PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSATIVEX®

delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Solution, 27mg/mL / 25mg/mL, Buccal spray

Antispastic

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SATIVEX® (delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)) is indicated as:

- an 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.

1.1 Pediatrics

Pediatrics (<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.

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

SATIVEX® is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- patients with cardiovascular diseases, such as ischemic 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 fertile men not on a reliable contraceptive (see “Use in Women of Child-Bearing Potential”)
- pregnant or nursing women (see “Use in Women of Child-Bearing Potential”).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

Driving or Operating Machinery: Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination.

Cardiovascular Risk: 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.

Seizures: 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.

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 Recommended Dose and Dosage Adjustment

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 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.

4.3 Administration

4.3.1 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.

4.3.2 Administration

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.

4.4 Missed Dose

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

5 OVERDOSAGE

5.1. 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.

5.2 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.

5.3 Experience with oral THC overdose

5.3.1 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).

5.3.2 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.

For management of a suspected drug overdose, contact your regional poison control centre for current information.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Buccal	Buccal spray delta-9-tetrahydrocannabinol 27mg/mL (from Tetranabinex® - Cannabis sativa L. extract) and cannabidiol25mg/mL (from Nabidiolex® - Cannabis sativa L. extract)	Ethanol anhydrous Peppermint oil Propylene glycol

Each 100 microliter 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 0.04g 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 microliters per actuation (spray).

Pack Sizes: 10 mL.
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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

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

Cannabinoids have cardiovascular effects that include tachycardia, and transient changes in blood pressure, including episodes of postural hypotension. Use of SATIVEX® is contraindicated in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure.

Dependence/Tolerance

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.

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.

SATIVEX® may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Patients should be aware that SATIVEX® has been known to cause cases of loss of consciousness.

This medicine can also impair perception and cognitive function and can affect a patient’s ability to drive safely.

Hematologic

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

Hepatic/Biliary/Pancreatic

Data from a single dose of 4 sprays of SATVEX® in individuals with normal hepatic function and

those with mild, moderate, and severe hepatic impairment are available. SATIVEX® can be administered to patients with mild hepatic impairment with caution, especially at ~~doses~~ higher doses. Administration to patients with moderate or severe hepatic impairment is not advised due to higher peak concentration and exposure to THC, CBD, and their metabolites (see **Special Populations and Conditions**). No data with multiple dosing is available in subjects with hepatic impairment.

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®.

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.

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.

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")

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

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.

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.

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%).

Renal

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

Sensitivity/Resistance

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

Sexual Health

Reproduction -Independent research in various animal species has found that cannabinoids have been associated with evidence of reproductive toxicity in early gestation and have been found to affect spermatogenesis. There is insufficient experience in humans regarding the effects of SATIVEX® on reproduction. Therefore women of child bearing potential and fertile men should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

Patients on hormonal contraceptives should be advised to use an additional alternative, non-hormonal/reliable barrier method of birth control during SATIVEX® therapy.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

SATIVEX® is contraindicated in 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.

7.1.3 Pediatrics

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

7.1.4 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.

8 ADVERSE REACTIONS

8.1 Adverse 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 discoloration (2.1%), oral mucosal disorder (2.2%), oral mucosal discoloration (0.7%), oral mucosal exfoliation (0.7%), stomatitis (0.6%), hypertension (0.3%), delusional perception (0.1%) and syncope (0.9%).

8.2 Clinical Trial Adverse Reactions

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 reaction information from

clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following data summarise the adverse events in patients in clinical trials with various neurological conditions.

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.

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		
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®

8.3 Less Common Clinical Trial Adverse Reactions

8.3.1 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.

8.3.2 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

8.5 Post-Market Adverse Reactions

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

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.

9.2 Overview

The two main components of SATIVEX®, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are metabolized by the Cytochrome P450 and UGT enzyme systems, including CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4, UGT1A9 and UGT2B7. 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.

9.3 Drug-Drug Interactions

Potential for SATIVEX® to affect other drugs/medicines

In vitro, SATIVEX® was observed to be a reversible inhibitor of CYP3A4, 1A2, 2B6, 2C9 and 2C19 at concentrations far in excess of those likely to be achieved clinically. In vitro investigations also demonstrated that SATIVEX® had the potential for time dependent inhibition of CYP3A4 at clinically relevant concentrations. The rate of the inactivation of the CYP3A4 enzyme is expected to be rapid.

Co-administration of SATIVEX® may increase the plasma concentration of the drugs metabolized by CYP3A4. 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. A review of the dosing regimen of such medication is advised.

An in vitro, CYP induction study data indicated that plasma concentrations of THC and CBD arising from clinical doses of SATIVEX® could be sufficient to cause induction of CYP1A2, 2B6 and CYP3A4 at the mRNA level. Co-administration of SATIVEX® with other drugs that are metabolised through these cytochrome P-450 enzymes may accelerate the metabolism and reduce the activity of these other drugs such as coumarins, statins, beta-blockers and corticosteroids. When sensitive CYP substrates are co-administered with SATIVEX®, review of their dosing regimen is advised.

UGT enzymes

In an in vitro study SATIVEX® was found to inhibit the UGT enzymes UGT1A9 and UGT2B7 at concentrations that could be achieved in the clinic. Care should be taken when prescribing SATIVEX® with concomitant medications which are solely metabolised by both or either of these UGTs (e.g. Propofol and certain antivirals). Patients with genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution when SATIVEX® is co-administered.

Potential for SATIVEX® to be affected by other drugs/medicines

The two main components of SATIVEX®, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P-450 enzyme system.

Cytochrome P-450 enzyme inhibition

Concomitant treatment with the CYP 3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC, (1.2- and 1.8-fold, respectively), its primary metabolite 11-hydroxy-THC (3- and 3.6-fold, respectively) and CBD (2- and 2-fold, respectively). Therefore, if concomitant drug treatment with CYP3A4 inhibitors (e.g. itraconazole, ritonavir, clarithromycin) is started or stopped during treatment with SATIVEX®, a new dose titration may be required (see section 4.2). There may be a potential risk of drug-drug interactions due to CYP450 inhibition by SATIVEX®.

Concomitant treatment of SATIVEX® (4 sprays) with the CYP2C9 inhibitor fluconazole (200 mg capsule) resulted in an increase in mean THC C_{max} of 22 % and mean AUC of 32 %. Exposure to the metabolite 11-OH-THC also increased by approximately 2.1-fold and 2.5-fold for C_{max} and AUC respectively, indicating that fluconazole may inhibit its subsequent metabolism. The C_{max} of CBD also increased by approximately 40 % but there was no significant change in AUC. There was no significant change in exposure to 7-OH-CBD either although an increase in the minor circulating metabolite of CBD, 6-OH CBD was noted (by up to

2.2-fold based on C_{max} and AUC) .The clinical relevance of this drug-drug interaction is not fully understood, however care should be taken when co-administering SATIVEX® with potent CYP2C9 inhibitors as it may lead to an increase in exposure to THC, CBD and their metabolites.

Cytochrome P-450 enzyme induction
Following treatment with the CYP3A4 inducer rifampicin reductions in C_{max} and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (85% and 87% reduction, respectively) and CBD (50% and 60% reduction, respectively) were observed. Therefore, concomitant treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) should be avoided whenever possible. If deemed necessary, careful titration is recommended, notably within the two weeks following the stop of the inducer.

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.

Inhibitory Agents

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

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

SATIVEX® may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using SATIVEX®, especially at the beginning of treatment or when changing dose. Patients should be advised that if they do drink alcohol while using SATIVEX® the additive CNS effects may impair their ability to drive or use machines, and increase the risk of falls.

Hormonal contraceptives

SATIVEX® has been observed to induce drug metabolizing enzymes and transporters in vitro.

SATIVEX® may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add an additional, barrier method.

9.4 Drug-Food Interactions

Grapefruit juice is a known inhibitor of CYP3A4. It should be avoided during treatment with SATIVEX®.

9.5 Drug-Herb Interactions

St John's Wort is a known inducer of CYP3A4. It should be avoided during treatment with SATIVEX® unless its benefits outweigh its risks of a drug interaction.

9.6 Drug-Laboratory Test 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").

9.7 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.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

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.

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Table 3: 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 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 administration of SATIVEX® (four sprays), both THC and CBD are absorbed fairly rapidly and appear in the plasma within 15 minutes after single oromucosal administration. With SATIVEX®, a mean C_{max} of about 4 ng/mL was reached some 45-120 minutes after a single dose administration of a 10.8 mg THC dose, and was generally well tolerated with little evidence of significant psychoactivity.

When SATIVEX® is co-administered with food the mean C_{max} and AUC for THC were 1.6- and 2.8-fold higher compared with fasting conditions. Corresponding parameters for CBD increased 3.3- and 5.1-fold.

There is a high degree of variability in pharmacokinetic parameters between patients. Following a single dose administration of SATIVEX® (four sprays) under fasted conditions, the mean plasma level of THC showed a 57.3% CV for C_{max} (range 0.97-9.34ng/mL) and a 58.5% CV for AUC (range 4.2-30.84 h*ng/mL). Similarly the %CV for CBD was 64.1% (range 0.24-2.57ng/mL) and 72.5% (range 2.18-14.85 ng/mL) for the same parameters respectively. After nine consecutive days of dosing the % CV values for the same parameters were 54.2% (C_{max} range = 0.92-6.37) and 37.4% (AUC_{0-t} = 5.34-15.01 h*ng/mL) for THC and 75.7% (C_{max} range 0.34-3.39 ng/mL) and 46.6% (AUC_{0-t} = 2.40-13.19 h*ng/mL) for CBD respectively.

There is a high degree of variability in pharmacokinetic parameters within patients following single and repeat dosing. Of 12 subjects who received four sprays of SATIVEX® as a single dose, eight had reductions in C_{max} after nine days of multiple dosing, whilst three had increases (1 drop-out). For CBD, seven had reductions in C_{max} after multiple dosing, whilst four had increases.

Distribution: As cannabinoids are highly lipophilic, they are quickly absorbed and distributed into body fat. The resultant concentrations in the blood following oromucosal administration of SATIVEX® are lower than those obtained by inhaling the same dose of THC because absorption is slower and redistribution into fatty tissues is rapid. Additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, the first metabolite of THC which then undergoes

further oxidation to 11-nor-9-COOH-THC, the most abundant metabolite of THC, and CBD similarly to 7-OH-CBD. Protein binding of THC is high (~97%). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream, then metabolized and excreted via the urine and faeces.

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

See section 4.5 for information on drug interaction and metabolism by the cytochrome P450 enzyme system.

Transporters
In vitro, SATIVEX® did not inhibit the following transporters at clinically relevant concentrations: BCRP, BSEP, OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, MATE1 and P glycoprotein.

Elimination: From clinical studies with SATIVEX®, a non-compartmental PK analysis shows that the first order terminal elimination half-life from plasma is 1.94, 3.72 and 5.25 hours for THC and 5.28, 6.39 and 9.36 for CBD following the administration of 2, 4 and 8 sprays respectively.

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

Special Populations and Conditions

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

The pharmacokinetics and tolerability of a single oromucosal dose of 4 sprays of SATIVEX® (containing 10.8 mg THC and 10 mg CBD) was studied in patients with impaired hepatic function and healthy subjects with normal hepatic function. The study dose resulted in variable peak concentrations and exposure of THC, CBD, and their metabolites in patients with mild hepatic impairment. The dose was tolerated and no new safety concerns were found. In patients with moderate and severe hepatic impairment, the study dose resulted in higher peak concentration of THC, CBD and their metabolites, associated with higher frequency of adverse

events.

No data with multiple dosing are available in subjects with hepatic impairment.

Renal Insufficiency: There are no studies in patients with impaired renal function. However, in these sub-populations the effects of SATIVEX® may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

11 STORAGE, STABILITY AND DISPOSAL

SATIVEX® should not be used beyond its expiry date. Once opened and in use, SATIVEX® should be used within 42 days.

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.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

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

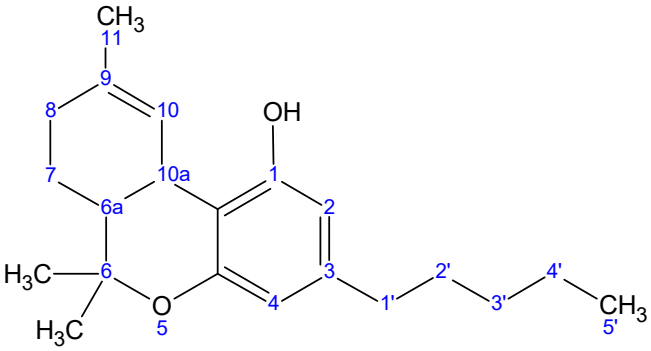
Molecular formula and molecular mass:

THC: C21H30O2 molecular mass: 314.47

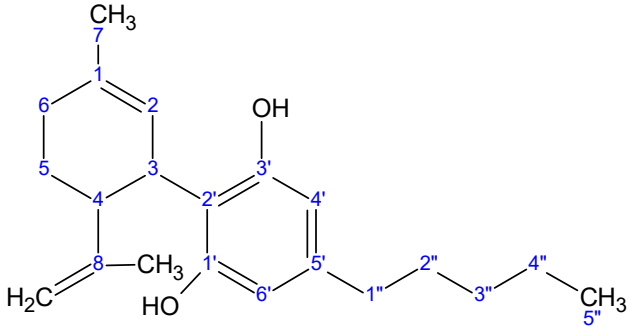
CBD: C21H30O2 molecular mass: 314.47

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:	Insoluble in:
Methanol Ethanol Acetone Dichloromethane	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:	Insoluble in:
Methanol Ethanol Acetone Dichloromethane	Water

14 CLINICAL TRIALS

14.1 EFFICACY as 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.

15 NON-CLINICAL TOXICOLOGY

The available 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.

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

Repeat Dose Toxicology in Rats

In a 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 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

In a 5-week dog study, 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.

In summary, 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.

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

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 6: 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 87.71 16.07	3.36 25.47 2.86	1251.41 657.11 883.14	482.38 199.86 302.23
4 mg/kg/day	131.69 110.67 388.98	37.06 26.16 108.52	2030.03 1407.65 1227.75	769.43 445.00 487.25

*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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr SATIVEX®

27 mg/mL delta-9-tetrahydrocannabinol and 25 mg/mL cannabidiol buccal spray

Read this carefully before you start taking **SATIVEX®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SATIVEX®.**

Serious Warnings and Precautions

- One of the ingredients in SATIVEX® can cause physical and psychological dependence and has the potential for being abused.
- SATIVEX® can cause changes in your heart. These include changes in your blood pressure, and a rapid heart beat. SATIVEX® is not recommended if you already have heart problems, including high blood pressure.
- Do not drive, operate machinery or carry out activities that require coordination and clear judgement.
- Talk to your doctor if you have a history of epilepsy or recurrent seizures.

What is SATIVEX® 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®.

How does SATIVEX® work?

SATIVEX® is used to improve symptoms related to muscle stiffness and make the muscles feel less stiff or rigid. You will know if your treatment is working if you have an improvement of your symptoms.

What are the ingredients in SATIVEX®?

Medicinal ingredients: Cannabis sativa L. extracts Tetranabinex® and Nabidiolex® equivalent to 27 mg/mL delta-9-tetrahydrocannabinol (THC) and 25 mg/mL cannabidiol (CBD).

Non-medicinal ingredients: Ethanol, Peppermint oil (flavouring), Propylene glycol.

SATIVEX® comes in the following dosage forms:

Buccal spray

27 mg/mL delta-9-tetrahydrocannabinol (THC) and 25 mg/mL cannabidiol (CBD).

Do not use SATIVEX® if you:

- have a known or suspected allergy to any cannabis-based products, peppermintoil, propylene glycol or ethanol .

- have a serious heart problem such as angina, a previous heart attack, poorly controlled high blood pressure or a problem with your heart rate or heart beat.
- suffer from schizophrenia or depression.
- 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®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SATIVEX®. Talk about any health conditions or problems you may have, including if you:

- have epilepsy
- have dizziness or fainting
- have any kidney or liver problems
- are addicted to drugs or alcohol
- or anyone in your family has had schizophrenia or psychotic episodes
- are going to have surgery
- are taking other medicines.

Other warnings you should know about:

- SATIVEX® may affect the way hormonal birth control methods, such as the "pill" or contraceptive implants, work. This means you should use and additional type of birth control.

  You and your partner must use a reliable barrier method of birth control, like a condom, diaphragm or cap. You should use these during your treatment with SATIVEX® and for at least 3 months after you stop taking SATIVEX®.

- If you see another doctor or go into hospital, let them know you are taking SATIVEX®.

- SATIVEX® contains about 50% v/v ethanol, which is an alcohol. Each spray contains about 0.04 g of alcohol. The usual daily dose will be greater than one spray. The amount of alcohol contained in SATIVEX® may be harmful if you have alcoholism. Your doctor will decide if you should still receive SATIVEX® if you have liver disease or epilepsy.

- SATIVEX® contains propylene glycol which may cause irritation.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SATIVEX®:

- sedatives/hypnotics like benzodiazepines, such as diazepam or triazolam; other sedatives, such as zopiclone, zolpidem, buspirone, St John's Wort (a herbal preparation)
- muscle relaxants such as baclofen
- antibiotics such as rifampicin, clarithromycin
- epilepsy or nerve pain medications such as phenytoin, phenobarbital, carbamazepine
- statins to treat high cholesterol; such as atorvastatin or simvastatin

- antifungals such as itraconazole, fluconazole and ketoconazole
- corticosteroids used for inflammation such as hydrocortisone, beclomethasone, prednisolone
- some hormone medicines used for contraception or some types of cancer such as ethinyloestradiol, levonorgestrel or dydrogesterone
- anaesthesia to put you to sleep before an operation/surgery or for relaxing muscles before surgery, such as propofol
- drugs to treat HIV/AIDS such as ritonavir
- drugs to thin your blood, such as warfarin
- betablockers used to treat high blood pressure, such as bisoprolol, propranolol
- opioid pain relief products such as fentanyl, sufentanil and alfentanil
- antidepressants such as amitriptyline
- cannabis (marijuana, pot). Do not smoke marijuana while using SATIVEX®,
- alcohol may interact with SATIVEX®, concentration and may affect your coordination and ability to respond quickly
- grapefruit juice

How to take SATIVEX®:

- Follow the instructions in this section 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.
- Spray SATIVEX® into your mouth, under your tongue or on the inside of your cheek.
- Do not spray the back of your throat. This will help you avoid inhaling SATIVEX® and will help you avoid getting an irritated throat.
- Spray SATIVEX® in different location in your mouth. This will help you to avoid stinging and discomfort in your mouth.
- Do not spray into your nose.
- There should be at least a 15 minute gap between sprays.
- If you experience any bothersome side effects, reduce your number of sprays or increase the time between each dose.

Usual dose:

You will determine the dose that is best for you. You can determine the dose that best suits you based on the relief you experience from taking SATIVEX®. You will figure out your regular daily dose by first starting slowly and 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 can gradually and carefully increase your dose by one spray each day. Do this as you need it and based on how well you tolerate it until you experience improved relief of your muscle stiffness.
- When you have found a daily number of sprays that controls your muscle stiffness, you may adjust the timing between them, depending on how you feel.
- Keep your dosing schedule constant once you figure out the timing and number of sprays that best controls your muscle stiffness.

The average dose of SATIVEX® is 4 - 8 sprays per day. Most 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.

HOW TO USE YOUR SPRAY

When you first open a new vial:

1. Shake the vial gently and remove the protective cap.
2. Place the vial between your thumb and second finger with your first finger placed on the actuator.
3. Press two or three times firmly and quickly into a tissue until a fine spray appears. See Diagram 1.
4. You can now use SATIVEX®.

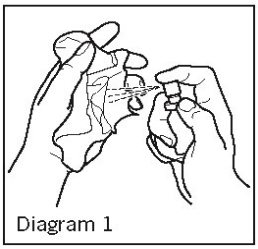


Diagram 1

SATIVEX® for daily use:

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Place the vial between your thumb and second finger with your 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.
5. Replace the protective cap

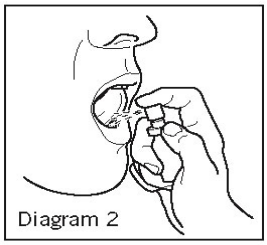


Diagram 2

Important:

- If you take 5 sprays each day you will notice after about 17 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 think you have taken too much SATIVEX®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you believe you have overdosed, you may have symptoms of intoxication, such as:

- 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).

If you need medical care, bring any remaining medicine and the container with you. Make a follow-up appointment with your usual doctor the day after an overdose.

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.

What are possible side effects from using SATIVEX®?

These are not all the possible side effects you may feel when taking SATIVEX®. If you experience any side effects not listed here, contact your healthcare professional.

You may have stinging or discomfort in your mouth if you spray SATIVEX® in the same place in your mouth on repeated occasions. You can help prevent this by varying the area in the mouth where you spray SATIVEX®. Do not continue spraying SATIVEX® onto sore or inflamed areas. Tell your doctor if your soreness persists.

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.

Serious side effects and what to do about them			
	Talk to your healthcare professional		
	Only if severe	In all cases	Stop taking drug and get immediate medical help
VERY COMMON Fatigue	✓		
Dizziness	✓		
COMMON Feeling over-excited or losing touch with reality			✓
Problems with your memory or having trouble concentrating	✓		
Difficulty speaking	✓		
Feeling disorientated or confused			✓
Depression (sad or low mood)		✓	
Increase or decrease in appetite		✓	
Feeling abnormal or drunk	✓		
Changed sense of taste, or a dry mouth	✓		
Loss of balance or falling over		✓	
Nausea or vomiting	✓		
Constipation or diarrhea	✓		
Blurred vision	✓		
Lack of energy or feeling weak or generally unwell.	✓		
UNCOMMON Seeing or hearing things that are not there (hallucinations)			✓
Thoughts about suicide			✓
Losing a sense of reality and not behaving normally			✓
Believing ideas that are not true			✓
Fainting	✓		
Tooth or mouth discoloration	✓		
Throat infection or irritation	✓		
Cough	✓		
Stomach pain	✓		
Feeling people are against you or excessive fear and anxiety			✓
High or low blood pressure		✓	
Rapid heartbeat			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Storage:

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

- Store upright.
- Store your unopened medicine in a refrigerator (2-8°C). Do not freeze.
- Once SATIVEX® is opened, use within 42 days. Opened vials of SATIVEX® may be stored at room temperature (15-25°C).
- This product is flammable. Do not leave SATIVEX in a hot place such as in direct sunlight or near a heat source.
- 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 reach and sight of children.
- SATIVEX® may not be legal in other countries because it contains cannabis extracts. Before you travel with SATIVEX®, you may want to look up if cannabis containing drug products are legal in the country/region you will visit.

If you want more information about SATIVEX®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.bayer.ca or by calling 1-800-265-7382

This leaflet was prepared by GW Pharma Ltd., Histon, Cambridge UK, CB24 9BZ

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