

PRODUCT MONOGRAPH

^NSATIVEX[®]

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

SATIVEX[®], indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults, has been issued a marketing authorization with conditions, to 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 authorization.

GW Pharma Ltd.
Salisbury, Wiltshire
U.K. SP4 0JQ

Submission Control No: 103080

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

Date of Preparation:
April 6, 2006

**This product has been approved under the
Notice of Compliance with Conditions (NOC/c) Policy for its indicated use.**

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.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	4
SUMMARY PRODUCT INFORMATION.....	4
INDICATIONS AND CLINICAL USE	5
CONTRAINDICATIONS	6
WARNINGS AND PRECAUTIONS	7
DRUG DEPENDENCE/ABUSE LIABILITY	10
ADVERSE REACTIONS.....	11
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION	17
OVERDOSAGE	18
ACTION AND CLINICAL PHARMACOLOGY	20
STORAGE AND STABILITY	22
SPECIAL HANDLING INSTRUCTIONS.....	22
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	22
PART II: SCIENTIFIC INFORMATION	22
PHARMACEUTICAL INFORMATION.....	23
CLINICAL TRIALS	26
DETAILED PHARMACOLOGY	27
MICROBIOLOGY	29
TOXICOLOGY	30
REFERENCES	35
PART III: CONSUMER INFORMATION.....	36

N^SSATIVEX[®]

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

PART I: HEALTH PROFESSIONAL INFORMATION

SATIVEX[®], indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults, has been issued a marketing authorization with conditions, to 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 authorization.

SUMMARY PRODUCT INFORMATION

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

NOC/c INDICATIONS AND CLINICAL USE

SATIVEX[®] may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis (MS) in adults.

The effectiveness of SATIVEX[®] in long-term use (i.e. more than 4-6 weeks) has not been evaluated in placebo-controlled clinical trials. The physician who elects to use SATIVEX[®] for extended periods in the treatment of neuropathic pain in MS should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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 and as such cannot be used or prescribed except for their recognized indication.

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.

NOC/c CONTRAINDICATIONS

SATIVEX[®] is contraindicated in:

- patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil
- patients with significant hepatic or renal impairment
- 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](#)”)

NOC/c 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, some of which are called “intoxication type reactions”. 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[®]. “Intoxication type reactions” (see Table 2) appear to be dose-related, increasing in frequency with higher dosages, and subject to great inter-patient variability. They usually remit 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 and the patient should be closely observed in an appropriate setting until his/her mental state returns to normal. 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](#)”).

Buccal Mucosa

Administration site irritation was very common (22.3%) during short-term use of SATIVEX[®].

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

Carcinogenesis and Mutagenesis

Please see data in Part II – [TOXICOLOGY](#).

Cardiovascular

See “[Serious Warnings and Precautions](#)”.

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

In long-term open-label studies, adverse events of elevated ALT were reported in 11 of 424 patients (2.6%). In no case did the elevation exceed 3 times ULN and in no case did an elevated ALT result in the cessation of treatment with SATIVEX[®].

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. It 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

In long-term Phase III extension studies with SATIVEX[®], the terms “depressed mood”, “depression” and “depression aggravated” have been reported by a total of 5% of patients in 4% of whom it was thought to be treatment-related. Suicidal ideation has been seen in two patients taking SATIVEX[®]. One event was attributable to an increase in abdominal pain but a causal relationship with SATIVEX[®] could not be ruled out, and the other case was attributed to the patient’s history of depression and suicidal ideation. There was also one other patient who died from an amitriptyline overdose but this was attributed to an accidental overdose. The incidence of these events is consistent with that observed in populations of MS patients followed for a prolonged period of time. 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. Use SATIVEX[®] with caution, if at all, in patients receiving other psychoactive drugs because of the potential for additive or synergistic CNS effects.

Intoxication Type Reactions

See Boxed Warning and [OVERDOSAGE](#)

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 his partner. If a female participant became pregnant, she had to discontinue from the trial.

Nursing Women:

In studies in laboratory species, as expected, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Following repeat dosing 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.

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

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

SATIVEX[®] has been administered to over 424 patients during Phase III long-term open-extension studies in various neurological conditions. A total of 207 patients have received more than six months treatment with SATIVEX[®], and 110 patients have received SATIVEX[®] for more than one year.

In addition to the adverse events reported in the controlled acute studies (refer to Table 1) the following adverse events were observed in patients (>2%) on long-term treatment with SATIVEX[®]: headache (8.7%), balance impaired (5%), depressed mood (4%), memory impairment (3.1%) and oral mucosal disorder (3.1%).

Clinical Trial Adverse Drug Reactions

In all placebo-controlled trials in various indications (brachial plexus injury, MS symptoms, other defects of neurological function) adverse events have usually been mild or moderate in severity with discontinuation rates from treatment due to undesirable effects of 7.1% of patients on SATIVEX[®] compared to 2.4% 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 2% or more of patients treated with SATIVEX[®], and at an incidence greater than placebo, in the acute phase in all Phase III trials are given below in Tables 1 and 2.

Table 1 excludes “intoxication type reactions”, while Table 2 lists only “intoxication type reactions”.

Table 1: Treatment-Emergent Adverse Events for SATIVEX® in placebo-controlled studies in various neurological conditions (excluding “intoxication type reactions”)

	SATIVEX® n = 166 (%)	Placebo n = 162 (%)
Ear and labyrinth disorders		
Vertigo	3	0
Gastrointestinal disorders		
Dry mouth	7.8	1.9
Diarrhoea	6	3.1
Mouth ulceration	3	0.6
Nausea	10.2	7.4
Oral pain	6.6	6.8
Vomiting	2.4	0.6
General disorders and administration site conditions		
Application site pain	7.8	6.8
Fatigue	11.4	5.6
Weakness	3.6	1.2
Fall	3	1.2
Lethargy	3	0.6
Thirst	3	0
Metabolism and nutrition disorders		
Appetite increased	3.6	1.9
Musculoskeletal and connective tissue disorders		
Sensation of Heaviness	2.4	0.6
Nervous system disorders		
Dysgeusia (abnormal taste)	4.2	2.5
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	3.6	1.9
Cough	2.4	1.9

Table 2: Treatment-Emergent “intoxication type reactions” for SATIVEX® in placebo-controlled studies in various neurological conditions

	SATIVEX® n = 166 (%)	Placebo n = 162 (%)
General disorders and administration site conditions		
Feeling drunk	7.2	0.6
Nervous system disorders		
Disturbance in attention	6.6	0
Dizziness	41.6	13
Somnolence	8.4	3.1
Psychiatric disorders		
Disorientation	4.8	0
Dissociation	3	0
Euphoric mood	5.4	0.6

Application Site

Application site type events were reported by 20-25% of patients receiving SATIVEX® or placebo. The incidences in SATIVEX® treated patients and placebo were: oral pain (6.6% SATIVEX®, 6.8% placebo) and application site pain (7.8% and 6.8% respectively). These data appear to indicate that some application 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 3% patients using SATIVEX®, and 0.6% in placebo. Two cases of possible leukoplakia were observed but neither was confirmed histologically.

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.

Neurological including “intoxication type reactions”

See BOXED Warning and [Table 2](#)

Infrequent Clinical Trial Adverse Drug Reactions (<1%)

The patient population in the placebo-controlled studies was small, so only those adverse events with an incidence of greater than 2% were detectable. Thus, infrequent clinical trial adverse drug reactions (<1%) are not available.

Abnormal Haematologic and Clinical Chemistry Findings

There is not sufficient information to adequately characterize the haematologic and clinical chemistry profiles of SATIVEX[®] at this time.

Post-Market Adverse Drug Reactions

There are no data available yet.

DRUG INTERACTIONS

Serious Drug Interactions

- Care should be taken with sedatives, drugs with sedating effect 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

THC is a weak inhibitor of the cytochrome P₄₅₀ enzyme systems CYP3A4, CYP1A2, CYP2C9 and CYP2C19. THC is not an inhibitor of CYP2D6.

CBD is a relatively potent inhibitor of CYP2C19 and CYP3A4 activity and a relatively weak inhibitor of CYP1A2, CYP2C9 and CYP2D6.

When CBD and THC extracts were incubated together in a 1:1 ratio with cytochrome P₄₅₀ enzyme systems, the combination of cannabinoid extracts was shown to be a weak inhibitor of CYP1A2, CYP2C6, CYP2D6, CYP2C19 and CYP3A4 with an ED₅₀ approximately two orders of magnitude greater than the plasma levels seen in clinical use.

The lowest IC₅₀ value for inhibition of any of the cytochrome P₄₅₀ enzymes *in vitro* (1887 ng/ml, CYP3A4) by 1:1 THC: CBD is significantly greater than the corresponding mean C_{max} achieved for each parameter following dosing with SATIVEX[®] in healthy volunteers (CBD: ≤ 3.33 ng/ml; THC: ≤ 5.45 ng/ml) or in patients following acute or chronic stable dosing with SATIVEX[®] (CBD: 16.97 ng/ml; THC: 33.63 ng/ml).

There is a relatively large range between the IC₅₀ concentrations required to produce significant inhibition of P₄₅₀ enzymes and plasma levels achieved following dosing at therapeutic levels. However, despite a considerable margin of safety, there is a potential for CBD to inhibit isoforms CYP2C19 and CYP3A4. Hence, care is advised in patients taking concomitant medications metabolised via these enzymes.

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 2D6 and/or CYP450 3A4, in particular fentanyl and the related opioids sufentanil and alfentanil.

Amitriptyline is metabolized by CYP2C19, CYP1A2, CYP2C9, CYP3A4 and CYP2D6, and there is thus a potential risk of an interaction with SATIVEX[®], leading to raised plasma levels of

amitriptyline. In clinical trials with SATIVEX[®], patients have been restricted to a maximum of 75 mg amitriptyline daily. No difference in the adverse event profile between patients taking amitriptyline and the general population of MS patients was noted.

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 interactions with food have been established.

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.

NOC/c 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. It should never be directed towards the pharynx because of potential irritation. It must not be sprayed into the nose.

In the extension phase of Study GWMS0107 in MS, the median daily dosage of SATIVEX[®] in the 63 patients was 5 actuations (sprays) after dose titration was completed. 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.

Dose Titration and Stabilization

Patients should titrate to their optimal dosing regimen. Patients should be advised that it might take a week or more to find the optimal dosing level. Patients should familiarize themselves with the symptoms of Mild, Moderate and Severe Overdose with THC before they start using SATIVEX[®] (see “[OVERDOSAGE](#)”).

Treatment initiation and stabilization

- Treatment should be started at a maximum rate of one spray every four hours on the first day, up to a maximum of four sprays on the first day.
- On subsequent days the patient may gradually increase the total number of sprays as needed and tolerated. During initial titration, doses should be evenly spread out over the day.
- If unacceptable adverse reactions such as dizziness or other intoxication 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.

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.

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 SATIVEX[®] by pressing two or three times firmly and quickly 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

There is no experience of deliberate overdose with SATIVEX[®]. Signs and symptoms of overdose/poisoning are expected to be related to the psychological and physical effects of cannabinoids, which would typically consist of intoxication, major or minor psychiatric symptoms such as hallucinations, delusions, anxiety or paranoia, tachycardia or bradycardia with postural hypotension. Treatment should be symptomatic and supportive.

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 *po*) 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. The nearest local Poison Control Center must be contacted.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mammalian tissues contain at least two types of cannabinoid (CB) receptor, CB₁ and CB₂. CB₁ receptors are present at nerve terminals 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. Within the brain, the distribution of CB₁ receptors is heterogeneous, with a pattern consistent with the demonstrated effects of cannabinoids on motor function, cognition and memory. Relevant for pain modulation, CB₁ 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. CB₂ receptors are present primarily on peripheral and central immune cells, where they may modulate immune function through release of cytokines.

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-OH-THC, a psycho-active metabolite. The main primary metabolite of CBD is 7-hydroxy-CBD.

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 3: Mean Pharmacokinetic Parameters (GWPK0112)**

Treatment	Analyte	T _{max} (hrs) (n=12)	C _{max} (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 4: 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 5: 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 P₄₅₀ 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, and should be used within 28 days once it has been opened and is in use.

SATIVEX[®] should be stored upright in a refrigerator (2°C-8°C). Do not freeze. Once opened, the spray may be stored at room temperature (15°C-25°C) and should be used within 28 days.

Keep away from sources of heat and direct sunlight. Keep away from reach 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)

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 Size: 5.5 ml.

The 5.5 ml vial contains up to 51 metered sprays.

4 amber glass vials per carton.

PART II: SCIENTIFIC INFORMATION

SATIVEX[®], indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults, has been issued a marketing authorization with conditions, to 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 authorization.

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: $C_{21}H_{30}O_2$

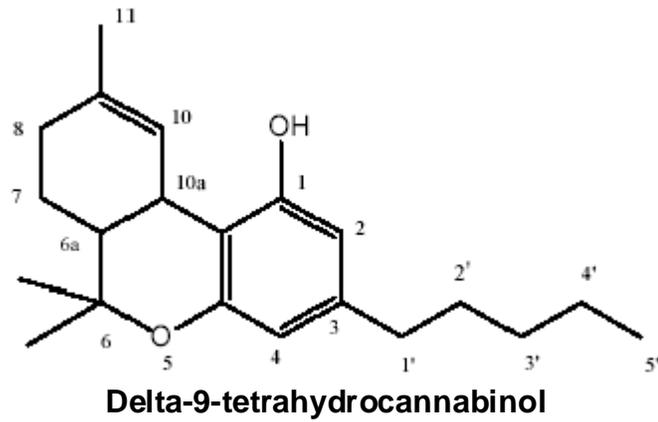
molecular mass: 314.47

CBD: $C_{21}H_{30}O_2$

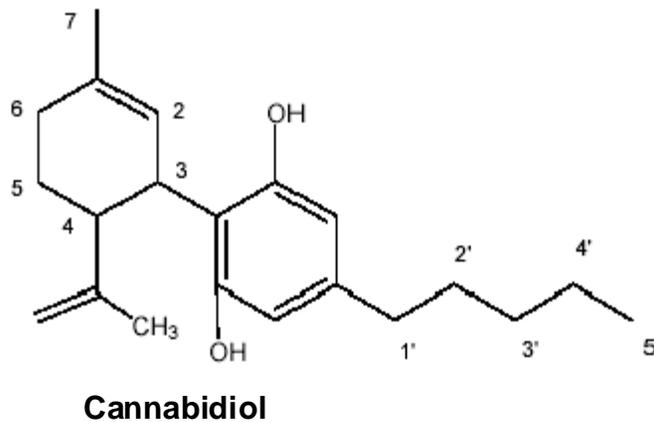
molecular mass: 314.47

Structural formula:

THC:



CBD:



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

NOC/c CLINICAL TRIALS

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.

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 a 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 by this route.

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, however this almost certainly reflects alimentary tract absorption of a 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, however this is not surprising. 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 (Huestis, 1992).

By 12-24 hours after dosing, CBD, THC and 11-OH-THC are usually at or below the limit of quantification in plasma. This clearance is thought to be 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-life of CBD, THC and 11-OH-THC has 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, CB₁ and CB₂, have been characterised by the use of specific agonists and antagonists and each has been cloned. In addition, two endogenous ligands, arachidonylethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), have been thus far investigated other endogenous ligands for cannabinoid receptors have been discovered but have not thus far been fully investigated. It is likely that other subtypes of cannabinoid receptors also exist.

Mammalian tissues contain at least two types of cannabinoid receptor, CB₁ and CB₂. These are both coupled to G_{i/o} protein, that inhibit adenylate cyclase but stimulate mitogen-activated protein kinase. The CB₁ receptor is also coupled to G protein that modulates certain types of calcium and potassium channel. CB₁ 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 CB₁ receptors are found mainly at nerve terminals and one function of these receptors is to inhibit neurotransmitter release. CB₂ 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 CB₁ receptor has a neuromodulatory role, the CB₂ receptor appears to be immunomodulatory.

Within the brain, the distribution of CB₁ receptors is heterogeneous, accounting for several well-documented pharmacological properties of CB₁ 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 CB₁ 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, CB₁ 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 CB₁ 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 CB₁ 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

Table 6: Overview of Acute Dose Toxicology Studies with THC¹ 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)	Reference
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	Thompson <i>et al</i> ; 1973a
Rat	Synthetic THC	Not stated	Acute	IV	Not stated	15 - 20	Marinol NDA 28-651 SBA
Dog	THC	65.6 – 3000	Acute	PO (gavage)	3000	No deaths	Thompson <i>et al</i> ; 1973a
Dog	Synthetic THC	3.9 – 210	Acute	IV	25	100	Marinol NDA 28-651 SBA
Monkey	THC	131 – 9000	Acute	PO (gavage)	9000	No deaths	Thompson <i>et al</i> ; 1973a
Monkey	Synthetic THC	3.9 – 1050	Acute	IV	3.9	62.5	Marinol NDA 28-651 SBA

¹ Other than smoked or inhalation routes of administration.

Table 7: 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	Reference
Mouse	THC	5 – 500	13 weeks (dosed 5 days/week)	PO (gavage)	500	No deaths attributable to THC	Chan <i>et al</i> ; 1996 (NTP Study)
Rat	THC	0.025 – 1.25	28 days	PO (gavage)	No deaths	No deaths	Manno <i>et al</i> ; 1977
Rat	THC	3.75 – 30	30 days	IP	No deaths	No deaths	Phillips <i>et al</i> ; 1972
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	Chan <i>et al</i> ; 1996 (NTP Study)
			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	Thompson <i>et al</i> ; 1973b
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	Rosenkrantz and Braude; 1976
Guinea pig	THC	3	6 months	IP	No deaths	No deaths	Huy <i>et al</i> ; 1975
Rabbit	THC	3 – 100	13 days	SC	No deaths	No deaths	Banerjee <i>et al</i> ; 1976

Table 8: 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	Reference
Rat (Fischer)	CBD (98%)	110 – 310	Acute	IV	160 (M) 210 (F)	232 (M) 252 (F)	Rosenkrantz <i>et al.</i> 1977
Monkey	CBD (98%)	150 – 320	Acute	IV	200	212	Rosenkrantz <i>et al.</i> 1977; 1981
Rat (Fischer)	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths	Rosenkrantz <i>et al.</i> 1978
Rat	CBD ³	5 – 75	14 days	IV	5 NOAEL	75 mg/kg/day	GW Report GPA001/010065
Rat	CBD ³	1 – 25	28 days	IV	1	5	GW Report GPA003/013834
Rat	CBD ³	25 – 225	90 days	PO (diet)	225	No deaths	GW Report No. JJG0002
Monkey	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths	Rosenkrantz <i>et al.</i> 1978

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 pharmacotoxicological 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. At the maximum dosage levels used in humans of about 2 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 and Carcinogenicity

A number of tests to evaluate genotoxic potential have been performed using THC and CBD individually and administered together. Although data on the genotoxic potential of THC and CBD have shown ambiguity in some studies, the risk of THC and CBD in causing genotoxicity in humans *in vivo* is estimated to be low.

THC has been fully evaluated for carcinogenic potential by well-documented and reported 2-year studies in mice and rats (NTP, 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.

CBD, like THC, is not structurally related to known carcinogens, has produced predominantly negative results in genotoxicity tests and has a spectrum of pharmaco-toxicological activity similar to, but generally weaker than, THC. It is considered very unlikely that CBD will pose any significant carcinogenic hazard to humans.

Reproductive and Developmental Toxicity

Although formal animal reproduction tests with SATIVEX[®] have not been performed, there exists sufficient published information on the effects of THC, CBD and cannabis extracts on reproductive function to allow an assessment of the potential effects of SATIVEX[®] on human reproductive function. Both THC and CBD have been demonstrated to reduce the weights of reproductive organs, including uterus and testes, in repeat-dosing studies. Functional effects such as increased oestrous cycle lengths and inhibitory effects on spermatogenesis have also been reported for both compounds and for cannabis extracts. These effects of cannabinoids appear to be mediated predominantly via effects on the hypothalamus and/or pituitary which result in reduced circulating levels of sex-related hormones including testosterone, progesterone, LH, FSH and prolactin.

Administration of cannabinoids or cannabis extracts during pregnancy has been reported, in several studies, to produce adverse effects in terms of number and weight of offspring and of their survival. Although these effects appear to be dosage-related, full dose-response curves for individual cannabinoids or for cannabis extracts have not been reported and it is therefore impossible to predict likely safe dosage levels in humans. There is some evidence which suggests that cannabinoids, particularly THC, may exert adverse effects on reproductive function at relatively low dosage levels. For example, Smith *et al.* (1983) reported that 1.25 mg subcutaneous of THC, administered three times weekly, disrupted the menstrual cycles of

monkeys and in the study of Ayalon *et al.* (1977), 2 mg/kg IP delayed ovulation and suppressed the rise in sex hormone levels in pro-oestrous rats. Although treatment with THC has been associated with increased embryo-foetal mortality in several species, only in some mouse studies at relatively high dosage levels, have teratogenic effects been reported. THC is non-teratogenic in rats and rabbits and probably also in Rhesus monkeys.

Possibly the most significant adverse reproductive effects of THC reported are alterations in foetal sexual and behavioural development induced by administration of dosage levels as low as 1 µg/kg to either pregnant rats or sexually immature offspring. These effects suggest that long-term adverse effects may occur in offspring of mothers exposed during pregnancy or during the nursing period to low doses of cannabinoids. Although fewer data are available for CBD, the results suggest that it is likely to produce similar effects to THC on embryo-foetal development but to be somewhat less potent.

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

REFERENCES

1. British Medical Association. Therapeutic uses of cannabis. Amsterdam: Harwood Academic Publishers; 1997. Chapter 2, p. 7-20.
2. Brown DT. The therapeutic potential for cannabis and its derivatives. Amsterdam: Harwood Academic Publishers; 1998.
3. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;323(7303):1-6.
4. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997;38(1):44-8.
5. Devins GM, Edworthy SM, Paul LC, Mandin H, Seland TP, Klein G, *et al.* Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *J Psychosom Res* 1993;37(2):163-70.
6. Greenberg HS, Werness SA, Pugh JE, Andrus RO, Anderson DJ, Domino EF. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clin Pharmacol Ther* 1994;55(3):324-8.
7. Grinspoon L, Bakalar JB. Marijuana, the forbidden medicine. New Haven (CT): Yale University Press; 1993.
8. Joy JE, Watson SJ, Benson JA, Institute of Medicine (US). The medical value of marijuana and related substances. In: *Marijuana and medicine: assessing the science base*. Washington DC: National Academy Press; 1999.
9. Mechoulam R. The pharmacohistory of cannabis sativa. In: *Cannabinoids as therapeutic agents*. Boca Raton (FL): CRC Press; 1986.
10. Noyes R, Jr., Baram DA. Cannabis analgesia. *Compr Psychiatry* 1974;15(6):531-535.
11. Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci* 2003;30(3):201-5.
12. Pertwee RG. Cannabinoids and multiple sclerosis. *Pharmacol Ther* 2002;95(2):165-74.
13. Robson P. Cannabis. In: *Forbidden drugs*. 2nd ed. Oxford: Oxford University Press; 1999.
14. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain* 2003;102(1-2):211-6.

PART III: CONSUMER INFORMATION

IMPORTANT: PLEASE READ

^NSATIVEX[®]

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

SATIVEX[®], indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults, has been issued a marketing authorization with conditions, to 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 authorization.

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 neuropathic pain (pain caused by damage to the nerves), in people with multiple sclerosis (MS).

What it does:

SATIVEX[®] provides pain relief.

When it should not be used:

If you have any of the following conditions, you should **not** use this product:

- known or suspected allergy to any cannabis-based products, propylene glycol, ethanol or peppermint oil
- significant liver or kidney problems
- serious heart disease
- history of schizophrenia or any other psychotic disorder
- in children or adolescents 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).

Important nonmedicinal ingredients:

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 amber glass vials.

The 5.5 ml vial contains up to 51 metered sprays.

SATIVEX[®] is packed as four vials in each carton.

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 effects 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

Drugs that may interact with SATIVEX[®] include drugs that are broken down in the liver using the same enzyme system that SATIVEX[®] uses. Therefore, it is important to talk to your doctor or pharmacist about any other medicines you are taking.

Care should be taken with sedatives and hypnotics as co-administration with SATIVEX[®] may possibly enhance the effect.

Smoked or other forms of cannabis may produce intoxication or increase other unwanted effects of SATIVEX[®]. 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. 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[®].

The starting dose for an adult is not more than one spray every four hours on the first day, to a maximum of four sprays on the first day, but it may be much less than this.

After the first day, you may gradually and carefully increase your intake each day, by a few sprays as needed and tolerated until you experience improved relief of your pain.

The average dose of SATIVEX[®] is 5 sprays per day. There is limited experience with doses higher than 12 sprays per day but you may need a higher number of sprays.

These doses should be spaced out evenly throughout the day. When you have found your regular daily dose, you may adjust the timing of your doses, depending on how you feel.

If you experience any unacceptable side effects you should reduce your dosing level 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

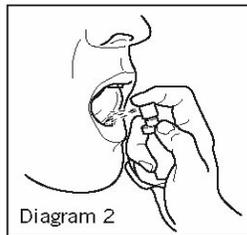
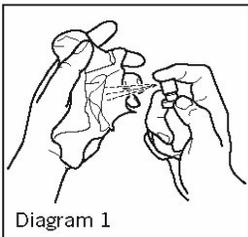
On first opening of a new vial:

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 nozzle. 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 nozzle.
4. Hold the vial in the upright position and direct the nozzle into your mouth under the tongue or onto the inside of the cheek. Vary the location in the mouth into which you spray SATIVEX[®], in order to avoid stinging and discomfort in the mouth. Press firmly and quickly. See Diagram 2.
5. Replace the protective cap.



Important:

If you take 5 sprays each day you will notice after about 10 days 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, or tell your doctor immediately. Bring any remaining medicine and container with you.

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 mouth, feeling sick, discomfort and stinging in the mouth, tiredness or drowsiness, confusion, dizziness or faintness, disorientation, poor concentration and/or impaired memory, hallucinations or strange ideas, a feeling of unreality, feeling abnormal or drunk, feeling people are against you and a feeling of general happiness or a “high” (easy laughing, heightened awareness.) Other side effects may include diarrhoea, rapid heart beat, increase in appetite, and falls.

Stinging or discomfort in the mouth may be experienced if SATIVEX[®] is sprayed in the same place in the mouth. 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 weakness tiredness feeling drunk disorientation mouth ulceration	✓ ✓ ✓ ✓ ✓		✓

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°C-8°C). Do not freeze.

Once SATIVEX[®] is opened, use within 28 days. SATIVEX[®] may be stored at room temperature (15°C-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.

KEEP OUT OF THE REACH OF CHILDREN

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadrmpp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness
Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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.

Manufactured by: GW Pharma Ltd., Salisbury, Wiltshire UK, SP4 0JQ.

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

This leaflet was prepared by GW Pharma Ltd.
Last revised: April 6, 2006