PRODUCT MONOGRAPH

^{N}SATIVEX®

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

Buccal spray

Cannabinoid Analgesic

Standard marketing authorization:
SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.
Marketing authorization with conditions:
SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.
Marketing authorization with conditions:
SATIVEX® may be useful 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.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

GW Pharma Ltd.
Salisbury, Wiltshire
U.K. SP4 0JQ
Control No: 149598

Distributed in Canada by:
Bayer Inc.,
Toronto, Ontario
M9W 1G6

Date of Revision:
March 30, 2012

This product has been approved under the Notice of Compliance with Conditions (NOC/c) Policy for its uses in adult patients with MS neuropathic pain and with cancer pain.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Mechanism of Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PART I: HEALTH PROFESSIONAL INFORMATION

NOC

SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c

SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

SATIVEX® may be useful 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.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	All Nonmedicinal Ingredients
Buccal	Buccal spray delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)	Ethanol anhydrous Propylene glycol Peppermint oil *This is a full listing of all nonmedicinal ingredients.*

INDICATIONS AND CLINICAL USE

NOC SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis (MS).

The physician who elects to use SATIVEX® for extended periods should periodically re-evaluate the long-term usefulness of SATIVEX® for the individual patient.

NOC/c SATIVEX® may be useful 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.

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the principal active components in SATIVEX®. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused. Both active components, THC and CBD, are scheduled under the Controlled Drugs and Substances Act.

Geriatrics: There are limited data available on the use of SATIVEX® in elderly patients, therefore, the drug should be prescribed cautiously and carefully monitored in this patient population.

Paediatrics (<18 years of age): The safety and efficacy of SATIVEX® have not been established in adolescents or children under 18 years of age, therefore SATIVEX® should not be used in adolescents or children.

CONTRAINDICATIONS

SATIVEX® is contraindicated in:

- patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil
- patients with serious cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure
- patients with a history of schizophrenia or any other psychotic disorder
- children under 18 years of age
- women of child-bearing potential not on a reliable contraceptive or men intending to start a family (see “Use in Women of Child-Bearing Potential”)
- pregnant or nursing women (see “Use in Women of Child-Bearing Potential”).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC and CBD are the principal active components in SATIVEX®. THC can produce physical and psychological dependence and has the potential for being abused.

THC has complex effects on the central nervous system (CNS). These can result in changes of mood, decrease in cognitive performances and memory, decrease in ability to control drives and impulses, and alteration of the perception of reality, particularly altered time sense. Fainting episodes have been observed with use of SATIVEX®. CNS effects, with dizziness being the most frequent (see Table 2), appear to be dose-related, increasing in frequency with higher dosages, and subject to great inter-patient variability. They usually resolve on reduction of doses, increasing the interval between doses or interruption of SATIVEX® (see "OVERDOSAGE"). Because of the potential of THC to alter the mental state, SATIVEX® should be used only as indicated and prescriptions should be limited to the amount necessary for the period between clinic visits. Drug administration should be discontinued in patients experiencing a psychotic reaction or a suicidal ideation and the patient should be closely observed in an appropriate setting until his/her mental state returns to normal. Patients should stop taking SATIVEX® if they become confused or disorientated. Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination.

Cannabinoids have cardiovascular effects that include tachycardia, and transient changes in blood pressure, including episodes of postural hypotension. Use of SATIVEX® is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure.

Published reports on cannabinoids are equivocal with regard to the effects of THC on seizure threshold. Until further information is available, caution should be used when treating patients with a history of epilepsy or recurrent seizures.

General

During the initial self-titration period, patients may experience unacceptable adverse events, including dizziness. These should resolve with down-titration or interruption of treatment (see "OVERDOSAGE, Signs and Symptoms").

Careful dose titration and monitoring are advised if SATIVEX® is used in patients on a drug product containing fentanyl, or its analogues such as alfentanil and sufentanil (see DRUG INTERACTIONS).

Care should be taken with sedatives, drugs with sedating or psychotropic effects and hypnotics as co-administration with SATIVEX® may have an additive effect.

Buccal Mucosa

Regular inspection of the oral mucosa is advised. Patients should be advised not to continue spraying on to sore or inflamed mucosa.

Administration site irritation was common both during short-term and long-term use of SATIVEX®.

Carcinogenesis and Mutagenesis

See Part II – TOXICOLOGY.

Cardiovascular

See "Serious Warnings and Precautions".

CNS Effects

See "Serious Warnings and Precautions", "OVERDOSAGE" and "ADVERSE REACTIONS".

Driving and Operating Machinery

SATIVEX® may impair the mental and/or physical abilities required for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination. Patients should also be cautioned about the additive/synergistic effects of SATIVEX® with other CNS depressants, including opioids, GABA inhibitors, sedative/hypnotics, and alcohol.

Genitourinary

See "Use in Women of Child-Bearing Potential" section below.

Haematologic

Clinical laboratory investigations did not reveal any trends of clinical significance in haematological parameters.

Hepatic/Biliary/Pancreatic

No consistent effect of SATIVEX® on clinical chemistry parameters has been observed.

No specific studies have been carried out in patients with significant hepatic or renal impairment, therefore SATIVEX® should be used with caution in such patients. Frequent review by the clinician is recommended.

SATIVEX® contains approximately 50% v/v of ethanol. Each dose contains up to 0.04 g of ethanol. The median daily dose of 5 sprays would be up to 0.2 g ethanol. Ethanol may be harmful for those suffering from alcoholism. This should also be taken into account in high-risk

groups such as patients with liver disease.

Immune

No clinically significant abnormalities of immune function have been observed in clinical trials with SATIVEX®.

Neurologic

In clinical studies with SATIVEX®, an increase in the number of falls has been observed. Whether this is due to dizziness, orthostatic hypotension or reduced spasticity has not been established. Patients should be made aware that care should be taken to avoid falls.

There is not sufficient information to characterize the effect of SATIVEX® on the seizure threshold. Caution should be used in treating patients with a history of epilepsy or recurrent seizures.

Peri-Operative Considerations

SATIVEX® may produce transient minor changes in blood pressure and heart rate. The central and peripheral effects of SATIVEX® should be taken into consideration in peri-operative situations.

Psychiatric

SATIVEX® should not be used in patients with a personal or strong family history of psychosis (including schizophrenia and affective psychosis) as symptoms may be aggravated by cannabinoids. SATIVEX® should be used with caution, if at all, in patients receiving other psychoactive drugs because of the potential for additive or synergistic CNS effects. In cases of disorientation (or confusion), hallucinations, delusional beliefs, or psychotic reaction, SATIVEX® should be stopped immediately and the patient monitored until the symptom has completely resolved (see "CONTRAINDICATIONS").

Suicidal ideations and other symptoms associated with depression have been reported. A causal association between SATIVEX® administration and suicidal ideation cannot be ruled out. The reported incidences of depression symptoms are consistent with that observed in populations of MS patients followed for a prolonged period of time. In case of a suicidal ideation, SATIVEX should be stopped immediately and the patient monitored until the symptom has completely resolved.

In acute studies with SATIVEX®, in people with multiple sclerosis, disorientation (4.1%), depression including depressed mood (2.9%), dissociation (1.7%), euphoric mood (2.2%), hallucination (0.9%), hallucination (auditory) (0.2%), hallucination (visual) (0.2%), illusion (0.1%), paranoia (0.5%) and suicidal ideation (0.5%) have been reported. In long-term Phase III extension studies (n=1016), the following additional adverse event, with a plausible causal relationship to SATIVEX®, has also been reported by patients with multiple sclerosis: delusional perception (0.1%).

Sensitivity/Resistance

SATIVEX® is contraindicated in patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil (see "CONTRAINDICATIONS").

Use in Women of Child-Bearing Potential

Independent research in laboratory species has found that cannabinoids have been associated with evidence of reproductive toxicity in early gestation and have been found to affect spermatogenesis. Therefore, women of child-bearing potential should take reliable contraceptive precautions for the duration of treatment and for three months after discontinuation of therapy. Male patients with a partner of childbearing potential should ensure that reliable contraceptive precautions are maintained for the duration of therapy and for three months after discontinuation of therapy.

Special Populations

Pregnant Women: Animal studies have indicated that cannabinoids may have detrimental effects on foetal development. SATIVEX® is contraindicated in pregnant women. SATIVEX® should not be used in women who intend to start a family.

In clinical trials with SATIVEX®, all female participants had to use a reliable contraceptive and all male participants had to ensure contraception with their partner. If a female participant became pregnant, she had to discontinue from the trial.

Nursing Women: In studies in laboratory species, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Even at 1mg/kg/day there were 40-60 times the plasma level of cannabinoids in the breast milk.

SATIVEX® is contraindicated in nursing women.

Paediatrics (<18 years of age): Animal data have indicated that cannabinoids interfere with the development of neonatal and adolescent rodents. SATIVEX® is contraindicated in children under 18 years of age.

Geriatrics: There are limited data available on the use of SATIVEX® in elderly patients, therefore, the drug should be prescribed cautiously and carefully monitored in this patient population.

Hepatic and Renal Impairment: No specific studies have been carried out in patients with significant hepatic or renal impairment. (See "WARNINGS AND PRECAUTIONS".)

Monitoring and Laboratory Tests

Routine laboratory monitoring, appropriate for the patient's disease condition and concomitant medication, is recommended. Due to accumulation of cannabinoids in the body fat, trace amount of cannabinoids may be detected in the blood and urine for some weeks after SATIVEX® is discontinued.

DRUG DEPENDENCE/ABUSE LIABILITY

Recreational cannabis is known to produce dependence in some users. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused.

SATIVEX® contains THC and should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence. Multiple substance abuse is common and marijuana, which contains the same active compounds, is a frequently abused substance. Therefore, SATIVEX® is not recommended in patients with addiction and drug abuse liability.

In a study designed to identify its liability for abuse, SATIVEX® at a dose of 4 sprays taken at one time, showed no more liability for abuse than placebo. Higher doses of SATIVEX® of 8 to 16 sprays taken at one time showed a greater liability for abuse than placebo.

In long-term open-label studies with SATIVEX®, no increase in the dosing level of SATIVEX® was observed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

SATIVEX® has been administered to 805 multiple sclerosis patients in placebo-controlled studies and to 1016 patients during long-term open-extension studies. 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 addition to the adverse events (all-causality) reported in the placebo-controlled acute studies (refer to Tables 1 and 2) the following adverse events observed in patients with MS (n=1016) on long-term treatment with SATIVEX® were considered to have a plausible causal relationship to SATIVEX®: palpitations (1.2%), tooth discolouration (2.1%), oral mucosal disorder (2.2%), oral mucosal discolouration (0.7%), oral mucosal exfoliation (0.7%), stomatitis (0.6%), hypertension (0.3%), delusional perception (0.1%) and syncope (0.9%).

Clinical Trial Adverse Drug Reactions

The following data summarise the adverse events in patients in clinical trials with various neurological conditions. Patients in clinical trials for relief of pain in cancer are described separately.

In all placebo-controlled trials in MS, adverse events have usually been mild or moderate in severity with discontinuation rates from treatment due to undesirable effects of 9.8% of patients on SATIVEX® compared to 4.7% on placebo. In most patients, adverse events have resolved without treatment, and some on a reduction of dosage of SATIVEX®. The studies from which these figures are derived incorporate a period of titration to optimal therapeutic and/or maximum tolerated dose during which unwanted effects are likely to be maximal. Because SATIVEX® is self-titrated to effect, patients are likely to experience a higher incidence of adverse events during the titration period than when the optimal dose is established.

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment-emergent adverse events that occurred in 1% or more of patients treated with SATIVEX®, and at an incidence greater than (or equal to) 1% more frequently than placebo, in the acute phase in all Phase III trials, are given below in Tables 1 and 2. Table 1 includes all adverse events related to the application site, as the placebo used in studies contained the same excipients (ethanol and propylene glycol) as used in SATIVEX®.

Table 1 excludes CNS effects, while Table 2 lists only CNS effects.

Table 1: Treatment-Emergent Adverse Events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≥ ≧1% more frequently than in placebo (excluding CNS effects)

	SATIVEX® n = 805 (%)	**Placebo n = 741 (%)**
Cardiac disorders		
Tachycardia	1.0	0.4
Ear and labyrinth disorders		
Vertigo	6.5	2.0
Eye disorders		
Vision blurred	1.9	0.4
Gastrointestinal disorders		
Abdominal pain upper	1.4	0.3
Constipation	2.4	0.5
Diarrhoea	5.5	3.9
Dry mouth	6.1	3.1
Glossodynia*	1.1	1.3
Mouth ulceration*	1.5	0.8
Nausea	9.6	5.7
Oral discomfort*	1.9	1.9
Oral pain*	2.1	2.2
Vomiting	3.5	2.2
General disorders and administration site conditions		
Application site irritation*	0.7	1.1
Application site pain*	2.0	2.3
Asthenia	5.6	3.1
Fatigue	12.5	8.4
Malaise	1.0	0.4
Infections and infestations		
Pharyngitis*	1.2	1.1
Injury, poisoning and procedural complications		
Fall	1.5	0.5
Metabolism and nutrition disorders		
Anorexia (includes appetite decreased)	2.1	0.7
Appetite increased	1.4	0.4
Nervous system disorders		

Table 1: Treatment-Emergent Adverse Events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≥1% more frequently than in placebo (excluding CNS effects)

	SATIVEX® n = 805 (%)	**Placebo n = 741 (%)**
Dysgeusia (abnormal taste)*	3.1	0.8
Respiratory, thoracic and mediastinal disorders		
Throat irritation*	0.5	0.1

* application site reaction

Table 2: Treatment-Emergent CNS adverse events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≧1% more frequently than in placebo

	SATIVEX® n =805 (%)	Placebo n =741 (%)
General disorders and administration site conditions		
Feeling abnormal	2.4	0.5
Feeling drunk	3.0	0.4
Nervous system disorders		
Amnesia (includes short term memory loss)	1.1	0.3
Balance disorder (balance impaired)	2.9	1.8
Disturbance in attention	3.9	0.1
Dizziness	25.0	8.2
Dysarthria	2.0	0.4
Lethargy	1.5	0.7
Memory impairment	1.4	0.1
Somnolence	8.2	2.3
Psychiatric disorders		
Anxiety*	0.9	0.9
Depression (includes depressed mood)	2.9	2.0
Disorientation (includes confusion)	4.1	0.8
Dissociation	1.7	0.1
Euphoric mood	2.2	0.9
Hallucination*	0.9	0.1
Hallucination, auditory*	0.2	0
Hallucination, visual*	0.2	0
Illusion*	0.1	0
Paranoia*	0.5	0.1
Suicidal ideation*	0.5	0.1

***** included as there is a plausible relationship with SATIVEX®

Application Site

Application site type events were reported by approximately 14% of patients receiving SATIVEX® or placebo. These included glossodynia, mouth ulceration, oral discomfort, oral pain, application site irritation, application site pain, pharyngitis, throat irritation and dysgeusia. The incidences were similar for SATIVEX® treated patients and placebo appearing to indicate that some application site type reactions may be due to the excipients (50% ethanol and 50% propylene glycol). The majority of these reactions consisted of mild to moderate stinging at the time of application. Mouth ulceration was observed in 1.5% of patients using SATIVEX®, and

0.8% in placebo. Two cases of possible leukoplakia were reported as related to SATIVEX®, but neither was confirmed histologically; a third case was unrelated.

Patients who complain of discomfort should be advised to vary the site of application within the mouth, and should not continue spraying onto sore or inflamed mucus membranes. Regular inspection of the oral mucosa is strongly recommended in long-term administration. If lesions are observed or persistent soreness reported, treatment should be interrupted until complete resolution occurs.

Cardiovascular

THC may cause tachycardia. Its effects on blood pressure are inconsistent, but occasionally patients may experience orthostatic hypotension and/or syncope upon abrupt standing, particularly during initial dose titration when caution is essential. SATIVEX® is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure. In a thorough QT study, there were no clinically relevant changes in QTc, PR or QRS interval duration, heart rate, or blood pressure, following five days of dosing in healthy volunteers with SATIVEX® up to 18 sprays twice daily.

Adverse events in patients with pain in cancer

Treatment-emergent adverse events that occurred in 3% or more of patients given SATIVEX® or placebo in a trial for patients with pain in cancer are given below in Table 3.

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	**Placebo n = 59 (%)**
Blood and Lymphatic System Disorders		
Anaemia Nos	0	5
Cardiac Disorders		
Cardio-Respiratory Arrest	0	3
Ear and Labyrinth Disorders		
Vertigo	5	2
Gastrointestinal Disorders		
Nausea	12	10
Vomiting	8	7
Constipation	5	10
Oral Pain	2	5
Diarrhoea	7	3
Glossodynia	3	0
Abdominal pain upper	2	3
Dry mouth	0	3
Stomatitis	2	3

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	**Placebo n = 59 (%)**
General Disorders and Administration Site Conditions		
Pain exacerbated	0	3
Pyrexia	0	3
Weakness	5	0
Disease Progression	3	0
Hepatobiliary Disorders		
Hepatic cytolysis	0	3
Infections and Infestations		
Oral Candidiasis	3	2
Urinary Tract Infection	0	7
Lower Respiratory Tract Infection	0	5
Investigations		
GGT Increased	3	5
Blood Urea Increased	2	5
Liver Function Tests Abnormal	5	3
Blood Creatinine Increased	2	3
Blood Calcium Increased	0	5
Musculoskeletal and Connective Tissue Disorders		
Pain in Limb	2	3
Buttock Pain	0	3
Neoplasms Benign, Malignant and Unspecified (incl.Cysts and Polyps)		
Neoplasm Progression	10	5
Malignant Neoplasm Progression	2	5
Nervous System Disorders		
Somnolence	15	14
Dizziness	12	5
Disturbance in Attention	3	0
Dysgeusia	3	0
Headache	3	0
Psychiatric Disorders		
Confusion	7	3
Hallucination	3	2
Insomnia	3	2
Panic Attack	3	0
Euphoric Mood	3	0

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	Placebo n = 59 (%)
Renal and Urinary Disorders		
Urinary Retention	5	0
Haematuria	3	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea	2	3
Vascular Disorders		
Hypotension	5	0

Urinary Retention and Infections

The combined incidence of urinary retention and urinary infections appear to be increased in the cancer patients taking SATIVEX® over those on placebo. Caution is advised in the urinary care of the cancer patients who are using SATIVEX®.

Abnormal Haematologic and Clinical Chemistry Findings

No consistent effect of SATIVEX® on haematologic and clinical chemistry parameters has been observed.

Post-Market Adverse Drug Reactions

Adverse event profile, based on post-market spontaneous reports, is consistent with those observed in clinical trials.

DRUG INTERACTIONS

Serious Drug Interactions

- Care should be taken with sedatives, drugs with sedating or psychotropic effects and hypnotics as co-administration with SATIVEX® may have an additive effect.
- Alcohol may interact with SATIVEX®, particularly in affecting coordination, concentration and ability to respond quickly.

Overview

The two main components of SATIVEX®, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are metabolized by the Cytochrome P450 enzyme system, including CYP1A2, CYP2C9, CYP2D6, CYP2C19 and CYP3A4. The inhibitory effects *in vitro* and in animal models were only seen at exposures significantly higher than the maximum observed in clinical trials. In clinical trials where SATIVEX® has been taken concomitantly with other drugs metabolized by the Cytochrome P450 enzyme system, no clinically apparent drug-drug interactions have been seen in these trials at clinical doses.

In an *in vitro* study with 1:1% (v/v) THC botanical drug substance (BDS) and CBD BDS, no relevant induction of Cytochrome P450 enzymes was seen for human CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes in human hepatocytes, at doses of up to 1µM (314 ng/mL).

Drug-Drug Interactions

There may be a potential risk of drug-drug interactions due to CYP450 inhibition by SATIVEX®. Caution should be exercised in patients taking drugs known to be substrates for CYP450 3A4 or CYP450 2C19, such as amitriptyline, fentanyl and the related opioids sufentanil and alfentanil.

Concomitant treatment with the CYP 3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC, 11-hydroxy-THC (11-OH-THC its primary metabolite) and CBD. The extent of this increase was less than the between subject variability. Following treatment with the CYP3A4 inducer rifampicin, a reduction in the C_{max} and AUC of THC, 11-OH-THC, and CBD was observed. The magnitude of this reduction for THC and CBD was less than the between subject variability.

Concomitant treatment with the CYP2C19 inhibitor omeprazole resulted in no notable change in any of the pharmacokinetic parameters.

Protein Binding

THC is highly bound to plasma proteins, and therefore might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering SATIVEX® to patients who are receiving other drugs which are tightly protein-bound.

Drug-Food Interactions

No clinically relevant food interaction has been observed.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

No laboratory interactions have been established. Cannabinoids may be detected in the plasma and urine several weeks after SATIVEX® is discontinued (see "Monitoring and Laboratory Tests").

Drug-Lifestyle Interactions

Effects of smoked or other forms of cannabis would be additive to those of SATIVEX® with a likelihood of producing intoxication or other unwanted effects and are not recommended while using this product.

DOSAGE AND ADMINISTRATION

Adults

Dosing Considerations

SATIVEX® is for buccal use only. The spray should be directed to below the tongue, or towards the inside of the cheeks. The site should be varied. The patient should be advised not to direct the spray towards the pharynx and not to inhale the spray. It must not be sprayed into the nose.

Treatment initiation and stabilization

- On day one of treatment, patients should take one spray during the morning and one spray during the afternoon/evening. The morning dose can be taken at any time between waking up and 12 noon and the afternoon dose can be taken at any time between 4 pm and bedtime.
- On subsequent days the patient may gradually increase the total number of sprays, by one spray each day, as needed and tolerated. There should be at least a 15 minute gap between sprays. During initial titration, sprays should be evenly spread out over the day.
- If unacceptable adverse reactions such as dizziness or other CNS-type reactions develop at any time, dosing should be suspended until they have resolved. Some patients may be able to continue therapy at the dose reached by increasing the interval between doses; others may require their subsequent doses reduced. Patients should then carefully re-titrate to a tolerated dosage regimen that gives acceptable pain relief.

Following the titration period, patients are advised to maintain the optimal dose achieved. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's conditions, changes in his/her concomitant medication or if unacceptable side effects develop.

The usual dose ranges between 4 – 8 sprays daily. The majority of patients require 12 sprays or less; dosage should be adjusted as needed and tolerated. There is limited experience with doses higher than 12 sprays per day. Some patients may require and may tolerate a higher number of sprays.

Missed Dose

SATIVEX® is a self-titration regime to be used "as required" for relief of pain, therefore "missed dose" is not applicable.

Administration

Priming

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Holding the vial in an upright position, prime the SATIVEX® vial by pressing on the actuator two or three times firmly and quickly, directing into a tissue until a fine spray appears.

Important

Point the spray safely away when priming it into a tissue. Do not prime it near children, pets or an open flame.

Normal use

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Hold the vial in the upright position and direct into the mouth. Press firmly and quickly towards the buccal surface in the following regions: below the tongue or towards the inside of the cheeks. The site should be varied. Never aim at the throat, as SATIVEX® can cause irritation.
4. Replace the protective cap.
5. Keep away from sources of heat and direct sunlight.

OVERDOSAGE

SATIVEX®

Signs and Symptoms

There is no experience of deliberate overdose with SATIVEX®. Signs and symptoms of overdose were reported from a thorough QT study conducted according to international standards. After receiving 18 sprays in 20 minutes, some subjects showed serious psychiatric signs and symptoms. The initial adverse reactions appeared within one to two hours and were consistent with the intoxication effects of cannabis and THC. In four patients out of 257, the intoxication symptoms developed into major psychiatric symptoms such as depression, anxiety, paranoia, delusions, hallucinations, and / or psychosis. These serious symptoms reached a plateau after two to three hours and lasted for nine to 24 hours.

Management

Recommended treatments include counselling and interventions to prevent injury. Additional treatments should be symptomatic and supportive. Benzodiazepines may be used in patients with severe agitation. The recovering patient must be followed up until all clinical symptoms dissipate. The possibility of multiple drug involvement should be considered. The nearest local Poison Control Centre must be contacted for current information.

Experience with oral THC overdose is as follows:

Signs and Symptoms

Following MILD THC intoxication, symptoms include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE THC intoxication, symptoms include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE THC intoxication, symptoms include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous THC is 30 mg/kg (2100 mg/70 kg).

Management

An overdose severe enough to cause depression of consciousness should be treated with the normal precautions for dealing with an unconscious patient by securing the airway and monitoring vital signs. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *per oral)* may be used for treatment of extreme agitation. In the case of hypotension, patients should be placed in the Trendelenburg position (head lower than feet) or modified Trendelenburg position (only the legs elevated) until the condition remits. Intravenous fluids or pressors are rarely required.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mammalian tissues contain at least two types of cannabinoid (CB) receptor, CB_1 and CB_2. CB_1 receptors are present at nerve terminals in the CNS and also in some peripheral tissues including dorsal root ganglia, sympathetic ganglia, adrenal gland, heart, lung, reproductive tissues, urinary bladder, gastrointestinal tissues, and immune cells. Within the brain, the distribution of CB_1 receptors is heterogeneous, with a pattern consistent with the demonstrated effects of cannabinoids on motor function, cognition and memory. Relevant for pain modulation, CB_1 receptors are found on pain pathways in the brain and spinal cord, as well as on terminals of peripheral nervous system primary afferent neurons where they may mediate cannabinoid-induced analgesia. CB_2 receptors are present primarily on peripheral and central immune cells, where they may modulate immune function through release of cytokines. Cannabidiol (CBD) is an agonist of TRPV-1 (vanilloid) receptor with an inhibitory action on adenosine uptake.

Pharmacodynamics: animal data

The principal pharmacological effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant and psychoactive effects. CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic activity. THC is metabolised to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), a psycho-active metabolite. The main primary metabolite of CBD is 7-hydroxy-cannabidiol.

Pharmacokinetics: human data

Summary of Pharmacokinetic Parameters for SATIVEX® in healthy volunteers – Single dose PK in two studies. The differences seen in the PK data may reflect the inter-subject variability and the conduct of the study.

Table 4: Mean Pharmacokinetic Parameters (GWPK0112)**

Treatment	Analyte	T_{max} (hrs) (n=12)	Cmax (ng/ml) (n=12)	$t_{1/2}$ (hrs) (n=12)	AUC_{0-t} (min*ng/ml) (n=12)	AUC_{inf} (min*ng/ml) (n=12)
SATIVEX® * (Under the tongue)	CBD	1.63	2.50	1.44	408.53	427.33
	THC	1.63	5.54	1.76	808.78	837.25
	11-OH-THC	1.58	6.24	2.15	1522.09	1632.46
SATIVEX® * (Inside the cheek)	CBD	2.80	3.02	1.81	384.13	407.79
	THC	2.40	6.14	1.34	751.23	770.62
	11-OH-THC	2.40	6.13	1.91	1293.14	1362.12

* 4 sprays (total 10.8 mg THC + 10 mg CBD)

** The pharmacokinetic data show great inter-subject variability. THC, CBD, and 11-OH-THC appear in the plasma from about 30 minutes after dosing.

Table 5: Mean Pharmacokinetic Parameters (GWPK0215)

Treatment	Analyte	T_{max**} (hrs) (n=24)	C_{max} (ng/ml) (n=24)	$t_{1/2}$ (hrs) (n=24)	AUC_{0-t} (min*ng/ml) (n=24)	AUC_{inf} (min*ng/ml) (n=24)
SATIVEX®* (Under the tongue)	CBD	4.22	3.33	1.81	680.61	718.46
	THC	4.38	4.90	1.40	894.80	918.81
	11-OH-THC	3.83	4.49	2.17	1423.20	1463.67

* 4 sprays (total 10.8 mg THC + 10 mg CBD)

** As the data here represent more than one peak, T_{max} may represent an early buccal absorption and later gastrointestinal absorption.

Individual subject plasma concentration data and pharmacokinetic parameters show a high degree of inter-subject variability.

Table 6: Summary of Pharmacokinetic Parameters for SATIVEX® in MS Patients – Steady-state PK

Parameters	Cannabinoid (Analyte)	Visit A (n = 13)	Visit B (n = 7)
Pre-dose trough (ng/ml)	CBD	0.12 – 4.41	0.75 – 4.19
	THC	0.16 – 4.64	0.47 – 5.67
	11-OH-THC	0.05 – 5.41	1.02 – 5.67
C_{max} (ng/ml)	CBD	1.09 – 16.97	3.83 – 13.69
	THC	2.30 – 28.66	2.86 – 33.63
	11-OH-THC	2.76 – 20.45	3.74 – 14.22
T_{max} (hours)	CBD	1 – 6	3.0 – 6
	THC	1 – 6	2.5 – 6
	11-OH-THC	1 – 6	1.5 – 6

Note: Visit A took place after at least 20 weeks on SATIVEX®. Visit B occurred 8 weeks after Visit A. All patients were using at least 5 sprays daily.

Plasma levels have been studied in a limited number of patients on stable self-titrated doses during chronic therapy in the extension phase of study GWMS0001EXT. Most patients apparently had self-titrated their dosing to a level at which plasma concentrations for both THC and CBD were generally in the range of 5-10 ng/ml or less. Sampling of plasma concentration levels during chronic dosing suggests that significant accumulation of cannabinoids does not occur.

Absorption: Following a single buccal administration, maximum plasma concentrations of both CBD and THC typically occur within two to four hours. When administered buccally, blood levels of THC and other cannabinoids are lower compared with inhalation of smoked cannabis. The resultant concentrations in the blood are lower than those obtained by inhaling the same dose because absorption is slower, redistribution into fatty tissues is rapid and additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, a psycho-active metabolite.

Distribution: Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

Metabolism: THC and CBD are metabolized in the liver by a number of cytochrome P_{450} isoenzymes, including CYP2C9, CYP2C19, CYP2D6 and CYP3A4. They may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream and metabolized via the renal and biliary systems.

Excretion: Elimination from plasma is bi-exponential with an initial half-life of one to two hours. The terminal elimination half-lives are of the order of 24 to 36 hours or longer. SATIVEX® is excreted in the urine and faeces.

Special Populations and Conditions:

No pharmacokinetic studies were done in any special population.

STORAGE AND STABILITY

SATIVEX® should not be used beyond its expiry date. Once opened and in use, SATIVEX® should be used within 28 days (5.5 ml vial) or 42 days (10 ml vial).

Prior to opening, SATIVEX® should be stored upright in a refrigerator (2-8°C). Do not freeze. Once opened, the spray may be stored at room temperature (15-25°C). Return unused portion of SATIVEX® to the pharmacy for safe disposal or dispose of according to local regulations.

Keep away from sources of heat and direct sunlight. Keep out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Buccal spray

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

Each 100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol.

This product contains approximately 50% v/v ethanol. Each spray contains approximately 0.04 g of alcohol.

SATIVEX® is contained in an amber glass vial 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 actuation (spray).

Non-medicinal ingredients:
Ethanol anhydrous
Propylene glycol
Peppermint oil

Pack Sizes: 5.5 ml or 10 ml.
The 5.5 ml vial contains up to 48 metered sprays.
The 10 ml vial contains up to 90 metered sprays.
1, 2, 3, 4, 5, 6, 8, 10 or 12 amber glass vials per carton.
(Not all presentations may be available in Canada).

PART II: SCIENTIFIC INFORMATION

NOC

SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c

SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

SATIVEX® may be useful 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.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

Tetranabinex® is an extract of a chemically and genetically characterised cannabis plant, containing delta-9-tetrahydrocannabinol as the principal cannabinoid (delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS)).

Nabidiolex® is an extract of a chemically and genetically characterised cannabis plant, containing cannabidiol as the principal cannabinoid (cannabidiol Botanical Drug Substance (CBD BDS)).

Chemical name:

THC:

3-pentyl-6,6,9-trimethyl-6A,7,8,10A-tetrahydro-6H-dibenzo(B,D)pyran-1-ol

or
6,6,9-trimethyl-3-pentyl-7,8,9,10-tetrahydro-6H-dibenzo(B,D)pyran-1-ol

CBD:
Based on numbering system related to monoterpenes:
2-[1-methyl-4-isopropenyl-cyclohexen-3-yl]-5-pentyl-1,3-benzenediol
Based on standard IUPAC numbering:
2-[3-methyl-6-isopropenyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol

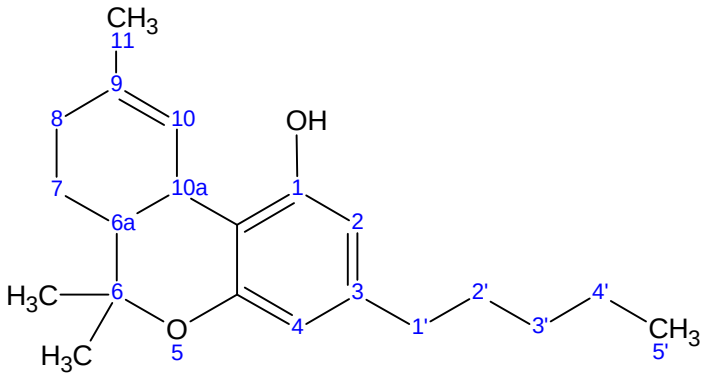
Molecular formula and molecular mass:

THC: $C_{21}H_{30}O_2$
molecular mass: 314.47

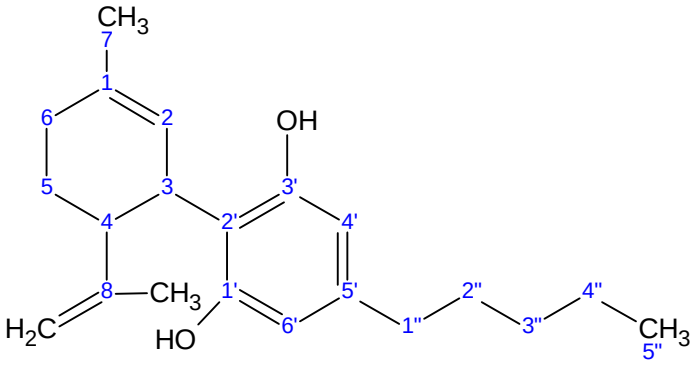
CBD: $C_{21}H_{30}O_2$
molecular mass: 314.47

Structural formula:

THC:



CBD (numbering system related to monoterpenes):



Physicochemical properties:

The THC BDS (Tetranabinex®) is a brown viscous semi-solid with an absence of immiscible liquid. It has a characteristic smell of decarboxylated cannabis. Typically it contains not less than 64% THC with the remainder being co-extracted plant extract.

Soluble in:

Methanol
Ethanol
Acetone
Dichloromethane

Insoluble in:

Water

The CBD BDS (Nabidiolex®) is a brown viscous semi-solid with an absence of immiscible liquid. It has a characteristic smell of decarboxylated cannabis. Typically it contains not less than 60% CBD with the remainder being co-extracted plant extract.

Soluble in:

Methanol
Ethanol
Acetone
Dichloromethane

Insoluble in:

Water

CLINICAL TRIALS

NOC Adjunctive treatment for the symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other medication and who demonstrate worthwhile improvement during an initial trial of therapy.

The efficacy of SATIVEX® in relieving spasticity in adult patients with MS was demonstrated with Study GWSP0604. This study was a 12-week placebo-controlled, double-blind, randomized withdrawal study in identified responders. The responders those who showed at least a 20% reduction in mean 11-point spasticity numerical rating scale (NRS) score during a 4-week period immediately prior to the withdrawal period. The patients were required to have at least moderate spasticity as defined by a score of ≥4 using a single spasticity severity NRS. Patients were required to have had spasticity due to MS of at least 3 months duration which was not wholly relieved with current anti-spasticity therapy and which was expected to remain stable for the duration of the study. Patients had to be either currently established on a regular dose of anti-spasticity therapy or to have previously tried and failed or could not tolerate suitable anti-spasticity therapy. A total of 241 patients, out of 572, qualified as responders (42%), 124 received SATIVEX® and 117 received placebo. The primary efficacy variable was the change in the mean Numerical Rating Scale (NRS) for spasticity from responder baseline to the last week of treatment. SATIVEX® was self-titrated to symptom resolution or maximum tolerated dose, though with a limit of 12 sprays per day. The change from responder baseline was -0.19 ± 1.35 standard deviation for those on SATIVEX® vs. +0.64 ± 2.14 standard deviation for those on placebo. The adjusted difference between the two groups (0.84) were statistically significant ($p = 0.0002$). Some of the secondary efficacy parameters, such as the responder rate at 30% and global impressions, were also statistically significant.

Supportive evidence of efficacy was found in Studies GWMS0106 and GWSP0702. Study GWMS0106 was a 6-week, placebo controlled, randomized parallel group study in MS patients with spasticity which was not adequately relieved with their existing therapy. Study GWSP0702 was 4-week placebo controlled, parallel group, randomized withdrawal study in MS patients with spasticity who had received beneficial effects of SATIVEX® as an add-on therapy for at least 12 weeks prior to the randomized withdrawal phase.

NOC/c Adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

The potential efficacy of SATIVEX® as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis was demonstrated by the results of a randomized, double-blind, placebo-controlled, parallel group, 4-week clinical study in multiple sclerosis patients with neuropathic pain (Study GWMS0107). There were 66 patients (14 male, 52 female) ranging in age from 27 to 51 (mean 49 ± 8.3 standard deviation). The primary efficacy measure was the change from baseline of the mean BS-11, 11-box Numerical Rating Scale (NRS). To enter the study, the patient was required to have a pain severity score ≥4 on the 11-box NRS on at least four occasions during the 7-10 day baseline period. Regular medication for neuropathic pain had to have been stable for at least two weeks prior to entry and was maintained during the

study. SATIVEX® was self-titrated to symptom resolution or maximum tolerated dose. Secondary efficacy measures included the Neuropathic Pain Scale (NPS) and sleep disturbance (also on an 11 point NRS). Completing patients from this study had the opportunity to enter an open-label extension study.

The baseline pain severity was 6.5 in the SATIVEX® group and 6.4 in the placebo group. Analysis of the change from baseline of the mean 11-box NRS pain score showed a statistically significant treatment difference of -1.25 in favour of SATIVEX® (p=0.005; 95% CI: -2.11, -0.39 units).

Efficacy was also observed in the following secondary outcome measures. A pain reduction on the 11-box NRS of at least 50% was seen in 48% of the patients treated with SATIVEX®, compared with 12% of the placebo group. Analysis of the change from baseline of the mean NPS showed a statistically significant treatment difference of -6.82 in favour of SATIVEX® (p=0.039; 95% CI: -13.28, -0.37). The NRS score for sleep improved by 2.73 from a baseline in the SATIVEX® group, and by 1.41 in the placebo group. The treatment difference of -1.39 was significantly in favour of SATIVEX® (p=0.003; 95% CI: -2.27, -0.50).

The study medication was well tolerated. There were no serious adverse events during the study, and only one patient on SATIVEX® discontinued due to an adverse event. Sixty-three of 66 (95%) eligible patients completing study GWMS0107 entered the long-term extension study.

NOC/c Adjunctive treatment for the relief of pain in adult patients with advanced cancer who experience inadequate analgesia during the highest tolerated dose of strong opioid therapy for persistent background pain

The efficacy of SATIVEX® was investigated in a two-week placebo-controlled, three-arm study in patients who reported moderate to severe pain despite already taking a strong opioid for persistent pain. The three groups were SATIVEX® (n=53), placebo (n=52), and THC cannabis extract (n=56). Some of the patients took high dose tramadol.

The primary comparison was between the SATIVEX® group and the placebo group. There were two co-primary outcome endpoints: reduction from baseline at the last observation on the 11-point Numerical Rating Scale (NRS) and the use of escape medication at the last observation. The analysis was based on the intent-to-treat (ITT) population.

Baseline NRS scores were 5.68 in the SATIVEX® group and 6.05 in the placebo group. The study outcomes showed a reduction from baseline on the NRS of 1.37 points on SATIVEX® compared with 0.69 points on placebo. The difference between the two primary comparison groups was significant in favour of SATIVEX® (p=0.024). An improvement of greater than 30% in pain score was reported by 43% of patients on SATIVEX® compared with 21% on placebo (Odds Ratio = 2.81; 95% CI: 1.22, 6.50). There was no difference in the use of escape medication between the two groups.

DETAILED PHARMACOLOGY

Pharmacokinetics

The therapeutic dose of THC is highly variable between patients, and therefore it is important that patients can accurately control their dose to get an adequate therapeutic response whilst avoiding intolerable side effects.

The oral mucosa is relatively permeable, well vascularised, and the blood supply permits systemic absorption. Therefore the oromucosal (oral cavity) route, including sublingual and buccal, offers a delivery route that allows patients to administer small, discrete increments as and when required to optimise individual dosing regimes. Thus, this route allows for greater precision in self-titration.

The high levels of 11-OH-THC following SATIVEX® administration is consistent with a proportion of the dose being swallowed, undergoing alimentary tract absorption and hepatic first pass metabolism.

Individual subject plasma concentration data and pharmacokinetic parameters show a high degree of inter-subject variability.

Following administration of SATIVEX®, T_{max} occurs later (98-253 minutes) than may be expected of a medicine administered via the oral mucosa. This almost certainly reflects alimentary tract absorption of the proportion of the administered dose that is swallowed. The locally absorbed proportion of the dose is not easily discernable from the plasma concentration data from these studies. This is not surprising as redistribution of cannabinoids from plasma is very rapid with an early phase half-life of 5-10 minutes, as has been shown following smoked marijuana and rapid automated blood sampling.

By 12-24 hours after dosing, CBD, THC and 11-OH-THC are usually at or below the limit of quantification in plasma. This is thought to be due to a combination of renal and hepatic clearance and re-distribution of the cannabinoids and their metabolites to adipose tissue.

The terminal half-lives of the principal cannabinoids in SATIVEX® have not been measured in man because of the slow release of cannabinoids from adipose tissue. Half-lives described in the published literature are of the order of 20 to 30 hours. In the clinical trials the plasma half-lives of CBD, THC and 11-OH-THC have been calculated to be of the order of 100 minutes, 85 minutes and 130 minutes respectively. (Study GWPK0112 and GWPK0215 – see Part 1, ACTION AND CLINICAL PHARMACOLOGY.)

Plasma levels have, however, been studied in patients on stable self-titrated doses during chronic therapy in the extension phase of study GWMS0001. Most patients seemed to have self-titrated their dosing to a level at which plasma concentrations were generally in the range of 5-10 ng/ml or less. Sampling of plasma concentration levels during chronic dosing suggests that significant accumulation of cannabinoids does not occur.

Pharmacodynamics

At present, two distinct cannabinoid receptors, CB_1 and CB_2, have been characterised by the use of specific agonists and antagonists and each has been cloned. In addition, two endogenous ligands, arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), have been thus far investigated. Other endogenous ligands for cannabinoid receptors have been discovered but have not yet been fully investigated. It is likely that other subtypes of cannabinoid receptors also exist.

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

Within the brain, the distribution of CB_1 receptors is heterogeneous, accounting for several well-documented pharmacological properties of CB_1 receptor agonists. For example, the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum are all populated with particularly high concentrations of CB_1 receptors, a distribution pattern that is consistent with the well-established ability of cannabinoids to alter motor function and to impair cognition and memory. Additionally, CB_1 receptors are found on pain pathways in the brain and spinal cord and also outside the CNS at the peripheral terminals of primary afferent neurons and it is thought these CB_1 receptors mediate cannabinoid-induced analgesia.

The principal pharmacological effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant and psychoactive effects (e.g. feeling drunk, disturbance in attention, dizziness, somnolence, disorientation, dissociation and euphoric mood). CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic activity.

It has been hypothesised that endogenous cannabinoids function in the CNS as “retrograde synaptic messengers” being released from postsynaptic neurons and travelling backwards across synapses to activate presynaptic CB_1 receptors and to suppress neurotransmitter release. The mechanisms by which the biological actions of endogenous cannabinoids are terminated, have not been fully evaluated. However, it appears likely that they are removed from the extracellular space by tissue uptake and that intracellular metabolism via an enzyme system, fatty acid amide hydrolase (FAAH), is also involved.

Onset of Action (PK/PD Relationships)

The pharmacokinetic studies have shown that following buccal administration of SATIVEX®, THC, CBD and 11-OH-THC (the main metabolite of THC) appear in the plasma almost simultaneously from about 30 minutes post-dose although there is wide inter-subject variability. (GWPK0112 and GWPK0215 - see Part 1, ACTION AND CLINICAL PHARMACOLOGY.) For those subjects who reported intoxication following dosing, this generally occurred between 30 and 150 minutes after dose administration but there was large inter-subject variability.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single and Repeat Dose Toxicology Studies – THC and CBD

Table 7: Overview of Acute Dose Toxicology Studies with THC[1] Identified in the Published Literature

Species	Test Article	THC Dose Range (mg/kg/day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	LD_{50} (mg/kg)
Rat	THC	225 – 3600	Acute	PO (gavage)	Not stated	Fischer: 1015 M; 800 F (for 96% pure THC); 1910 M; 1040 F (for 90% pure THC) Wistar-Lewis: 1160 M; 860 F
Rat	Synthetic THC	Not stated	Acute	IV	Not stated	15 - 20
Dog	THC	65.6 – 3000	Acute	PO (gavage)	3000	No deaths
Dog	Synthetic THC	3.9 – 210	Acute	IV	25	100
Monkey	THC	131 – 9000	Acute	PO (gavage)	9000	No deaths
Monkey	Synthetic THC	3.9 – 1050	Acute	IV	3.9	62.5

[1] Other than smoked or inhalation routes of administration.

Table 8: Overview of Repeat Dose Toxicology Studies with THC Identified in the Published Literature

Species	Test Article	THC Dose Range (mg/kg/ day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	Mortalities
Mouse	THC	5 – 500	13 weeks (dosed 5 days/week)	PO (gavage)	500	No deaths attributable to THC
Rat	THC	0.025 – 1.25	28 days	PO (gavage)	No deaths	No deaths
Rat	THC	3.75 – 30	30 days	IP	No deaths	No deaths
Rat	THC	5 – 500	13 weeks (dosed 5 days/week)	PO	150	2/10 M died at 50 mg/kg/day and 1/10 F at 15 mg/kg/day
			13 weeks followed by 9 week recovery (dosed 5 days/week)		15	1/10 M died at 50 mg/kg/day and 7/10 F at 500 mg/kg/day
Rat	9 & 8–THC	50 – 500	17 weeks	PO (gavage)	250	23% M and 27% F died at 400 mg/kg/day
Rat	THC	2 – 50	14, 28, 90 or 180 days and 180 days plus 30-day recovery	PO (gavage)	2	7% death in M in 10 mg/kg group; 22% M and 28% F death in 50 mg/kg group by Day 173
Guinea pig	THC	3	6 months	IP	No deaths	No deaths
Rabbit	THC	3 – 100	13 days	SC	No deaths	No deaths

Table 9: Overview of Single and Repeat Dose Toxicology Studies on CBD Identified in the Published Literature or Sponsored by GW Pharmaceuticals

Species	Test Article	CBD Dose Range (mg/kg/day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	LD_{50} (mg/kg)[2]
Rat (Fischer)	CBD (98%)	110 – 310	Acute	IV	160 (M) 210 (F)	232 (M) 252 (F)
Monkey	CBD (98%)	150 – 320	Acute	IV	200	212
Rat (Fischer)	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths
Rat	CBD[3]	5 – 75	14 days	IV	5 NOAEL	75 mg/kg/day
Rat	CBD[3]	1 – 25	28 days	IV	1	5
Rat	CBD[3]	25 – 225	90 days	PO (diet)	225	No deaths
Monkey	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths

[2] or lowest group in which deaths occurred for repeat dose toxicity studies
[3] CBD content 69% (doses stated in terms of CBD)

Overall, the toxicological data suggest that both THC and CBD have very low acute toxicity after single doses, suggesting a likely good margin of safety for SATIVEX® in humans. There is some evidence, from repeat dose studies, for cumulative toxicity for THC in rodents which may be due to metabolic overload. Both THC and CBD appear to have similar pharmaco-toxicological profiles in laboratory species, although at dose levels up to 300 mg/kg/day in repeat-dosing studies, in rats and monkeys, CBD produced no evidence to suggest significant effects on behaviour or on CNS function generally. Both THC and CBD reduced the weight of sex organs, an effect that is more pronounced for THC and which appears to be due to change in the functional status of the organs probably mediated via inhibitory effects on the release of sex hormones. These effects are reversible for both compounds. Both compounds caused increases in weight of the liver and adrenal glands but these effects are not associated with any histopathological changes.

Repeat Dose Toxicology Studies (1:1 THC BDS:CBD BDS)

Two repeat dose studies have been carried out using the THC BDS and CBD BDS in the same 1:1 ratio as used in SATIVEX® buccal spray.

Table 10: Overview of Repeat Dose Toxicology Studies with 1:1 THC BDS: CBD BDS

Species	Drug	Doses THC+CBD (mg/kg/day)	Duration	Route	No Observed Adverse Effect Level NOAEL) (mg/kg/day)
Rat	1:1 THC BDS: CBD BDS	50, 100, 200	6 weeks	Dietary	50 (M) 100 (F)
Dog	1:1 THC BDS: CBD BDS	10, 60, 100	4 weeks (5 weeks exposure)	Dietary	10

Repeat Dose Toxicology in Rats

In the 6-week rat study, there were no deaths during the study and no treatment-related clinical observations or ophthalmoscopic findings. Food consumption and bodyweight gain were markedly reduced at all dose levels, though not in a dosage-related manner. Although treatment-related changes were noted in a few haematology and blood chemistry parameters and in urinary pH, these were not considered to be toxicologically significant. There were notable changes in the weight of several organs, all of which correlated with histopathological findings.

Histopathological changes considered to be related to treatment were seen in the adrenal glands, liver, seminal vesicles, bone marrow, thymus, ovaries and uterus. Although some changes were generally confined to the high and intermediate dosages, the hypertrophy of the zona glomerulosa in the adrenal glands was seen in all groups. The changes seen in the bone marrow at the low dose were considered equivocal.

It was not possible to determine a No Observed Effect Level (NOEL) under the conditions of this study. However based on the pathology, the No Observed Adverse Effect Level (NOAEL) was 50 mg/kg/day for males and 100 mg/kg/day for females.

The extent of systemic exposure (AUC 0-last) for CBD and THC was similar in male and female rats and generally increased approximately in proportion with increasing dose level. The toxicokinetic parameters are presented below.

Table 11: Toxicokinetic Parameters for 6 week Exposure in Male Rats

Week 4 (Day 1 of Steady State)						
	THC	THC	THC	CBD	CBD	CBD
Dose	50	100	200	50	100	200
C_{max} (ng/ml)	509.19	1130.36	1498.45	87.12	224.61	491.17
T_{max} (hours)	24:00	04:00	08:00	24:00	04:00	08:00
AUC (0 - last) (hr*ng/ml)	7253.53	16127.18	22517.08	1120.15	3136.49	7073.30

The C_{max} for THC and CBD are far in excess of the plasma levels achieved by repeat dosing with SATIVEX® in human patients gaining therapeutic benefit (5-30ng/ml, Study GWMS0001EXT). The C_{max} plasma levels achieved in this study at the top dose are 50 times

the anticipated plasma exposure in humans for THC and 50 times the anticipated plasma exposure in humans for CBD.

Repeat Dose Toxicology in Dogs

The intended maximum dose level was 200 mg/kg/day. In order to dose the animals up to this level, dose titration is necessary. During the ascending dose phase of the study a spectrum of clinical observations was noted in the high dose animals that were directly related to the drug administration, thus the maximum dose was reduced during the steady state period to 100 mg/kg/day. The corresponding toxicokinetic parameters are presented in the table below.

Table 12: Toxicokinetic Parameters for 9 week Exposure in Male Dogs

Week 4 (Day 1 of Steady State)						
	THC	THC	THC	CBD	CBD	CBD
Dose	10	45	200	10	45	200
C_{max} (ng/ml)	545.01	1011.76	8648.41	385.07	863.52	8341.80
T_{max} (hours)	6.67	4.67	4.00	6.67	4.67	4.00
AUC (0 - last) (hr*ng/ml)	6980.78	12830.38	76127.19	5053.85	11803.53	89098.66
Week 9 (Day 25 of Steady State)						
Dose	10	45	100	10	45	100
C_{max} (ng/ml)	434.46	1179.00	2937.10	362.16	1440.16	3280.48
T_{max} (hours)	4.67	6.00	3.00	4.67	6.67	3.00
AUC (0 - last) (hr ng/ml)	6325.67	17238.66	32903.15	5402.50	23102.60	44380.32

In conclusion, a spectrum of transient but severe clinical observations, some of which were CNS related, led to reduced food consumption and body weight gain and accounted for the reduction of the repeat high dose level from 200 to 100 mg/kg/day. However other changes were limited to elevated liver weight and a possibly adaptive hepatocellular hypertrophy at dose levels of 45 mg/kg/day and above. In addition, the elevated alkaline phosphatase activation noted in these animals was probably associated with this liver change. Therefore, the NOAEL for 1:1 CBD BDS: THC BDS could be considered as 10 mg/kg/day when administered orally to the dog over 30 days.

The C_{max} for THC and CBD are far in excess of the plasma levels achieved by repeat dosing with SATIVEX® in human patients gaining therapeutic benefit (5-30ng/ml, Study GWMS0001EXT). The C_{max} plasma levels achieved in this study at the top dose are 98 times the anticipated plasma exposure in humans for THC and 110 times the anticipated plasma exposure in humans for CBD.

Repeat Dose Toxicology Studies - SATIVEX®

Repeat Dose Toxicology in Rats

SATIVEX® was administered by daily oral gavage Sprague-Dawley rats in a 26-week repeated dose toxicology study. The study included three active treatment groups, one vehicle (placebo) group and one sham (purified water) group. The doses for the active treatment groups were 5.4:5.0, 13.5:12.5 and 40.5:37.5 THC:CBD mg/kg/day. The high dose was reduced to 27:25 THC:CBD mg/kg/day with a reduction of dosage volume from 1.5 to 1.0 mL/kg/day because of continued mortality. Three subsets of animals were included to study recovery (4-week), toxicokinetics and immunotoxicity.

A high mortality rate (33 – 38%) was observed in the two upper dose groups and the placebo group. Clinical signs and pathological examinations indicated that the mortalities were caused by accidental delivery of the test items into the trachea. The survivors showed dose dependent toxicities attributable to the excipients and cannabinoids. The excipient-related toxicities included loud breathing, abdominal breathing, pallor of extremities, etc. The cannabinoid-related toxicities included ptyalism, ataxia, body tremors, scabs, etc. The adverse effects were more frequent in the female rats.

Table 13: Toxicokinetic Parameters for 6 month Exposure in Male Rats

Week 26 (of Steady State)						
	THC	THC	THC	CBD	CBD	CBD
Dose	5.4	12.5	27	5.0	13.5	25
C_{max} (ng/ml)	245	952	1243	53.1	155	255
T_{max} (hours)	2	9	9	2	9	9
AUC (0 - last) (hr*ng/ml)	1938	8366	12575	295	1246	2650

The plasma THC/CBD levels indicated that exposure increased near/supra-linearly with dose level. Gender effect for THC (levels generally higher in females) and accumulation for both THC and CBD were also observed. Abnormalities in biochemistry, haematology and immunology were observed, but their significance in toxicology was unclear. The NOAEL seemed to be lower than 5.4:5.0 THC:CBD mg/kg/day.

Implications of the animal toxicity studies with regard to patients

At the maximum dosage levels used in humans of about 1 mg/kg/day for each, it is considered that SATIVEX® is unlikely to produce any significant target organ toxicity in humans. However, detrimental effects on reproductive function cannot be ruled out at this dosage level.

Genotoxicity

A full battery of four genotoxicity assays, (the AMES test (bacterial mutation assay), the mouse mammalian cell mutation assay (mouse lymphoma), the mouse micronucleus assay and the unscheduled DNA synthesis assay), have been conducted using 1:1 THC BDS:CBD BDS or

with CBD BDS. They all produced negative results and have shown that at the concentrations tested, there were no genotoxic effects.

Three genotoxicity tests were carried out with SATIVEX®. SATIVEX® did not show any mutagenic activity in the bacterial reverse mutation test with *Salmonella typhimurium* (AMES test). In a mouse lymphoma assay, no mutagenic activity was noted in the presence of SATIVEX® with the exogenous metabolic activation system (S-9 mix). However, there was a slight increase in mutation frequency without S-9 mix. In order to evaluate and confirm the biological significance of the positive results obtained in the mouse lymphoma test with SATIVEX®, an *in vivo* rat micronucleus assay was conducted. Under the experimental conditions, SATIVEX® did not induce any damage to chromosomes or the mitotic apparatus of rat bone marrow cells after two oral administrations separated by a 24-hour interval at dose levels of 0.5, 1 or 2 mL/kg/day.

Carcinogenicity

Carcinogenicity - THC

THC has been fully evaluated for carcinogenic potential by well-documented and reported 2-year studies in mice and rats in the US National Toxicology Programme in 1996. The results obtained in both species were generally consistent in terms of clinical signs, body weight changes and incidences of non-neoplastic and neoplastic lesions. The results obtained in rats were clearly negative whilst in mice a non-dosage related increase in thyroid follicular cell tumours was seen at a single dosage level (125 mg/kg/day, which is 100 times the highest tested dose in humans, on a mg/kg basis). This effect is considered to be of doubtful toxicological significance in view of the lack of a dose-response relationship and the lack of evidence to suggest that hyperplasia of thyroid follicular cells progressed to adenomas or carcinomas. This evidence, taken together with the lack of structural relationship of THC to any known carcinogen and to its negative responses in most genotoxicity tests, suggests that it is likely to have a very low carcinogenic potential in humans. Positive carcinogenic effects reported for THC after subcutaneous administration in mice are considered of doubtful scientific validity since the results have not been published in full or confirmed by other workers.

Carcinogenicity - CBD

The carcinogenic potential of CBD BDS was evaluated in a 2-year carcinogenicity study in rats (GW Study No JJG003). No apparent effects on survival were noted. There was no increased incidence of any factor contributory to death when treated animals were compared with Controls. Clinical signs observed were those expected for rats of this age and strain and were considered to be unaffected by administration of CBD BDS. There was no evidence of an adverse effect of the drug on the incidence or time of onset of palpable masses.

A clear treatment and dose related reduction in overall bodyweight gain (Weeks 1 – 104) was seen for males and females given 15 or 50 mg/kg/day; at 50 mg/kg/day, males had a 26 % reduction and females had a 35 % reduction in bodyweight gain compared with Controls. A dosage related reduction in food consumption and food conversion efficiency was present for both sexes throughout the study.

There were no effects of treatment with CBD BDS on haematological parameters in males or females during Weeks 52 or 78. During Week 103 only, the white blood cell counts were statistically significantly lower than those of Controls for males given 15 or 50 mg/kg/day; however individual values were within the background ranges found in this laboratory and the differences from Controls were considered to be of no toxicological significance. There was no evidence of an increased incidence of leukaemia in the CBD BDS treated groups.

There was an apparent increase in the incidence of abnormal size of the thyroid glands in CBD BDS-treated males. There was a reduction in the number of skin masses recorded in both males and females of the 50 mg/kg/day group and in the number of findings recorded in the pituitary gland and mammary tissue in the females of this group. In association with the reduced number of findings in the pituitary gland there was a reduction in the number of ventral depressions in the brain that are generally caused by pituitary enlargement.

There was no indication of carcinogenic potential. Indeed, there was, in animals given 50 mg/kg/day, an apparent reduction in the incidence of tumours generally associated with hormonally-mediated neoplasia in ageing animals. Non-neoplastic findings considered to be associated with treatment included an increased incidence of centrilobular hypertrophy in the liver of males in the 15 mg/kg/day and the 50 mg/kg/day groups and females in the 50 mg/kg/day group. There was an increase in focal follicular hyperplasia in the thyroid glands of males given 50 mg/kg/day.

It was concluded that administration of both 15 and 50 mg/kg/day of CBD BDS in the diet resulted in a greater than 10 % reduction in overall bodyweight gain in both sexes and there was good survival in all groups over 104 weeks of treatment. There was no evidence that administration of CBD BDS at dose levels of up to 50 mg/kg/day to the HsdBrlHan:WIST rat influenced tumour formation. There was no apparent increase in the incidence of neoplasia, alteration in the time of tumour onset or induction of rare tumours. There was some evidence of reduction in some of the commonly seen hormone mediated ageing changes, especially those seen in ageing females.

Reproductive and Developmental Toxicity

Four reproductive toxicology studies have been completed using 1:1 THC BDS: CBD BDS, comprising:

- Embryo-foetal developmental toxicity (teratology) in rats
- Embryo-foetal developmental toxicity (teratology) in rabbits
- Pre- & Post-natal developmental toxicity in rats
- Fertility and early embryonic developmental toxicity in rats

Table 14: Reproductive Toxicology Studies with 1:1 THC BDS: CBD BDS

Study	Species	Dose 1:1 THC BDS:CBD BDS mg/kg/day	Route	Findings
Embryo-foetal developmental toxicity (teratology)	Rat	1,5,25	Oral (gavage)	NOEL of 1 mg/kg/day for foetal development

Table 14: Reproductive Toxicology Studies with 1:1 THC BDS: CBD BDS

Study	Species	Dose 1:1 THC BDS:CBD BDS mg/kg/day	Route	Findings
Embryo-foetal developmental toxicity (teratology)	Rabbit	5,10,25	Oral (gavage)	NOEL less than 5 mg/kg/day for maternal toxicity. NOEL of 25 mg/kg/day for developmental toxicity
Pre-and post-natal developmental toxicity	Rat	1,2,4 mg/kg/day	Oral (gavage)	NOAEL 1 mg/kg/day for maternal toxicity
Fertility and early embryonic developmental toxicity	Rat	1,5,25 mg/kg/day	Oral (gavage)	NOAEL for male fertility was 25 mg/kg/day. NOAEL for female fertility and embryonic development was 25 mg/kg/day

Embryo-foetal Developmental Toxicity (Teratology) in Rats

The doses selected for this study were taken from a dose range finding study. Three groups of 24 timed-mated, sexually mature female rats of the Crl:CD (SD) IGS BR VAF PLUS strain were dosed once daily, by oral (gavage), with 1:1 THC BDS: CBD BDS at dose levels of 1, 5 and 25 mg/kg/day on Day 6 to Day 17 of gestation, inclusive.

At 5 and 25 mg/kg/day dose-related significant losses in bodyweight and lower food consumption were observed along with persistent clinical observations in the period after dosing. Therefore the NOEL for maternal toxicity was considered to be 1 mg/kg/day. At this dose level, maternal systemic exposure for the three analytes were as follows: for CBD AUC 0-last: 4.74-15.81 hr*ng/ml, for THC AUC 0-last: 22.28-68.00 hr*ng/ml and for 11-hydroxy THC AUC 0-last 14.31-22.53 hr*ng/ml.

At 1 mg/kg/day values for foetal abnormalities were comparable with the control animals and were therefore considered to be within the normal range for rat foetuses. It is therefore considered that 1 mg/kg/day is the NOEL for foetal development. Increased incidences of minor abnormalities and variants at 5 or 25 mg/kg/day were generally related to a slight delay of ossification of the foetal skeleton. These findings were not considered to have an adverse effect on foetal development.

Embryo-foetal Developmental Toxicity (Teratology) in Rabbits

Three groups of twenty time-mated female New Zealand White Rabbits were dosed once daily, via the oral (gavage) route, from Day 6 to Day 18 of gestation (total of 13 days inclusive), with 1:1 THC BDS: CBD BDS. The dose levels used were 5, 10, and 25 mg/kg/day.

Two females (10 mg/kg/day) aborted or started to abort on Days 25 and 28 of gestation, and 2 females (25 mg/kg/day) aborted on Days 27 and 24, respectively. Clinical signs of unsteady gait and changes in activity were recorded at 10 and 25 mg/kg/day. Reductions in group mean bodyweight were noted, especially at 10 and 25 mg/kg/day. Bodyweight performance improved after cessation of dosing, but the absolute group mean bodyweight on Day 28 of

gestation was lower than controls and there was an overall loss in bodyweight over the treatment period.

Over Days 6 to 9 of gestation, dosage-related reductions in food consumption were observed at 10 and 25 mg/kg/day. Dosage-related reductions in food consumption were observed in all groups treated with 1:1 THC BDS: CBD BDS over Days 9-19 of gestation. Two females from each of the groups dosed at 10 and 25 mg/kg/day aborted. There were no other findings recorded at necropsy considered to be related to treatment.

Pregnancy Data: There were 18 (90%), 17 (85%), 16 (80%) and 14 (70%) of females with live foetuses on the scheduled day of necropsy at 0, 5, 10 and 25 mg/kg/day. There was a slightly lower number of pregnant females in the groups treated with 5, 10 and 25 mg/kg/day THC BDS: CBD BDS, however, values were within the background data range. There was no effect of treatment with 1:1 THC BDS: CBD BDS on any pregnancy parameter.

There were marginal reductions in group mean litter weight and reductions in group mean foetal weight were observed at 10 and 25 mg/kg/day. Higher incidences of minor abnormalities and variants in the groups treated with 1:1 THC BDS: CBD BDS were generally associated with the incomplete or non-ossification of the skeleton and were considered to be indicative of slightly delayed foetal development as a result of an indirect effect of maternal treatment.

Based on the results of this study the NOEL was considered to be less than 5 mg/kg/day with regard to maternal toxicity and 25 mg/kg/day with regard to developmental toxicity.

Pre- & Post-natal Developmental Toxicity in Rats

The objective of this study was to investigate the effects of 1:1 THC BDS: CBD BDS on embryonic, foetal and post-natal development of the rat following administration to mated females from Day 6 of gestation throughout lactation to Day 20 of lactation inclusive. The F1 generation was allowed to mature, untreated and the effects on growth, development, behaviour and reproductive performance were assessed.

Three groups of 25 time-mated female rats were dosed, once daily by oral (gavage), from Day 6 of gestation to Day 20 of lactation, inclusive, with the drug (1:1 THC BDS: CBD BDS). The dose levels used were 1, 2 and 4 mg/kg/day.

Maternal treatment with 1:1 THC BDS: CBD BDS at 2 and 4 mg/kg/day during gestation and at 4 mg/kg/day during lactation resulted in a reduction in food consumption and corresponding lower mean gains in bodyweight. At 1 mg/kg/day lower bodyweight gain was observed at the start of treatment on Day 6 of gestation until Day 7 of gestation. Therefore the NOAEL for maternal treatment with the drug was considered to be 1 mg/kg/day.

Table 15: Comparison of Plasma & Breast Milk Levels

	Plasma Levels (8hrs Post Dose)		Breast Milk Levels (6hrs Post Dose)	
Dose Level	THC (ng/ml)	CBD (ng/ml)	THC (ng/ml)	CBD (ng/ml)
1 mg/kg/day	1.99* <1.00* <1.00*	<1.00* <1.00* <1.00*	356.76 464.97 547.27	97.71 171.65 185.23
2 mg/kg/day	13.36	3.36	1251.41	482.38

Table 15: Comparison of Plasma & Breast Milk Levels

	Plasma Levels (8hrs Post Dose)		Breast Milk Levels (6hrs Post Dose)	
	87.71	25.47	657.11	199.86
	16.07	2.86	883.14	302.23
4 mg/kg/day	131.69	37.06	2030.03	769.43
	110.67	26.16	1407.65	445.00
	388.98	108.52	1227.75	487.25

*Data from Embryo-foetal toxicity study in rats

Pup Growth and Pup/F1 Development:

Maternal administration of drug at 4 mg/kg/day resulted in a slightly lower lactation index. Lower mean pup bodyweights were recorded throughout lactation for males and females so that at selection to the F1 generation group mean bodyweights were lower than those of the controls and remained marginally lower through the maturation period. Associated with this finding there was a lower percentage of pups with the righting reflex on Day 5 of lactation. Additionally, there was marginally less mean time spent on the Rotarod (assessment of locomotion) for F1 males following maternal administration of the drug at 4 mg/kg/day.

Therefore the NOEL was considered to be 2 mg/kg/day. As expected, due to the lipophilic nature of the molecules, there were considerable levels of cannabinoids in the maternal breast milk. Even at 1mg/kg/day there were 40-60 times the plasma level of cannabinoids in the breast milk.

F1 Reproductive Performance:

There was no adverse effect of maternal treatment with 1:1 THC BDS: CBD BDS on fertility or mating performance for F1 males and females or on gestation of the F1 females. Therefore the NOAEL was considered to be 4 mg/kg/day.

Fertility and Early Embryonic Developmental Toxicity in Rats

The aim of the study was to investigate the effects of the drug on the fertility and early embryonic development of the rat following administration to males for 28 days prior to pairing and during pairing until necropsy, and to females for 14 days prior to pairing, during pairing and then to Day 6 of gestation. Three groups of 25 male and 25 female Sprague-Dawley derived rats were dosed once daily, by oral (gavage), with 1:1 THC BDS: CBD BDS at dose levels of 1, 5 and 25 mg/kg/day. The males were dosed for 28 days prior to pairing, during pairing and for at least two weeks after the end of the pairing period. The females were dosed for 14 days prior to pairing, during pairing and up to and including Day 6 of gestation.

Dosing was associated initially with clinical signs of decreased activity, reduced bodyweight and food consumption. There was no effect of treatment on fertility, therefore the NOAEL for male fertility was considered to be 25 mg/kg/day.

Oral (gavage) administration of the test article to female rats at 5 or 25 mg/kg/day for 14 days prior to pairing, during pairing and until Day 6 of gestation was associated with lower gains in mean bodyweight and reduced food consumption. Additionally, at 25 mg/kg/day clinical signs of decreased activity were seen during the initial dosing period. At 5 or 25 mg/kg/day there was

no effect of treatment on the number of females that became pregnant. There was a treatment-related effect on the mean number of corpora lutea resulting in a statistically significant reduction in the number of implants and live embryos per female compared with the controls, however, values were within background ranges and were therefore considered not to be of toxicological significance. The NOAEL for female fertility and early embryonic development was considered to be 25 mg/kg/day.

Based on these data, it would be inadvisable to use the preparation in human females either during pregnancy or nursing. Adequate contraceptive precautions should be taken in all females of child-bearing potential treated with SATIVEX® and the preparation is unsuitable for use in pre-pubertal children.

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PART III: CONSUMER INFORMATION

[N]SATIVEX®

delta-9-tetrahydrocannabinol 27 mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25 mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

SATIVEX® is indicated, as add-on treatment, for symptomatic relief of muscle stiffness in adult patients with multiple sclerosis (MS) who have not responded adequately to other medication and who demonstrate worthwhile improvement during an initial trial of therapy.

SATIVEX® may be useful, as add-on treatment, for the symptomatic relief of pain caused by damage to the nerves in adult patients with multiple sclerosis (MS).

SATIVEX® may be useful, as add-on pain control treatment, in adult patients with advanced cancer who continue to experience moderate to severe pain even after receiving the highest tolerated dose of a strong opioid pain medication.

SATIVEX® has been approved with conditions for the second and third indications above, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

This leaflet is part III of a three-part "Product Monograph" published when SATIVEX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SATIVEX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SATIVEX® is used to relieve muscle stiffness in people with multiple sclerosis who do not get enough relief from other drugs they are using and who find additional relief with SATIVEX®.

SATIVEX® is used to relieve neuropathic pain (pain caused by damage to the nerves), in people with multiple sclerosis (MS). It is also used to relieve pain in patients with advanced cancer who are not getting enough pain relief even at the highest tolerated dose of a strong opioid pain medication.

What it does:

SATIVEX® helps to relieve your pain.

When it should not be used:

You should **not** use this product if you:

- Have a known or suspected allergy to any cannabis-based products, propylene glycol, ethanol or peppermint oil.
- Have serious heart disease.
- Have a history of schizophrenia or any other psychotic disorder.
- Are a child or adolescent under 18 years of age.
- Are pregnant or nursing.
- Are female at risk of pregnancy and not using a reliable contraceptive.
- Are male and intending to start a family while on treatment with SATIVEX®.

Medicinal ingredients:

SATIVEX® contains *Cannabis sativa* L. extracts Tetranabinex® and Nabidiolex® equivalent to 27 mg/ml delta-9-tetrahydrocannabinol (THC) and 25 mg/ml cannabidiol (CBD).

What the nonmedicinal ingredients are:

Ethanol
Propylene glycol
Peppermint oil (flavouring)
This is a full listing of all nonmedicinal ingredients.

Dosage forms:

SATIVEX® is provided as a solution in a spray pump. It is contained in an amber glass vial fitted with a metering pump delivering 100 microlitres per actuation (spray). The pump is protected with a plastic cap.

SATIVEX® is for buccal use. This means SATIVEX® is to be sprayed into the mouth, under the tongue or on to the inside of the cheek. Each 100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol.

SATIVEX® is available in 5.5 ml and 10 ml amber glass vials. *(Not all presentations may be available in Canada)*

The 5.5 ml vial contains up to 48 metered sprays.
The 10 ml vial contains up to 90 metered sprays.

(Not all presentations may be available in Canada)

SATIVEX® is packed as individual, two, three, four, five, six, eight, ten or 12 vials in each carton.
(Not all presentations may be available in Canada)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC, one of the principal active components of SATIVEX®, has numerous effects on the central nervous system such as changes in mood, decreased mental performance and memory and altered perceptions of reality. Symptoms such as fainting and interference in the physical ability to carry out complicated tasks have been seen in patients taking SATIVEX®. Therefore you should not drive, operate machinery or engage in activities that require unimpaired judgement and coordination.

While taking SATIVEX® you should not drink alcohol or take other drugs which may have an effect on the central nervous system such as sedatives or hypnotics, without consulting your doctor, as these products have a further additive effect on some of the symptoms listed above.

BEFORE you use SATIVEX® talk to your doctor or pharmacist if you:

- suffer from any allergic reactions
- suffer from epilepsy
- suffer from any liver, kidney or heart disease
- suffer from schizophrenia or depression
- have an irregular heart beat/rhythm, including a fast or slow pulse
- have high blood pressure
- are addicted to drugs or alcohol
- are taking other medicines.

You and your partner must ensure reliable contraceptive precautions are taken during your treatment and for at least three months after you stop taking SATIVEX®.

There may be a potential for abuse or development of dependence in some individuals with long-term use. Discuss with your doctor.

If you see another doctor or go into hospital, let them know what medicines you are taking.

This product contains approximately 50% v/v ethanol. Each spray contains approximately 0.04 g of alcohol. The usual daily dose will be greater than one spray. It may be harmful for those suffering from alcoholism. The alcohol content should be taken into account when the product is to be used in high-risk groups such as patients with liver disease or epilepsy.

INTERACTIONS WITH THIS MEDICATION

Some drugs may interact with SATIVEX®. Therefore, it is important to talk to your doctor or pharmacist about any other medicines you are taking such as but not limited to:

- sedatives
- hypnotics
- fentanyl and the related opioid drugs sufenatil and alfenatil
- amitriptyline
- cannabis (marijuana, pot). Do not smoke marijuana while using SATIVEX®.
- Alcohol may interact with SATIVEX®, particularly in affecting coordination, concentration and the ability to respond quickly.

PROPER USE OF THIS MEDICATION

Usual dose:

SATIVEX® is to be sprayed into your mouth, under your tongue or on to the inside of your cheek. Do not spray the back of the throat to avoid inhaling and to avoid throat irritation. Vary the location in the mouth into which you spray SATIVEX®, in order to avoid stinging and discomfort in the mouth. **Do not spray into the nose.**

The dose you require is determined by you. You can determine the dose that best suits you according to the pain relief you experience from taking SATIVEX®. Your regular daily dose is determined by increasing your dose gradually over the first few weeks of taking SATIVEX®.

- On day one, you should take one spray during the morning and one spray during the afternoon/evening. The morning dose can be taken at any time between waking up and 12 noon, and the afternoon/evening dose can be taken at any time between 4 pm and bedtime.

- After the first day you may gradually and carefully increase your intake by **one spray each day**, as needed and tolerated until you experience improved relief of your pain.

- There should be at least a 15 minute gap between sprays.
- When you have found a daily number of sprays that controls your pain, you may adjust the timing between them, depending on how you feel.
- Once you establish the timing and number of sprays that controls your pain, maintain that schedule.
- The best dosing schedule of sprays varies from person to person.

The average dose of SATIVEX® is 4 - 8 sprays per day. The majority of patients need 12 sprays a day or less; there is limited experience with doses higher than 12 sprays a day but you may need a higher number of sprays.

If you experience any bothersome side effects reduce your number of sprays or increase the time between each dose.

Follow these instructions unless your doctor gives you different advice. If there is something you do not understand, ask your doctor or pharmacist. Continue to take this medicine for as long as your doctor prescribes.

HOW TO USE YOUR SPRAY

On first opening of a new vial:

Shake the vial gently and remove the protective cap. Place the vial between the thumb and second finger with the first finger placed on the actuator. Press two or three times firmly and quickly into a tissue until a fine spray appears. See Diagram 1.

The medicine is now ready for use.

On normal use:

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Place the vial between the thumb and second finger with the first finger placed on the actuator.
4. Hold the vial in the upright position and direct the spray into your mouth under the tongue or onto the inside of the cheek. Hold your breath and press firmly and quickly. See Diagram 2.

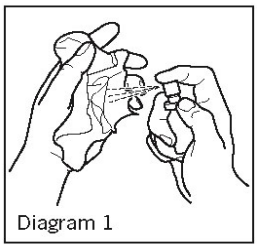
Diagram 1

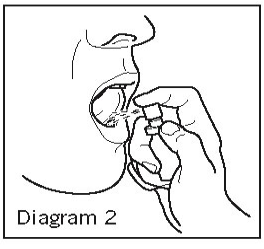
Diagram 2

5. Replace the protective cap.

Important:

If you take 5 sprays each day you will notice after about 10 days for the 5.5 ml vial (17 days for the 10 ml vial) that the noise of the spray action may change. You may also become aware of a different feeling in your mouth. This is indicating your medicine container is nearly empty. At this point start a new container of medicine.

Keep spray away from eyes. If the spray comes into contact with your eyes or skin it should be washed away immediately with lots of water.

Do not spray near children or pets.

Do not use the spray near an open flame or heat source.

Overdose:

If you accidentally take more than you normally do and you experience severe intoxication reactions, contact your nearest hospital emergency department, regional Poison Control Centre or tell your doctor immediately. Symptoms of intoxication reactions include hallucinations (seeing/hearing things that are not there), delusions (believing things that are not true), anxiety or paranoia (excessive anxiety or fear), increased or decreased heart rate with postural hypotension (feeling dizzy upon standing up). Bring any remaining medicine and the container with you.

The day following an overdose, you should make a follow-up appointment with your usual doctor.

Missed Dose:

If you forget to take a dose, do not worry. SATIVEX® is a medicine that is taken as required. Just take another as soon as you feel you need to.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SATIVEX® may cause side effects in some patients. They may include dry or sore mouth, feeling or being sick, discomfort and stinging in the mouth or mouth ulcers, tiredness, drowsiness, confusion, dizziness or faintness, disorientation, poor concentration, impaired memory or poor recall, strange ideas, a feeling of unreality, feeling abnormal or drunk, poor balance, slurred speech, feeling people are against you and a feeling of general happiness or a “high” (easy laughing, heightened awareness). Other side effects may include palpitations (rapid heartbeat), vertigo, blurred vision, constipation, diarrhoea, weakness, feeling ill, tooth or mouth discolouration, throat infection, upset stomach, increase or decrease in appetite, abnormal taste, cough or throat irritation.

You may also have side effects of stomach pain or disturbance in attention.

Stinging or discomfort in the mouth may be experienced if SATIVEX® is sprayed in the same place in the mouth on repeated occasions. This is usually overcome by varying the area in the mouth where SATIVEX® is sprayed. Do not continue spraying SATIVEX® onto sore or inflamed areas. If soreness persists inform your doctor.

If unacceptable and unwanted effects occur, stop taking SATIVEX®. These effects can be expected to wear off within a few hours. When returning to your medicine the dose should be reduced or the time between doses increased.

If you suffer any of these side effects and they become troublesome or continue, or you feel unwell in any other way, seek advice from your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom /Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	fatigue	✓		
	dizziness	✓		
Common	fainting			✓
	high or low blood pressure		✓	
	rapid heartbeat			✓
	panic attacks (suddenly being afraid)	✓		
	disorientation/confusion			✓
	depression (sad or low mood)		✓	
	paranoia (excessive fear and anxiety)			✓
	anorexia (decreased appetite)		✓	
	feeling drunk	✓		
	difficulty passing urine	✓		
	falls		✓	
Uncommon	hallucinations (seeing or hearing things that are not there)			✓
	thoughts about suicide			✓
	transient toxic psychosis (losing a sense of reality and not behaving normally)			✓

This is not a complete list of side effects. For any unexpected effects while taking SATIVEX®, contact your doctor or pharmacist.

HOW TO STORE IT

Store upright.

This product is flammable. Replace cap after use.

Store your unopened medicine in a refrigerator (2-8°C). Do not freeze.

Once SATIVEX® is opened, use within 28 days for the 5.5 ml vial (42 days for the 10 ml vial). Opened vials of SATIVEX® may be stored at room temperature (15-25°C).

Shake the vial gently before use.

Do not leave your medicine in a hot place such as in direct sunlight or near a heat source.

Store in a secure place. Do not give your medicine to anyone else.

Do not use SATIVEX® after the expiry date shown on the product packaging.

Return unused portion of SATIVEX® to the pharmacy for safe disposal or dispose of according to local regulations.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

1. Report online at www.healthcanada.gc.ca/medeffect
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
   - Fax toll-free to 1-866-678-6789, or
   - Mail to: Canada Vigilance Program
     Health Canada
     Postal Locator 0701D
     Ottawa, Ontario
     K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained by contacting the importer, Bayer Inc., at: 1-800-265-7382.

E-mail: canada.medinfo@bayer.com
Bayer Canada web address: www.bayer.ca

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