

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.

Treatment Emergent All-Causality AEs with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; MS Population (1)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)
Overall Subjects with an Event	**628 (78.0%)**	**492 (66.4%)**	**686 (67.5%)**	**123 (15.3%)**	**63 (8.5%)**	**216 (21.3%)**
Cardiac Disorders						
Tachycardia	8 (1.0%)	3 (0.4%)	4 (0.4%)	1 (0.1%)	0	0
Ear and Labyrinth Disorders						
Vertigo	52 (6.5%)	15 (2.0%)	34 (3.3%)	7 (0.9%)	0	3 (0.3%)
Eye Disorders						
Vision blurred	15 (1.9%)	3 (0.4%)	16 (1.6%)	0	0	1 (0.1%)
Gastrointestinal Disorders						
Nausea	77 (9.6%)	42 (5.7%)	98 (9.6%)	4 (0.5%)	2 (0.3%)	14 (1.4%)
Dry Mouth	49 (6.1%)	23 (3.1%)	60 (5.9%)	5 (0.6%)	2 (0.3%)	0
Diarrhoea	44 (5.5%)	29 (3.9%)	84 (8.3%)	5 (0.6%)	1 (0.1%)	19 (1.9%)
Vomiting	28 (3.5%)	16 (2.2%)	57 (5.6%)	4 (0.5%)	3 (0.4%)	17 (1.7%)
Constipation	19 (2.4%)	4 (0.5%)	47 (4.6%)	2 (0.2%)	2 (0.3%)	6 (0.6%)
Oral Pain	17 (2.1%)	16 (2.2%)	48 (4.7%)	2 (0.2%)	0	2 (0.2%)
Oral Discomfort	15 (1.9%)	14 (1.9%)	20 (2.0%)	1 (0.1%)	0	1 (0.1%)
Mouth Ulceration	12 (1.5%)	6 (0.8%)	28 (2.8%)	2 (0.2%)	0	5 (0.5%)
Dyspepsia	11 (1.4%)	12 (1.6%)	26 (2.6%)	0	0	2 (0.2%)
Abdominal pain upper	11 (1.4%)	2 (0.3%)	11 (1.1%)	0	0	2 (0.2%)
Glossodynia	9 (1.1%)	10 (1.3%)	32 (3.1%)	0	1 (0.1%)	3 (0.3%)

Treatment Emergent All-Causality AEs with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; MS Population (2)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)
General Disorders and Administration Site Conditions						
Fatigue	101 (12.5%)	62 (8.4%)	99 (9.7%)	5 (0.6%)	3 (0.4%)	7 (0.7%)
Asthenia	45 (5.6%)	23 (3.1%)	63 (6.2%)	9 (1.1%)	2 (0.3%)	11 (1.1%)
Feeling drunk	24 (3.0%)	3 (0.4%)	19 (1.9%)	2 (0.2%)	0	2 (0.2%)
Feeling abnormal	19 (2.4%)	4 (0.5%)	25 (2.5%)	1 (0.1%)	0	0
Application site pain	16 (2.0%)	17 (2.3%)	27 (2.7%)	1 (0.1%)	1 (0.1%)	0
Pain	10 (1.2%)	17 (2.3%)	29 (2.9%)	1 (0.1%)	4 (0.5%)	3 (0.3%)
Malaise	8 (1.0%)	3 (0.4%)	15 (1.5%)	0	0	3 (0.3%)
Infections and Infestations						
Urinary Tract Infection	71 (8.8%)	66 (8.9%)	164 (16.1%)	3 (0.4%)	3 (0.4%)	22 (2.2%)
Nasopharyngitis	22 (2.7%)	25 (3.4%)	74 (7.3%)	0	0	4 (0.4%)
Pharyngitis	10 (1.2%)	8 (1.1%)	26 (2.6%)	0	0	3 (0.3%)
Viral infection	10 (1.2%)	2 (0.3%)	12 (1.2%)	1 (0.1%)	0	1 (0.1%)
Lower respiratory tract infection	8 (1.0%)	10 (1.3%)	33 (3.2%)	2 (0.2%)	3 (0.4%)	7 (0.7%)
Injury, Poisoning and Procedural Complications						
Fall	12 (1.5%)	4 (0.5%)	43 (4.2%)	1 (0.1%)	0	1 (0.1%)
Metabolism and Nutrition Disorders						
Anorexia	17 (2.1%)	5 (0.7%)	30 (3.0%)	3 (0.4%)	0	1 (0.1%)
Increased appetite	11 (1.4%)	3 (0.4%)	8 (0.8%)	0	0	0
Musculoskeletal and Connective Tissue Disorders						
Muscle Spasms	24 (3.0%)	20 (2.7%)	48 (4.7%)	5 (0.6%)	0	14 (1.4%)
Back Pain	19 (2.4%)	14 (1.9%)	37 (3.6%)	2 (0.2%)	1 (0.1%)	11 (1.1%)

Treatment Emergent All-Causality AEs with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; MS Population (3)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)
Pain In Extremity	16 (2.0%)	19 (2.6%)	35 (3.4%)	5 (0.6%)	5 (0.7%)	10 (1.0%)
Muscular Weakness	11 (1.4%)	10 (1.3%)	30 (3.0%)	0	1 (0.1%)	5 (0.5%)
Arthralgia	9 (1.1%)	3 (0.4%)	32 (3.1%)	1 (0.1%)	0	7 (0.7%)
Nervous System Disorders						
Dizziness	201 (25%)	61 (8.2%)	211 (20.8%)	23 (2.9%)	3 (0.4%)	14 (1.4%)
Somnolence	66 (8.2%)	17 (2.3%)	65 (6.4%)	4 (0.5%)	1 (0.1%)	4 (0.4%)
Headache	49 (6.1%)	56 (7.6%)	82 (8.1%)	6 (0.7%)	3 (0.4%)	8 (0.8%)
Disturbance in Attention	31 (3.9%)	1 (0.1%)	37 (3.6%)	1 (0.1%)	0	0
Dysgeusia	25 (3.1%)	6 (0.8%)	36 (3.5%)	6 (0.7%)	0	5 (0.5%)
Muscle spasticity	26 (3.2%)	25 (3.4%)	21 (2.1%)	2 (0.2%)	4 (0.5%)	2 (0.2%)
Balance disorder	23 (2.9%)	13 (1.8%)	46 (4.5%)	1 (0.1%)	0	2 (0.2%)
Multiple Sclerosis Relapse	20 (2.5%)	24 (3.2%)	46 (4.5%)	2 (0.2%)	2 (0.3%)	11 (1.1%)
Dysarthria	16 (2.0%)	3 (0.4%)	13 (1.3%)	3 (0.4%)	0	1 (0.1%)
Lethargy	12 (1.5%)	5 (0.7%)	26 (2.6%)	2 (0.2%)	0	3 (0.3%)
Paraesthesia	12 (1.5%)	12 (1.6%)	12 (1.2%)	2 (0.2%)	0	1 (0.1%)
Memory Impairment	11 (1.4%)	1 (0.1%)	20 (2.0%)	1 (0.1%)	0	0
Amnesia	9 (1.1%)	2 (0.3%)	13 (1.3%)	1 (0.1%)	0	0
Tremor	9 (1.1%)	6 (0.8%)	10 (1.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Psychiatric Disorders						
Disorientation	33 (4.1%)	6 (0.8%)	21 (2.1%)	4 (0.5%)	2 (0.3%)	2 (0.2%)
Depression	23 (2.9%)	15 (2.0%)	47 (4.6%)	5 (0.6%)	1 (0.1%)	3 (0.3%)
Euphoric Mood	18 (2.2%)	7 (0.9%)	24 (2.4%)	2 (0.2%)	0	2 (0.2%)
Dissociation	14 (1.7%)	1 (0.1%)	12 (1.2%)	2 (0.2%)	0	0
Insomnia	11 (1.4%)	16 (2.2%)	23 (2.3%)	3 (0.4%)	1 (0.1%)	2 (0.2%)

Treatment Emergent All-Causality AEs with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; MS Population (4)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Total (n=1016)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	11 (1.4%)	7 (0.9%)	20 (2.0%)	0	0	1 (0.1%)
Pharyngolaryngeal pain	8 (1.0%)	11 (1.5%)	1 (0.1%)	1 (0.1%)	0	0
Vascular Disorders						
Hypertension	9 (1.1%)	4 (0.5%)	15 (1.5%)	2 (0.2%)	0	1 (0.1%)

Overview of Common Adverse Events

In the MS population, the most commonly reported all-causality AEs (in at least 5% of subjects) in both the comparative and non-comparative studies in order of incidence were dizziness, fatigue, nausea, urinary tract infection, somnolence, vertigo, headache, dry mouth, asthenia and diarrhoea. These events were typically mild or moderate in severity.

Other less commonly reported (incidence >1% but <5%) all-causality AEs were disorientation, disturbance in attention, vomiting, dysgeusia, muscle spasticity, feeling drunk, muscle spasms, balance disorder, nasopharyngitis, depression, multiple sclerosis relapse, constipation, feeling abnormal, back pain, euphoric mood, oral pain, application site pain, anorexia, pain in extremity, dysarthria, vision blurred, oral discomfort, dissociation, mouth ulceration, fall, lethargy, paraesthesia, dyspepsia, abdominal pain upper, increased appetite, muscular weakness, memory impairment, insomnia, cough, pain, pharyngitis, viral infection, glossodynia, arthralgia, amnesia, tremor, hypertension, tachycardia, malaise, lower respiratory tract infection, and pharyngolaryngeal pain. These events were typically mild or moderate in severity. Only dizziness (2.9% vs. 0.4%) and asthenia (1.1% vs. 0.3%) were reported as severe in more than 1% of patients

A number of these CNS AEs are anticipated with the use of cannabinoids and also as manifestations of MS and due to concomitant medication. In the earlier comparative studies the subjects were asked to titrate up their dose until either a therapeutic benefit was reached or unacceptable adverse side effects were experienced. In the new studies GWSP0604 and GWMS0501 upwards dose titration during the first week of exposure was more gradual than in the earlier studies and in these studies there appeared to be fewer reports of the most common AEs. The applicant argues that this shows that the rate of increase of dose during the dose titration period plays a significant role in determining the AE rate. However it is difficult to make such comparisons across trials as there may be differences in study design and/or conduct that could produce such differences.

In the MS population, the common CNS all-causality AEs showing an excess over placebo rates of greater than 1% in the comparative studies were: dizziness, fatigue, somnolence, vertigo, disorientation, disturbance in attention, feeling drunk and balance disorder. Other

less common all-causality CNS AEs, where there was not a notable difference compared with the reported rate in the placebo subjects (less than 1% difference) were: headache, muscle spasticity, depression, multiple sclerosis relapse, and lethargy.

The pattern of adverse events seen in the long-term studies was generally similar to that seen in the short term Phase III studies.

Assessor's comment
The excess over placebo of typical cannabinoid CNS effects including is not inconsiderable. In the MS population the rates were dizziness (25% vs. 8%), somnolence (8.2% vs. 2.3%), disorientation (4.1% vs. 0.8%), disturbance in attention (3.9% vs. 0.1%), and balance disorder (2.9% vs. 1.8%). Other effects not classified as CNS but which might reflect CNS effects showed a similar pattern including vertigo (6.5% vs. 2%), fatigue (12.5% vs. 8.4%), feeling drunk (3% vs. 0.4%), asthenia (5.6% vs. 3.1%).

The AE profile is broadly in line with that expected from the known pharmacology of cannabis and the high level of morbidity and polypharmacy in this patient population. The issues are mostly of tolerability rather than safety, although there is potential for Sativex to worsen overall disability in some patients and the risk of accidental injury may be increased. These are the principal potential concerns that are identified from the AE listings.

There is little indication of a clear dose relationship of the incidence of common AEs, although this is likely to be at least partly a reflection of the lack of studies designed in such a way as to be able to provide clear evidence of dose-response (just as this is the case also for efficacy).

As indicated above there appeared to be fewer reports of the most common AEs in the new studies GWSP0604 and GWMS0501 in which upwards dose titration during the first week of exposure was more gradual than in the earlier studies. This might suggest that the AE rate using this slower titration as advised in the proposed SPC might be lower than those reported above. This also makes some sense on theoretical grounds. However it is difficult to make such comparisons across trials and no clear conclusions can be drawn.

Comparison with the non-MS population
Separate tables are presented for the MS population and non-MS population. This facilitates an appraisal of the extent to which MS patients might be particularly susceptible to certain undesirable effects such as psychiatric morbidity and falls.

All Causality Adverse Events with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; Non-MS Population (1)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-Comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)
Overall Subjects with an Event	**359 (84.5%)**	**282 (67.3%)**	**494 (82.6%)**	**83 (19.5%)**	**51 (12.2%)**	**146 (24.4%)**
Cardiac Disorders						
Palpitations	6 (1.4%)	4 (1.0%)	6 (1.0%)	1 (0.2%)	0	1 (0.2%)
Ear and Labyrinth Disorders						
Vertigo	12 (2.8%)	4 (1.0%)	17 (2.8%)	4 (0.9%)	0	1 (0.2%)
Eye Disorders						
Vision blurred	10 (2.4%)	6 (1.4%)	15 (2.5%)	1 (0.2%)	0	2 (0.3%)
Gastrointestinal Disorders						
Nausea	70 (16.5%)	43 (10.3%)	83 (13.9%)	7 (1.6%)	4 (1.0%)	11 (1.8%)
Dry Mouth	42 (9.9%)	11 (2.6%)	53 (8.9%)	1 (0.2%)	0	1 (0.2%)
Vomiting	37 (8.7%)	21 (5.0%)	45 (7.5%)	9 (2.1%)	7 (1.7%)	12 (2.0%)
Diarrhoea	27 (6.4%)	25 (6.0%)	40 (6.7%)	7 (1.6%)	5 (1.2%)	7 (1.2%)
Oral Pain	17 (4.0%)	11 (2.6%)	20 (3.3%)	2 (0.5%)	0	0
Abdominal pain upper	14 (3.3%)	5 (1.2%)	14 (2.3%)	2 (0.5%)	0	2 (0.3%)
Constipation	11 (2.6%)	9 (2.1%)	14 (2.3%)	(0.5%)	0	4 (0.7%)
Dyspepsia	10 (2.4%)	10 (2.4%)	18 (3.0%)	3 (0.7%)	2 (0.5%)	2 (0.3%)
Oral discomfort	10 (2.4%)	12 (2.9%)	8 (1.3%)	1 (0.2%)	0	1 (0.2%)
Mouth ulceration	9 (2.1%)	9 (2.1%)	27 (4.5%)	1 (0.2%)	0	2 (0.3%)
Abdominal pain	5 (1.2%)	5 (1.2%)	7 (1.2%)	0	4 (1.0%)	1 (0.2%)
Hypoaesthesia oral	5 (1.2%)	2 (0.5%)	4 (0.7%)	0	0	1 (0.2%)
General Disorders and Administration Site Conditions						
Fatigue	46 (10.8%)	19 (4.5%)	52 (8.7%)	6 (1.4%)	4 (1.0%)	5 (0.8%)
Feeling Drunk	24 (5.6%)	4 (1.0%)	36 (6.0%)	5 (1.2%)	1 (0.2%)	4 (0.7%)
Application Site Pain	15 (3.5%)	9 (2.1%)	15 (2.5%)	1 (0.2%)	0	0
Oedema peripheral	9 (2.1%)	6 (1.4%)	15 (2.5%)	2 (0.5%)	0	3 (0.5%)
Feeling abnormal	9 (2.1%)	2 (0.5%)	13 (2.2%)	2 (0.5%)	0	1 (0.2%)

All Causality Adverse Events with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; Non-MS Population (2)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-Comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)
Application Site Irritation	9 (2.1%)	9 (2.1%)	10 (1.7%)	0	0	1 (0.2%)
Malaise	6 (1.4%)	3 (0.7%)	13 (2.2%)	0	0	4 (0.7%)
Thirst	6 (1.4%)	1 (0.2%)	5 (0.8%)	1 (0.2%)	0	1 (0.2%)
Pain	5 (1.2%)	2 (0.5%)	24 (4.0%)	0	0	5 (0.8%)
Asthenia	5 (1.2%)	2 (0.5%)	13 (2.2%)	3 (0.7%)	1 (0.2%)	2 (0.3%)
Influenza like illness	5 (1.2%)	1 (0.2%)	9 (1.5%)	1 (0.2%)	0	1 (0.2%)
Infections and Infestations						
Nasopharyngitis	21 (4.9%)	16 (3.8%)	30 (5.0%)	2 (0.5%)	1 (0.2%)	1 (0.2%)
Urinary Tract Infection	14 (3.3%)	18 (4.3%)	33 (5.5%)	0	2 (0.5%)	2 (0.3%)
Lower Respiratory Tract Infection	12 (2.8%)	12 (2.9%)	30 (5.0%)	0	0	1 (0.2%)
Influenza	6 (1.4%)	4 (1.0%)	16 (2.7%)	1 (0.2%)	0	1 (0.2%)
Injury, poisoning and procedural complications						
Accident	6 (1.4%)	2 (0.5%)	11 (1.8%)	0	1 (0.2%)	4 (0.7%)
Metabolism and Nutrition Disorders						
Anorexia	13 (3.1%)	6 (1.4%)	19 (3.2%)	1 (0.2%)	0	2 (0.3%)
Increased appetite	13 (3.1%)	3 (0.7%)	6 (1.0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Hypoglycaemia	10 (2.4%)	6 (1.4%)	14 (2.3%)	3 (0.7%)	0	1 (0.2%)
Musculoskeletal and Connective Tissue Disorders						
Back Pain	7 (1.6%)	10 (2.4%)	18 (3.0%)	1 (0.2%)	3 (0.7%)	3 (0.5%)
Pain In Extremity	5 (1.2%)	8 (1.9%)	19 (3.2%)	1 (0.2%)	3 (0.7%)	4 (0.7%)
Joint swelling	5 (1.2%)	3 (0.7%)	5 (0.8%)	0	1 (0.2%)	0
Sensation of heaviness	5 (1.2%)	0	1 (0.2%)	1 (0.2%)	0	1 (0.2%)

All Causality Adverse Events with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; Non-MS Population (3)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-Comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)
Nervous System Disorders						
Dizziness	138 (32.5%)	36 (8.6%)	144 (24.1%)	14 (3.3%)	2 (0.5%)	18 (3.0%)
Headache	34 (8.0%)	33 (7.9%)	42 (7.0%)	4 (0.9%)	4 (1.0%)	8 (1.3%)
Dysgeusia	31 (7.3%)	8 (1.9%)	56 (9.4%)	2 (0.5%)	0	6 (1.0%)
Somnolence	29 (6.8%)	14 (3.3%)	49 (8.2%)	2 (0.5%)	1 (0.2%)	7 (1.2%)
Lethargy	16 (3.8%)	4 (1.0%)	13 (2.2%)	0	1 (0.2%)	2 (0.3%)
Disturbance in attention	14 (3.3%)	3 (0.7%)	17 (2.8%)	1 (0.2%)	1 (0.2%)	2 (0.3%)
Memory impairment	11 (2.6%)	4 (1.0%)	19 (3.2%)	1 (0.2%)	0	2 (0.3%)
Tremor	8 (1.9%)	2 (0.5%)	7 (1.2%)	1 (0.2%)	0	2 (0.3%)
Amnesia	6 (1.4%)	2 (0.5%)	10 (1.7%)	0	0	3 (0.5%)
Neuropathy peripheral	6 (1.4%)	4 (1.0%)	9 (1.5%)	3 (0.7%)	2 (0.5%)	2 (0.3%)
Balance disorder	5 (1.2%)	4 (1.0%)	19 (3.2%)	1 (0.2%)	1 (0.2%)	3 (0.5%)
Sedation	5 (1.2%)	1 (0.2%)	4 (0.7%)	0	0	0
Psychiatric Disorders						
Disorientation	19 (4.5%)	2 (0.5%)	29 (4.8%)	2 (0.5%)	0	5 (0.8%)
Depression	18 (4.2%)	6 (1.4%)	41 (6.9%)	2 (0.5%)	0	2 (0.3%)
Dissociation	14 (3.3%)	1 (0.2%)	12 (2.0%)	3 (0.7%)	1 (0.2%)	1 (0.2%)
Euphoric Mood	10 (2.4%)	1 (0.2%)	10 (1.7%)	0	0	2 (0.3%)
Anxiety	7 (1.6%)	2 (0.5%)	16 (2.7%)	2 (0.5%)	1 (0.2%)	2 (0.3%)
Panic attack	7 (1.6%)	2 (0.5%)	2 (0.3%)	0	0	1 (0.2%)
Insomnia	5 (1.2%)	12 (2.9%)	19 (3.2%)	3 (0.7%)	3 (0.7%)	2 (0.3%)
Agitation	5 (1.2%)	1 (0.2%)	0	1 (0.2%)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngolaryngeal pain	13 (3.1%)	9 (2.1%)	11 (1.8%)	1 (0.2%)	0	1 (0.2%)
Dyspnoea	7 (1.6%)	6 (1.4%)	15 (2.5%)	0	0	2 (0.3%)

All Causality Adverse Events with an Incidence of at Least 1% compared to All Causality Severe Adverse Events for Sativex in Comparative Studies; Integrated Safety; Non-MS Population (4)

	All Causality			Severe All Causality		
	Comparative Subjects		Non-Comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)	Sativex Total (n=425)	Placebo Total (n=419)	Total (n=598)
Throat irritation	6 (1.4%)	1 (0.2%)	6 (1.0%)	1 (0.2%)	0	0
Cough	5 (1.2%)	11 (2.6%)	22 (3.7%)	1 (0.2%)	1 (0.2%)	2 (0.3%)
Skin and Subcutaneous Tissue Disorders						
Rash	6 (1.4%)	6 (1.4%)	6 (1.0%)	0	0	0
Vascular disorders						
Hypertension	5 (1.2%)	4 (1.0%)	13 (2.2%)	1 (0.2%)	0	3 (0.5%)
Flushing	5 (1.2%)	2 (0.5%)	1 (0.2%)	0	0	0

Source: ISS, Non-MS Tables B.3.1.1 and B.3.1.4;,Appendix 7

Assessor's comment on MS population vs. non-MS population

The pattern in the non-MS and cancer populations were generally similar. In particular there was no clear signal of a greater susceptible of MS patients to certain undesirable effects such as psychiatric morbidity and falls. Such trends as there were if anything tended to be in the direction of more such side effects in the non-MS population.

Serious adverse events

During the comparative studies, the overall incidence of all-causality treatment-emergent SAEs was higher amongst subjects receiving Sativex (4.6%) compared with those receiving placebo (3.2%). The SOC with the highest incidence was Infections and Infestations (Sativex: 1.6%, placebo: 1.5%) followed by the Nervous system disorders SOC (Sativex: 0.7%, placebo: 0.9%). In the Infections and Infestations SOC, the most frequently reported SAE was urinary tract infection (Sativex: 0.6%, placebo 0.5%) whilst in the Nervous system disorder SOC multiple sclerosis relapse was the most commonly reported SAE (Sativex and placebo: 0.4% each).

During comparative studies, the overall incidence of treatment-emergent SAEs amongst subjects receiving Sativex in all SOCs was higher in the Non-MS (6.6%) compared to the MS population (4.6%). In both populations, the reported incidence of treatment-emergent SAEs amongst subjects on Sativex was less than 1% in all SOCs, except in the Infections and Infestations where the incidence was the same (1.6%) for both.

A similar pattern in overall incidence of treatment-emergent SAEs was also observed in the non-comparative studies: Non-MS (10.5%) compared to MS population (8.3%).

In both the MS and non-MS population, in non-comparative studies it was only in the Nervous system disorders SOC where the incidence of treatment-emergent SAEs was 2% or more (MS 2.0% compared to Non-MS 2.7%). The higher incidence of nervous system SAE in both populations is not unexpected given the nature of the study populations i.e. MS patients, diabetic patients and those with various pre-existing neurological disorders such as brachial plexus and spinal cord injuries. SAEs in the Infections and Infestations SOC occurred with a much higher incidence (2.7%) amongst the MS compared to the Non-MS

populations. This could possibly be explained by the increased incidences in urinary tract infection associated with detrusor instability commonly seen in MS.

The overall incidence of treatment-emergent SAEs observed in the non-comparative studies was 10.5%. SAEs in the Nervous system disorder SOC occurred with a higher incidence (2.7%) than in comparative studies. The other SOCs with high incidence of treatment-emergent SAEs were Infections and Infestations and Gastrointestinal disorders (1.5% each) and General disorders and administration site conditions SOC (1.3%).

In the phase III double blind studies the number of serious adverse events was small and other than relapse of MS and transient ischaemic attack (2 Sativex vs. 1 placebo in non-MS population), none of the events were reported in more than a single patient.

Assessor's comment
Most of these SAEs are of a nature and frequency that would be expected in this patient population regardless of study medication. 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, which is reassuring. The only area of potential concern that is identified here is the occurrence of psychiatric disorders in two patients and a confusional state in one other. This is considered in more detail below.

In the open label extension studies again most of these SAEs were 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 four patients; paranoid delusion in one, suicidal ideation in one and a suicide attempt in another, and one SAE report of disorientation. However the number is too small to draw any conclusions and MS is associated with psychiatric morbidity in any case. This aspect requires continued vigilance. There do not appear to be any reported SAEs in which CNS side effects caused major personal safety incidents, although this is clearly a potential issue (e.g. with food and hot drink preparation). The occurrence of ventricular extrasystoles and bigeminy is not of particular concern. However it should be included in the SPC, particularly in view of the cardiac effects reported in the clinical 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). The SAEs reported here are adequately addressed in the SPC.

Loss of consciousness
Cases of loss of consciousness and syncope were reported. The table below shows all AEs that have been reported for all of the terms described above, from comparative clinical trials, open-label non-comparative clinical studies, and from post-marketing experience.

Preferred Term	Comparative Studies		Non-Comparative Studies	Post Marketing SADRs
	Sativex (n=805)	Placebo (n=741)	Sativex (n=1016)	
Syncope	5 (0.6%)	2 (0.3%)	16 (1.6%)	0
Loss of Consciousness	1 (0.1%)	1 (0.1%)	0	0
Altered State of Consc	0	0	2 (0.2%)	0
Depressed Level of Consc	1 (0.1%)	1 (0.1%)	3 (0.3%)	0
Circulatory collapse	0	0	4 (0.4%)	0
Coma	0	0	0	0
Concussion	0	0	1 (0.1%)	0
Syncope vasovagal	0	1 (0.1%)	3 (0.3%)	1*
Presyncope	1 (0.1%)	0	2 (0.2%)	0

There were no SAEs in the MS population of 805 subjects taking Sativex in controlled clinical studies. There was one SAE of syncope and one SAE of depressed level of consciousness in 741 subjects with MS taking placebo. One subject (of 1016) in non-comparative studies (GWEXT0102) experienced a SAE of depressed level of consciousness (MCN 200604GBGW0291; the subject recovered) which was considered unrelated to study medication.Similarly there were reports, mostly of syncope, in the non-MS patient population but with no clear sign of an excess over placebo.

Assessor's Comments

The applicant concludes that loss of consciousness has also occurred in placebo group, may be a feature of MS and may be associated with concomitant medication (beta-interferon for example). The narrative summaries are consistent with a possible causal role of Sativex in a very small number of cases and possibly related to concomitant treatments but there were also cases with placebo and there is no clear evidence of an association with Sativex. The SPC mentions syncope and fainting episodes in section 4.8 and in the driving warning (section 4.7). This is satisfactory.

Psychiatric adverse events

Patients with MS have a significant background rate of psychiatric co-morbidity and cannabinoids in recreational doses are believed to be associated with psychiatric morbidity. The potential for psychiatric adverse events in association with long-term use of Sativex, whether de novo or exacerbating existing morbidity, therefore requires careful consideration. Adverse events which code to the System Organ Class of Psychiatric Disorders are common with Sativex than placebo. The majority of the events seen are reported to have been of mild severity, transient and did not require cessation of treatment.

The frequency of psychiatric adverse events reported in clinical trials is presented below.

All causality AEs in the Psychiatric disorders SOC occurring with a frequency greater than 2% in the MS and non-MS populations

	MS Population-All Causality			Non-MS Population-All Causality		
	Comparative Studies		Non-Comparative Studies	Comparative Studies		Non-Comparative Studies
	Sativex (N=805)	Placebo (N=741)	Sativex (N=1016)	Sativex (N=425)	Placebo (N=419)	Sativex (N=598)
Subjects with Event in System	142 (17.6%)	58 (7.8%)	165 (16.2%)	81 (19.1%)	39 (9.3%)	132 (22.1%)
Disorientation	33 (4.1%)	6 (0.8%)	21 (2.1%)	19 (4.5%)	2 (0.5%)	29 (4.8%)
Depression	23 (2.9%)	15 (2.0%)	47 (4.6%)	18 (4.2%)	6 (1.4%)	41 (6.9%)
Euphoric Mood	18 (2.2%)	7 (0.9%)	24 (2.4%)	10 (2.4%)	1 (0.2%)	10 (1.7%)
Dissociation	14 (1.7%)	1 (0.1%)	12 (1.2%)	14 (3.3%)	1 (0.2%)	12 (2.0%)
Insomnia	11 (1.4%)	16 (2.2%)	23 (2.3%)	5 (1.2%)	12 (2.9%)	19 (3.2%)
Anxiety	7 (0.9%)	7 (0.9%)	16 (1.6%)	7 (1.6%)	2 (0.5%)	16 (2.7%)
Panic Attack	1 (0.1%)	0	6 (0.6%)	7 (1.6%)	2 (0.5%)	2 (0.3%)
Agitation	2 (0.2%)	0	2 (0.2%)	5 (1.2%)	1 (0.2%)	0

The occurrence of serious psychiatric adverse events reported in clinical trials is discussed by category in the sub-sections below.

Psychosis

Psychosis possibly related to Sativex, has been reported in a five clinical trial patients, three in the MS population and two in the non-MS population.

MS population:

1. A 56-year-old male patient became agitated, irritable and paranoid one day after receiving his last dose of Sativex. These events resolved completely after four days supportive treatment. Both the investigator and the company attributed them to withdrawal of Sativex.
2. A 55-year-old female patient had been receiving Sativex (8 sprays daily) for almost 2 years when she gradually developed paranoid ideas and delusional beliefs. The dose of Sativex was halved, and the symptoms fully resolved within a month.
3. A 38-year-old male patient developed altered mood and somnolence along with non-serious paranoia one day after commencing open label Sativex. The drug was temporarily withdrawn and the symptoms rapidly resolved. Sativex was restarted two days later and continued for three weeks at which point it was withdrawn again.

Non-MS population:

4. A 30-year-old male patient became paranoid and confused one week after beginning Sativex treatment. The medication was withdrawn and the symptoms disappeared one day later. The patient was also found to have a urinary tract infection which the applicant states may have been a confounding factor although on balance, it was felt the symptoms were probably related to Sativex.
5. A 49-year-old male patient developed paranoia and non-serious hallucinations approximately 4 months after commencing open-label Sativex (18 sprays daily). He was receiving numerous other medications including oxycodone. Sativex was withdrawn, and the hallucinations and paranoia resolved fully.

There is clear evidence that recreational cannabis can produce a transient toxic psychosis in larger doses or in susceptible individuals, which is said to characteristically resolve within a week or so of abstinence (Johns 2001). Transient psychotic episodes as a component of acute intoxication are well documented (Hall et al 1994). 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 (Arsenault et al 2004). However, this remains a controversial issue, and a causal link between cannabis smoking and schizophrenia has not yet been established (Degenhardt and Hall 2002). The level of cannabinoid exposure in 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. The clinical trial safety data for Sativex are suggestive of a risk of toxic psychosis developing both in the short/medium term or following long term use. However this is based on just 5 case reports in which there are various confounding factors so the link with Sativex is considered to be likely rather than proven. The SPC and PIL indicate the possibility of such a risk.

Hallucinations

In the comparative studies to date there have been 11 reports of hallucinations, including visual and auditory hallucinations, related to Sativex, of which all but one, were rated mild or moderate. 10 of these cases resolved completely within a week, the other within 2 weeks. Transient hallucinations are well known to occur in association with recreational cannabis use (Johns 2001). The causal relation to the use of Sativex is not proven but it may have been a precipitating cause in a small number of cases. The proposed SPC includes “hallucination (unspecified, auditory, visual)” in the section 4.8 listings. This is satisfactory.

Paranoia

Paranoia does not necessarily indicate psychosis unless held with delusional intensity. It was reported in 12 patients in association with Sativex. It was part of a psychotic syndrome in one patient in association also with 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 (all within one month). Additionally, there was one patient found with episode of paranoia on placebo, which was not considered serious. Three cases of 'thinking abnormal' of moderate intensity were reported, all resolved completely within one week. In non-comparative studies (n = 1016) there were five reports of paranoia. Paranoia is well recognised as a manifestation of acute intoxication during recreational cannabis use (Tart 1970). The clinical trial safety data seem to indicate that paranoia may occur in association with Sativex, but importantly it appears to be resolvable with dose reduction or cessation of treatment and there have been no reports of the precipitation of a chronic mental illness.

Depression

Patients with MS have significant co-morbidity of mood disorder, notably depression. Assessment of mood was undertaken in a number of the placebo-controlled clinical studies including the most recent clinical study, GWSP0604. Scales included the Beck Depression Inventory, Hospital Anxiety and Depression Scale, and the EQ-5D.

Within the clinical trials database the frequency of depression as an AE was 2.9% on Sativex compared with 2.0% on placebo. In the most recent clinical study, GWSP0604, where the rate of initial dose increase was slower, there was a frequency of depression of 1% in 592 subjects with MS during Phase A. During Phase B, the rate was 1.6% on Sativex compared with 0.9% on placebo.

In conclusion there is a trend towards higher rates of depression in patients treated with Sativex compared with placebo and causal effect cannot be concluded on the data available. his

Suicidality

Patients with MS have an understandably high rate of suicidal ideation and suicide, as much as seven times higher than the background rate.

There were three events of suicidal ideation in subjects taking Sativex (events) compared with one for placebo, (note that the number of patients treated with active and placebo are unequal). There were no such events in comparative studies in the Non-MS subject population. In non-comparative studies involving more than 800 patient years of exposure to Sativex, there has been one event of suicidal ideation in the MS population, but three events of suicidal ideation and two events of suicide attempt in the Non-MS population.

There have been two successful suicides, one spontaneous report in a patient with MS, and one in an open-label non-comparative study in a subject with spina bifida who took an overdose of amitriptyline. Both events were considered to be unrelated to Sativex.

The assessor agrees with the applicant that with such small numbers of events, and in a condition where an increased rate of suicidal ideation and suicide is well-documented, it is not possible to draw any firm conclusions about causality.

Susceptibility of the MS population to Sativex induced psychiatric morbidity

There was a higher incidence of psychiatric AEs in MS patients than in non- MS patients treated with Sativex in clinical trials in other indications, which is not surprising as there is known to be a high incidence of psychiatric morbidity in MS. In this context a key issue of whether Sativex might have more potential to cause psychiatric morbidity in the MS population than in the general population. There was however no evidence of a greater excess over placebo in MS patients than in other (non-cancer) patients that might suggest they are more susceptible to psychiatric AEs.

Assessor's conclusions on psychiatric morbidity

The clinical expert accepts that "in view of the known psychoactivity of THC it would be surprising if Sativex did not produce some unwanted psychiatric effects", but argues that "the profound differences from cannabis in terms of constituents, pharmacokinetics and intention of the recipient would be expected to modulate these effects".

Psychiatric AEs occurred more frequently in the Sativex than placebo groups. The majority of events occur early in treatment, and most were of mild or moderate intensity and self limiting. 17 out of 805 (2%) subjects withdrew from Sativex as a result of psychiatric AEs.

There was no signal that MS patients are more susceptible to psychiatric AEs than other (non-cancer) patients.

In view of the ongoing controversy about a possible link between heavy use of recreational cannabis in adolescence and subsequent increased risk of serious functional psychosis (schizophrenia) in adulthood, the incidence, severity and persistence of hallucinations and delusional beliefs in subjects receiving Sativex was monitored. There seems to be no evidence from controlled clinical studies to date to indicate that Sativex is likely to pose any long-term or irreversible neuropsychiatric risk to patients. Indeed no cases of functional psychiatric illness were reported to have occurred in patients receiving Sativex, even though substantial numbers of subjects have received the drug over an extended period. This is an important finding but does not exclude the possibility that Sativex could precipitate psychiatric illness in a small number of vulnerable individuals.

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. The few reported cases of suicidal ideation and suicide during the use of Sativex were all associated with 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.

Similarly there is no signal of a higher risk of psychosis in patients treated with Sativex but this is thought to be an issue with recreation cannabis (which typically involves much higher drug exposure) and the possibility of an association cannot be ruled out.

According to the SPC Sativex is contraindicated if there is 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. This might be considered to be over-cautious but at the present time erring on the side of caution is sensible.

In addition to the tabulated listings the following paragraphs are included in the SPC (4.8):

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

transient CNS effects and are generally mild to moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of Sativex medication.

Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In any of these circumstances, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved.

The wording is satisfactory.

Safety related to drug-drug interactions and other interactions
Many subjects participating in the comparative studies were receiving numerous medications within seven days of the start of study medication, or were receiving drugs concomitantly during the studies on a steady dose. A review is presented in the clinical summary of the data regarding possible interactions with the most common concomitant medications administered in the subject populations studied, amitriptyline, baclofen, gabapentin, benzodiazepines, opioids and strong opioids.

Assessor's comment
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. This is satisfactory.

Tolerance, withdrawal, rebound and addiction potential
The sudden withdrawal of any medicine with central nervous system effects (psychoactivity) can be problematic, and the consequences of the sudden withdrawal of Sativex have been studied within both an open-label and a randomised withdrawal study.

The company reports that there have been no reports of drug abuse associated with Sativex. Although Sativex clearly has abuse potential as shown by the CNS effects experienced by subjects in the high dose QT study, this would seem to be relatively 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 small compared to that observed with alcohol.

A drug interruption sub-study was performed in 25 MS patients who had been maintained on Sativex for at least one year in the extension part of study GWMS0001 to investigate the potential for a withdrawal syndrome. At the end of a two week abstinence period, all new adverse events were recorded and subjects were asked to rate their MS symptoms as 'much worse', 'worse', 'no change', 'better' or 'much better. No subject met the criteria recently proposed for a cannabis withdrawal syndrome (Budney et al., 2004). Five subjects (20%) resumed Sativex prematurely because of re-emergence of unacceptable MS-related

symptoms. Almost half (46%) experienced at least one symptom that has been reported in connection with abrupt withdrawal from regular use of recreational cannabis, such as hot and cold feelings, interrupted sleep, emotional lability, tiredness, intoxication or vivid dreams. However, these did not occur in a consistent pattern or time-profile and no subjects withdrew from the study as a result. Abstinence from Sativex was associated with re-emergence of MS-related symptoms in most subjects. There were no SAEs associated with the drug interruption study. These 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.

Assessor's comment
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.

Abuse potential and effects on cognition and memory
The Applicant has carried out an abuse liability study GWCP0605, in which 30 subjects with a history of recreational marijuana use assessed the 'like-ability' and value of a range of three doses of Sativex compared with THC alone (in the form of Marinol, dronabinol) and placebo. Secondary objectives were safety profile and impact on measures of cognitive and psychomotor performance. It was a randomized, double-blind, balanced, placebo-controlled, crossover study with 6 treatment sessions separated by 7 - 21 days. The study was blinded by over-encapsulating and a double dummy.

The following doses were administered:
- Placebo
- Sativex 4 sprays
- Sativex 8 sprays
- Sativex 16 sprays
- Marinol 20 mg
- Marinol 40 mg

Serial pharmacodynamic evaluations consisted of Addiction Research Center Inventory (ARCI) scales, Drug Liking and other subjective effects VASs, Subjective Drug Value (SDV), Drug Similarity VASs, Choice Reaction Time (CRT), Divided Attention (DA), and Sternberg Short-Term Memory (STM) tests.

Mean maximum effect (Emax), mean minimum effect (Emin), area under the effect curve to 24 hours (AUE24), time of peak effect (TEmax or TEmin), and/or mean scores at each timepoint were calculated for the above pharmacodynamic measures.

Results
Marinol was associated with significant effects compared to placebo on measures of balance of effects, positive effects, cannabinoid effects, sedative and other relevant subjective effects at both the 20 mg and 40 mg doses. These results demonstrate the known effects of Marinol at these doses and its significant abuse potential and serve to valid the study sensitivity.

Sativex 4 sprays had effects that were modestly greater than placebo but not significantly different to placebo for the primary variables.

Sativex 8 sprays had significantly greater Emax values compared to placebo on most balance and positive measures but not on a number of measures of other subjective effects.

Most AUE values were not significantly different from placebo at either dose which appears to reflect a relatively short duration of effects at these doses..

Sativex 16 sprays was significantly different from placebo on most measures, including both Emax and AUE parameters.

The results demonstrate that Sativex 8 sprays has modest abuse potential, and Sativex 16 sprays has substantial abuse potential when administered as a single dose. As the typical daily dose of 8 sprays and the maximum recommended dose of 12 sprays are not substantially different from these levels (but administered in more divided doses) the potential for abuse and diversion is not insignificant.

On a nominal dose-per-dose basis, Sativex effects were moderately lower than those of Marinol; the effects of Sativex 43.2 mg were intermediate between those of Marinol 20mg and 40 mg. There are big PK differences between oral and Marinol and sublingual Sativex so it is fairly meaningless to say that on a dose-per-dose basis Sativex has less abuse potential. This comparison does however raise the question of how much THC is absorbed from Sativex sublingually and how much is absorbed enterally following absorption. Dose-adjusted AUCs of THC and 11-OH-THC were similar between Marinol and Sativex but C_{max} for Marinol was higher and levels declined more rapidly. Since the first pass metabolism is said to be 90+% this suggests that much of a dose of Sativex is swallowed rather than absorbed transmucosally. In any event the lower peak and "flatter" curve seen with Sativex is preferable so there is no concern.

No significant differences between Sativex and placebo are reported on short-term memory, manual tracking, attention, or accuracy. There was also little effect of Marinol on these measures so the tests might lack sensitivity and the applicant's conclusion that there was no evidence of cognitive impairment caused by Sativex is flawed. The Applicant has committed to monitor mood and cognition as part of the post-marketing risk management plan.

Overall, Sativex 16 sprays (84.6%) and Marinol 40 mg (84.0%) had the highest incidences of AEs followed by Marinol 20 mg (70.8%) and Sativex 8 sprays (66.7%). Placebo and Sativex 4 sprays had the lowest incidence of AEs (both 50%).

Similar incidences of AEs were observed between comparable dose levels of Sativex and Marinol, (i.e., Sativex 8 sprays and Marinol 20 mg and Sativex 16 sprays and Marinol 40 mg). The AE profile, much of which was considered by investigators to be related to the study drugs, was generally an exaggerated version of the general safety database reflecting the high single doses. There were no serious AEs.

In conclusion Sativex had significant abuse potential that was comparable to Marinol at the 8-spray dose and above. Marinol is approved in the US but not the UK. The clinical expert states that the potential for addiction to, abuse of and diversion of Sativex is very low, if present at all but concedes that this should be monitored as part of a post-registration risk management plan. The assessor does not agree. Considerable abuse potential has been demonstrated but this should be potentially manageable as with opioids for chronic pain and patient population abuse of Sativex is not considered to be an issue of great concern, subject to sensible precautions.

Effects on the risk of falls

Falls in patients with MS are a significant hazard. The known psychomotor effects of cannabinoids and the AE profile of Sativex suggest a potential for an increased risk. Effects on muscle tone could also in theory affect susceptibility to falls.

Falls were commonly reported in the comparative and non-comparative studies. In the MS clinical trial population there was slight preponderance of falls in subjects taking Sativex (1.5%) compared with placebo (0.5%), although in the non-MS population there were more subjects taking placebo who fell (0.5% on Sativex: 1.4% on placebo). The incidence of falls reported in the non-comparative MS population (n=14, 1.4%) was essentially the same as that reported for Sativex in the comparative studies.

In the most recent key efficacy study, GWSP0604 there were no falls in either the Sativex or placebo treated groups during the placebo-controlled portion of the study. In this study, the rate of increase of dose during initial dose titration was slower than in all other studies.

There were 2 serious adverse events of a fall in subjects with MS taking Sativex, one in a comparative study in a subject receiving Sativex and the other in a non-comparative study. Both were considered unrelated to Sativex and resolved fully.

Assessor's comment

Although there were more falls in the MS subjects taking Sativex than in those taking placebo, the opposite is the case with Non-MS subjects. This could support the theoretical possibility that an effect of Sativex on muscle tone could increase susceptibility to falls in some patients. The available data are insufficient to draw firm conclusions at the present time and this should be addressed in the risk management plan.

Effects on Ability to Drive and Use Machines

The clinical expert states that with regard to driving, the absence of short-term effects on cognition in the abuse potential study is reassuring. However the sensitivity of this study is questioned as there was no validation with a positive control and it is apparent that the first few weeks of treatment are associated with dizziness, vertigo and somnolence, all of which could affect driving ability. The recommendation in the SmPC that subjects should not drive until they have determined that they are not experiencing such events seems sensible but the PIL advice needs to be much more cautious. In clinical studies 3 adverse events of a road traffic accident were reported, 2 of which were on placebo and none of which were considered related to study drug.

Application site reactions and leukoplakia

Oral leukoplakia is a premalignant lesion of the oral mucosa caused by prolonged local irritation. It is seen quite commonly in the general population (1 – 5%, Sciubba 1995), and the incidence is increased in the elderly and in cigarette smokers. It is also seen in chewing tobacco and smoke-free tobacco users. Other potential aetiological agents include alcohol, chronic friction, ultraviolet radiation and local Candida spp.infection (Banocyz).

Application site type reactions have been documented with the use of Sativex, and are listed in the proposed SPC. These reactions are defined by preferred terms: 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 only been two SAEs, and both of these were clinically diagnosed as 'oral leukoplakia' (MCN 20020096 and 20020095). There has also been one non-serious unrelated case of leukoplakia (subject no. 80004). 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 are reported in the SPC section 4.8.

Assessor's Comments
Application site reactions could be underreported, as they may be more likely to increase with time of use of the medicine. However it is reassuring that no new cases have apparently been reported since the previous application 3 years ago.
The warnings on application site type reactions in the SPC are satisfactory.

Discontinuation due to AEs
148 subjects (12%; n=79 MS, n=69 Non-MS) out of a total of 1230 (n=805 MS, n=425 Non-MS) subjects receiving Sativex and 57 (6%; n=35 MS, n=22 Non-MS) subjects out of 1160 (n=741 MS, n=419 Non-MS) receiving placebo withdrew in comparative studies due to adverse events (all causality).

230 of 1614 subjects (14.3%), receiving Sativex were withdrawn from the non-comparative studies due to adverse events (all causality).

In the MS population comparative studies, 79 of 805 subjects (9.8%) in the Sativex population withdrew, and 35 of 741 subjects (4.7%) withdrew in the placebo groups. The incidence of adverse events leading to withdrawal in the MS population non-comparative studies was 105 of 1016 subjects (10.3%).

In the Non-MS population comparative studies, 69 of 425 subjects (16.2%) in the Sativex population withdrew, and 22 of 419 subjects (5.3%) withdrew in the placebo groups. The incidence of adverse events leading to withdrawal in the Non-MS population non-comparative studies was 125 of 598 subjects (20.9%).

In the cancer population comparative study, 10 of 60 subjects (17%) in the Sativex population withdrew and 2 of 59 subjects (3%) withdrew in the placebo groups.

Other than dizziness and nausea (Non-MS comparative and non-comparative studies), there were no other individual events that lead to withdrawal in 2% or more of subjects in the MS or non-MS populations.

The overall withdrawal rate is low but there is a two to three fold higher withdrawal rate in the Sativex group compared to the Placebo group in the comparative studies, with a higher rate in the Non-MS population. The difference between withdrawal rate in the Sativex group and placebo group in the cancer population was slightly higher (approx. 5-fold). Examination of the MS and Non-MS data shows that the withdrawal rate is higher in the non-comparative than the comparative studies, and withdrawals are again greater in the non-MS population.

Comparison of AEs leading to withdrawal and the most common AEs shows that the reasons for withdrawal are very similar to the common AEs and are primarily CNS effects or application site reactions.

In the MS population, an overall withdrawal rate of less than 10% may be considered low, given the nature of the population.

Assessor's comment
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 as appears to be shown in the new short term efficacy study. These are issues of tolerability rather than safety.

Deaths
73 deaths occurred across all studies in subjects receiving Sativex of which 69 were considered to be unrelated to study drug. Seven fatal events were also reported in subjects randomised to placebo (during the cancer studies) and two occurred prior to administration of study medication.

There were four fatal cases in which the Investigators stated that there was a reasonable possibility that the events may have been related to Sativex, although in all of these cases there were significant confounding factors. This assessor considers that none of these deaths gives particular cause for concern as non-drug related causes are more probable.

As might be expected the majority of fatal events occurred during the terminal cancer pain control studies. None of the events were considered related to Sativex.

Assessor's comment
Overall, the assessor agrees with the company's position that there were no unexpected patterns or concerns identified from the incidence of fatal events.

Laboratory findings
Table 2.7.4.2.4.2.1A in the safety summary provides a summary of all laboratory values. The only chemical pathology finding of note were some increases in γ-GT and bilirubin that were not associated with increase in transaminases or alkaline phosphatase. A similar pattern was seen in the Sativex and placebo groups and a quarter of patients showed rises at baseline so the changes are presumably related to the disease itself or to the broad range of concomitant medication. These are not of concern. However abnormal liver function tests were reported as AEs and SAEs numerically more frequently than for placebo and are therefore included in the SPC section 4.8. The statement regarding GGT in the proposed SPC is considered acceptable.

ECG and QT findings
Detailed ECG analysis was undertaken during two Phase I studies (GWPK0112 and GWPK0215) and before and after treatment ECGs were taken in the three Phase 3 studies GWMS0001, GWPS0105 and GWMS0107. No clinically relevant QT prolongation or other ECG abnormalities were found in association with GW 1000 02.

The Applicant has carried out a formal and large randomized, double-blind, placebo- and active-controlled, four-arm, parallel group thorough QT/QTc study (TQT), in compliance with ICH Topic E14. 258 subjects were randomized to the treatment phase and 229 subjects completed the study. There were 3 dose groups of Sativex, 8, 24 and 36 sprays of Sativex (administered as

single administrations 4, 12 and 18 sprays twice daily), plus placebo and moxifloxacin controls. This study is also useful as it exposed cannabis naive subjects to substantial multiples of the therapeutic dose, providing information on the consequences of overdose.

There were no ECG/QT issues of concern and the reported effects of cannabis on increased heart rate were not seen to any significant extent with Sativex. The lower dose of 4 sprays over 20 minutes twice daily was generally well-tolerated, while the highest dose of 18 sprays daily over 20 minutes twice daily was not well-tolerated with numerous CNS psychiatric and nervous system AEs. The adverse event profile at these dose levels gives insight into the dose-response in terms of the potential for Sativex to cause undesirable CNS effects and also its abuse potential.

Safety in special populations

Age

38 MS subjects over the age of 65 received Sativex in placebo-controlled clinical studies (and 24 received placebo). In the non-MS population 110 subjects over the age of 65 have been exposed to Sativex (compared with 83 on placebo).

Elderly patients are likely to be more susceptible to certain CNS AEs, with implications for various aspects of personal safety. The SPC (section 4.2) states that "No specific studies have been carried out in elderly patients, although patients up to 90 years of age have been 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". This is satisfactory.

Prior Cannabis Use

A detailed review was conducted in order to investigate whether "cannabis-naïve" or "cannabis-experienced" subjects are likely to have different susceptibility to psychiatric adverse events, looking at the relative incidence, type and severity of psychiatric adverse events in the two groups. Overall the proportion of subjects with prior experience of cannabis was fairly similar between the two treatment groups: 121/363 (33%) in the Sativex group and 110/303 (36%) in the Placebo group.

The table below presents the treatment-related psychiatric adverse events experienced by MS patients enrolled into the randomised, double-blind, placebo-controlled studies. There is no apparent difference in incidence of psychiatric adverse events experienced by cannabis-experienced and cannabis-naïve MS patients who took Sativex in the randomised studies.

Table UK C9-2: Incidence of Psychiatric Adverse Events (MS Subjects) – All Sativex Studies

Psychiatric Disorders (MS Subjects) – Randomised Studies				
Preferred Term	Treatment Related			
	Randomised Study Subjects Sativex Total (n=496)		Randomised Study Subjects Placebo Total (n=434)	
	Previous Cannabis Use		Previous Cannabis Use	
Number of Subjects	No	Yes	No	Yes
	322	174	262	171
Any Event in SOC	59 (18.3%)	39 (22.4%)	14 (5.3%)	7 (4.1%)
Disorientation	15 (4.7%)	12 (6.9%)	4 (1.5%)	0
Euphoric Mood	7 (2.2%)	5 (2.9%)	3 (1.1%)	3 (1.8%)
Depressed Mood	3 (0.9%)	4 (2.3%)	1 (0.4%)	0
Depression	3 (0.9%)	2 (1.1%)	0	1 (0.6%)
Anxiety	2 (0.6%)	1 (0.6%)	2 (0.8%)	1 (0.6%)
Insomnia	3 (0.9%)	0	3 (1.1%)	1 (0.6%)

Source: Sativex dossier August 2006, Tables A6, A13; Sativex Integrated Safety; MS Subjects

The overall incidence of adverse events was similar in both groups. Cannabis naive patients reported dizziness, headache, pharyngitis, nausea and oral pain more frequently. Patients who had used cannabis before had higher incidence of dry mouth, increased appetite, disorientation, diarrhoea, urinary tract infection, fall, dissociation and oral discomfort, paranoia, feeling of relaxation and muscle spasms. A similar incidence of severe psychiatric adverse events was reported in the long-term extension studies.

Assessor's comment

Although these are not entirely comparable patient populations and there are likely to be confounding factors, the AE profile does not appear to be substantially influenced by prior cannabis use.

Risks to non-responders in a 4-week therapeutic trial

A detailed report quantifying the risks to which non-responders would be exposed during a 4 week therapeutic trial was presented by the applicant. The adverse event profile apparent after 4 weeks of Sativex therapy was very similar to that at the end of the studies. The great majority of adverse events were of mild or moderate intensity and related to tolerability rather than to safety. 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. Few severe or serious psychiatric adverse events of disorientation, depressed mood, dissociation, apathy and confusional state were recorded. Nevertheless, as reflected in the proposed Summary of Product Characteristics text, patients

undergoing a therapeutic trial with Sativex should be monitored for these psychiatric adverse events.

The findings from the pivotal clinical trial 0604 in which a 4 week Sativex therapeutic trial period was part of the trial design were generally consistent with those of the earlier trials although the reporting rates of AEs were generally lower. The applicant attributes this to the slower dose titration in this study and this may have some validity although various other differences in study conduct could also account for this.

Overall the potential risks of a 4-week Sativex treatment period appear to be fairly low but not insignificant. 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 some cause for concern. It would be necessary in normal clinical practice for patients undergoing a therapeutic trial with Sativex to be monitored for these psychiatric adverse events.

Post marketing experience

In September 2004, the UK Home Office allowed prescription of Sativex as an unlicensed medicine in the UK to patients who had participated in GW Pharma Ltd trials. Named patient prescribing in the UK has been extensive. More than 2000 patients have since been prescribed Sativex as an unlicensed medicine in the UK. All of these patients are subject to spontaneous reporting of adverse reactions.

Sativex has been marketed in Canada where the product has held a provisional license for the relief of central neuropathic pain due to multiple sclerosis since June 2004, and for the relief of pain in patients with advanced cancer since There have been seven six-month periodic safety update reports (PSURs) for Sativex in Canada covering adverse drug reaction case reports and other data reported during the period from 15 April 2005 to 15 October 2008. It is estimated that during this period there has been over 5500 patient years of exposure to Sativex from post-marketing and named patient or compassionate use (see table below) including the 2000+ patients who have been prescribed Sativex as an unlicensed medicine in the UK.

Exposure Period/ Duration		NPS* / CUP# (UK & Spain)*	Marketed (Canada)*
15 April 2005 to 15 October 2008	Number of vials	87,546	59,996
	Mean daily dose	3.57	5
	No. patient days	1,399,822.5	611,959
	Patient exposure in Years	3,835	1,676.6

* Numbers are estimated either upon bulk sales for marketed or from prescriptions provided to NPS

* NPS = Named Patient Supply

CUP = Compassionate Use Programme

There have been few spontaneously reported adverse drug reactions. This can be demonstrated by reference to the cumulative tabulated presentation (Table 3A in Appendix 5) of serious and unexpected adverse reactions that was submitted as part of the seventh PSUR for Sativex in December 2008. Although there is no evidence of new safety risk from the available data, GW continues to carefully monitor all reported ADRs very closely for potential safety signals.

A review of the spontaneously reported data reveals the following significant events:

- One subject with secondary progressive MS died approximately 20 months after her last known prescription of Sativex.
- A possible withdrawal syndrome with symptoms of diaphoresis, uncontrolled tremors, piloerection and vomiting five days after the patient stopped Sativex medication.
- A serious spontaneous case of an aggressive reaction (patient tried to kill his wife) and anxiety. Past history of anxiety and verbally aggressive reactions. The company considered a relationship between the event and Sativex administration to be highly unlikely. A possible partial causal role of Sativex seems possible however.
- A serious case of an MS patient on Sativex who had stiffness of her limbs, extreme fatigue, staring eyes, sensation of cold and an inability to speak. Two episodes, each lasting approximately two to three minutes, both on the same day five hours after taking 3 sprays of Sativex. Resolved without medical intervention and she recommenced Sativex. Very limited information available for this case, and no medical history or concurrent medication details were provided. The company considered that there was a possible relationship between the event and Sativex.
- A 49-year old patient developed abnormal renal function during use of Sativex for pain due to fibromyalgia / osteoarthritis. Cause not established. No strong temporal association with Sativex but the possibility of a causal role could not be ruled out.
- A report of a psychotic episode. The patient had underlying (unspecified) psychiatric illness. The reporter considered the episode of psychosis to be 'multifactorial in nature' but did not provide an assessment of causality and further requested information was not provided. In response 'psychotic reaction' was added to the Company Core Safety Information dated 09 April 2008. This could be a case in which Sativex precipitated acute worsening of an underlying psychotic illness.
- A report of suspected anaphylactic reaction in a patient with end stage MS. The patient was receiving multiple concomitant medications "some of which list tongue swelling and sore throat as potential side effects". Continued Sativex up to 48 hours after onset of symptoms, and symptoms persisted for one week after onset.
- Episode of hypertension in a subject with no history of hypertension or cardiovascular disease but who had previously experienced hypertension with smoked cannabis.

In conclusion the majority of the above reports are of doubtful causal link to Sativex, but the psychotic episode, an aggressive reaction and the unknown psychomotor reaction could represent the potential for Sativex to cause – or at least precipitate in susceptible subjects – significant CNS morbidity. The risk-benefit evaluation for Sativex from the clinical trials remains essentially unchanged by these data.

Proposals for post authorisation follow-up/risk management
Safety Specification
1. Non-clinical
The Applicant discusses the relevance of their non clinical findings in relation to potential risk to humans and concludes:
- There are no potential safety concerns identified in general safety pharmacology studies or in non-clinical drug interaction studies that have not been addressed in human clinical studies.
- There may be some potential for endocrine effects of Sativex.
- There may be potential for abuse of Sativex, and this has been addressed in a specific human abuse liability study.
- There is a likelihood of reproductive toxicity with the suggestion that Sativex should not be used during pregnancy or during the period of breast feeding

Assessor's comments
The summary of toxicity findings and general safety pharmacology would appear comprehensive and balanced.

2. Clinical
The clinical safety database is composed of patients treated with Sativex for Multiple Sclerosis (MS), non MS indications mainly comprised of chronic neuropathic pain of various aetiologies, and cancer.

Assessor's comments
The safety database has expanded since the last submission, but there are still limited data on long-term treatment, for an indication that will mean long term use.

Exposure information
Sativex was first launched in Canada in 2005 and is now used as an adjunctive treatment for symptomatic relief of neuropathic pain in MS adults. It is also indicated as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

This licensed use is also supplemented by unlicensed use in over 20 countries, with the main use being in the UK, Spain and Italy. The estimate of patient years is shown on page 68 of this report.

Identified/potential risks and missing information
The identified and potential risks missing data are summarised in the table below.

1.10 Summary – Ongoing safety concerns

Important identified risks	Central Nervous System Effects- Memory loss Psychiatric Effects – Psychiatric morbidity; Mood changes; long term psychiatric effects
Important potential risks	Suicide and Suicidal Ideation Effects on Ability to Drive and Use Machines Misuse for illegal purposes Abuse liability and Addiction Increased risk of falls
Important missing information	With significant Hepatic or Renal Impairment No studies have been conducted in subjects of less than 18 years of age. Few data in elderly subjects Exposure to other ethnic populations is limited (primarily Caucasian) Limited experience of the effect of Sativex on Human pregnancy and lactation.

As a preamble to their discussion of these risks the Applicant emphasises that they consider that Sativex as a medicine is clearly distinguished from cannabis used recreationally. They quote pharmacokinetic arguments summarised as:

- The composition and dose form of Sativex mean that the pharmacokinetics are not comparable to the pharmacokinetics of smoked cannabis.
- The maximum plasma concentration of THC is reached very quickly following smoked administration, a feature which is accepted to maximise the psychoactive effects and facilitate abuse; this is in marked contrast to Sativex.
- The maximum plasma concentration of THC is about 50 times greater after smoked cannabis compared with Sativex.
- In conclusion, it is highly unlikely on pharmacokinetic grounds that the THC in Sativex will have the same CNS effects as are seen with smoked cannabis.

Against this background, and in relation to abuse potential, the Applicant differentiates between short and long term impacts, noting the overlap with the overdose issue. They suggest that the long-term impact of administration of Sativex in adults does not appear to be associated with adverse health consequences. This would seem questionable in the light of the observation that there are relatively little long-term data.

The Applicant has discussed the risk for a clearly defined withdrawal syndrome or dependence, and does not consider that such a risk exists. In practice this section should only retain the risks which will be followed up in the Pharmacovigilance plan.

Suicidal ideation remains a potential risk however the Applicant says that all cases examined had a documented psychiatric history prior to administration.

With regard to psychiatric effects whether they are long term psychiatric effects or memory impairment the Applicant has covered these issues, and has added an additional section that provides a detailed overview of psychiatric effects in MS and non MS patients. From this they conclude such effects are likely, but to date all serious events have resolved fully. This

discussion, in summary form, should either be incorporated into the existing section 1.5.2 or integrated into the epidemiology section.

The lack of long-term follow up data brings into question the assertion that no long-term psychological morbidity has been seen.

Potential for overdose
The Applicant has reviewed the data from their clinical trial programme looking separately at the potential for overdosing under acute dosing and repeat-dosing scenarios. They conclude:-

Due to the high inter-subject variability, the THC plasma levels achieved in overdose with Sativex, are likely to be similar to those achieved by some subjects taking therapeutic doses. This confirms the high margin of safety associated with Sativex in overdose (THC C_{max} ~ 10ng/mL at 36 sprays per day), as these levels remain many times lower than the C_{max} achieved from smoked cannabis / inhaled THC (approximately C_{max} of 160ng/mL).

Assessor's comments
In accordance with the EU template requirements the issue of overdose has been addressed. From the clinical trial data it can be seen that the median dose is in the region of 8 sprays per day, but there are subjects who have used up to 48. If the arguments regarding the THC levels are sound then even with this extreme frequency of dosing then the margin of safety would seem adequate.

Potential for off-label use
The Applicant describes various populations of non-MS patients in which Sativex has been used, for which they believe the safety profile is similar to the safety profile of the MS population.

Assessor's comments
The Applicant acknowledges the off label use in Europe, particularly in the UK. They do indicate that they are open to discuss with each regulator the best way to ensure correct use of the product in the approved indication.

Pharmacovigilance System and Risk Management Plan

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has committed to implementing a robust risk management plan in order to identify and characterise uncommon serious adverse events, in particular psychiatric morbidity and other central nervous system effects. The applicant has provided a detailed assessment of safety concerns with post marketing commitments to carry out studies.

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 cannabis 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 is not unexpected but these issues 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 although the possibility of an increased incidence of pre-malignant leukoplakia cannot be excluded.

The profile of AEs and SAEs is broadly in line with that expected from the known pharmacology of cannabis. 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 are concerns regarding the potential for psychological and psychiatric morbidity and 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. There is no signal that MS patients have increased susceptibility to psychiatric adverse effects from cannabinoids than the general population although the possibility cannot be excluded. 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.

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

In conclusion the safety profile is considered acceptable in principle for the proposed patient population and indication.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Sativex Oromucosal Spray are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

The likely overall safety of Sativex has been adequately evaluated from both published reports and newly-commissioned studies, and potential adverse effects identified. In particular, there is low potential for genotoxicity, carcinogenicity and local toxicological effects with adequate/sufficient margin of safety estimated for the finished product. Clinically significant drug-drug interactions are unlikely. In addition, major organ toxicity at clinical doses is not expected.

Some potential for reproductive effects in terms of pup development and nursing behaviour has been observed. Overall, the available animal data suggest that Sativex should not be used during pregnancy or during the period of breast-feeding.

New preclinical mechanistic data are provided, including published data and a new mouse pharmacodynamic study. The Applicant has supplied details of a body literature of data confirming cannabinoids to relieve motor dysfunction and spasticity in accepted animal models.

A study in mice showed that Sativex BDS, administered at an intravenous dose of $5mg \cdot kg^{-1}$ THC + $5mg \cdot kg^{-1}$ CBD, produced an approximate 20% peak reduction in hindlimb stiffness (spasticity). Furthermore, Sativex BDS, administered at an intravenous dose of $10mg \cdot kg^{-1}$ THC + $10mg \cdot kg^{-1}$ CBD, produced an approximate 40% peak reduction in hindlimb stiffness (spasticity). It was evident that the compounds within Sativex have the potential to dose-dependently inhibit spasticity in an experimental mouse model of multiple sclerosis.

EFFICACY/SAFETY

Preclinical mechanistic data are provided, including published data and a mouse pharmacodynamic study, show a significant effect of Sativex on an objective measure of the physiological phenomenon of spasticity in validated animal models. Human evidence of this is essentially limited to the Ashworth scale as a secondary endpoints in the main pivotal study GWSP 0604, where a strong trend favouring the Sativex group was seen (95% CI -3.80, 0.30 and p-value 0.094), but not conventional statistical significance. An objective effect of Sativex on the physiological phenomenon of spasticity has been shown.

There is clear evidence from the pivotal trials of a substantial treatment effect of Sativex on the primary efficacy measure, the patient reported spasticity symptom Numeric Rating Scale (NRS). This was a symptomatic measure and the indication claimed is symptomatic. Earlier concerns relating to the question of what that endpoint is a measure of and its validity as a measure of spasticity is considered resolved.

The safety profile is acceptable for the proposed patient population and indication, although there are clearly some significant safety issues, in particular the potential for psychological and psychiatric morbidity. However it is considered that these are outweighed by significant benefit in terms of efficacy in this difficult to treat patient population.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable. A positive risk-benefit is concluded in the patient population studied for a symptomatic indication.

A robust risk management plan will need to be implemented in order to identify and characterise uncommon serious adverse events, in particular psychiatric morbidity and other CNS effects. The applicant has provided a detailed assessment of safety concerns with post marketing commitments to carry out studies.

STEPS TAKEN AFTER ASSESSMENT

The following table lists some non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Description	Outcome
13/12/2013	VAR Medical Type IB	To update sections 2, 4.5, 4.8, 5.2 & 6.3 of the SmPC following a commitment to submit a post MRP variation to update the SmPC with wording as agreed by the RMS/CMS, including updates in line with the QRD template.	Variation granted 12/02/2014

Annex 1

Reference: **PL 18024/0009- application 0028**

Product: **Sativex Oromucosal Spray**

MAH: **GW Pharma Limited**

Active Ingredient: **DELTA(9)-TETRAHYDROCANNABINOL and CANNABIDIOL**

Reason:
To update sections 2, 4.5, 4.8, 5.2 & 6.3 of the SmPC following a commitment to submit a post MRP variation to update the SmPC with wording as agreed by the RMS/CMS, including updates in line with the QRD template.

Supporting evidence:
The applicant has submitted updated Sections of the SmPC.

Evaluation
The updated SmPC is satisfactory.

Conclusion
The variation was approved on 12th February 2014 and updated SmPC has been incorporated into this Marketing Authorisation.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Following approval of the variation on 12th February 2014 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.