NEW ZEALAND DATA SHEET

1 PRODUCT NAME (STRENGTH PHARMACEUTICAL FORM)

SATIVEX (27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol) oromucosal spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains
38-44 mg and 35-42 mg of two extracts (as soft extracts) from *Cannabis sativa* L., folium cum flore (Cannabis leaf and flower) corresponding to 27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol and equivalent to 80 mg nabiximols.

Extraction solvent: Liquid carbon dioxide.

Each 100 microlitre spray contains:
2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

Excipient(s) with known effect:
Each 100 microlitre spray contains up to 40 mg ethanol.
Each 100 microlitre spray contains 52 mg propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oromucosal spray

Yellow/brown solution in a brown, plastic-coated glass spray container.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dosage and method of administration

Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

Dose

Adults

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

Patients should be advised that it might take up to two weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider

maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.

Titration period

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

The number of sprays should be increased each day following the pattern given in the Table 1. The afternoon/evening dose should be taken at any time between 4 pm and bedtime. When the morning dose is introduced, it should be taken at any time between waking and midday. The patient may continue to gradually increase the dose by one spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays.

Table 1. Titration of dose

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Maintenance period

Following the titration period, patients are advised to maintain the optimum dose achieved. The median dose in clinical trials for patients with multiple sclerosis is eight sprays per day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses of greater than 12 sprays per day are not recommended and should only be considered where the potential benefits outweigh the risks.

Review by the physician

A thorough evaluation of the severity of spasticity related symptoms and of the response to standard anti-spasticity medication should be performed prior to initiation of treatment. SATIVEX is only indicated in patients with moderate to severe spasticity that have responded inadequately to other anti-spasticity medication. The patient's response to SATIVEX should be reviewed after four weeks of treatment. If a clinically significant improvement in spasticity

related symptoms is not seen during this initial trial of therapy, then treatment should be stopped. In the clinical trials this was defined as at least a 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale (see section 5.1). The value of long term treatment should be re-evaluated periodically.

Paediatric population

SATIVEX is not recommended for use in children or adolescents below 18 years of age. A randomised placebo-controlled trial was performed in children and adolescents with cerebral palsy or traumatic central nervous system injury and its results regarding efficacy were negative. The data is described in section 5.1.

Elderly

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

Patients with significant hepatic or renal impairment

No data with multiple dosing are available in subjects with hepatic impairment. SATIVEX can be administered to patients with mild hepatic impairment without any dose adjustment. Administration to patients with moderate or severe hepatic impairment is not advised due to the lack of information on the potential for accumulation of THC and CBD with chronic dosing (see section 5.2).

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.

Method of administration

SATIVEX is for oromucosal use only.

4.3 Contraindications

SATIVEX is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients listed in section 6.1.
- With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.
- Who are breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants).

4.4 Special warnings and precautions for use

Identified precautions

Mild or moderate dizziness is commonly reported. This most frequently occurs in the first few weeks of treatment.

Use of SATIVEX is not recommended in patients with serious cardiovascular disease. However, following dosing in healthy volunteers with SATIVEX up to 18 sprays twice daily, there were no clinically relevant changes in QTc, PR or QRS interval duration, heart rate, or blood pressure.

Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.

There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of SATIVEX could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in clinical trials with SATIVEX. However, patients should be warned of this possibility.

Women of childbearing potential

SATIVEX may reduce the effectiveness of hormonal contraceptives (see section 4.5).

Women of childbearing potential must use highly effective contraception while taking SATIVEX. It is currently unknown whether SATIVEX may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should use an additional method of contraception for the duration of therapy and for three months after discontinuation of therapy (see section 4.5 and section 4.6).

Pregnancy and lactation: see section 4.6.

Abuse potential and withdrawal

Patients, who have a history of substance abuse, may be more prone to abuse SATIVEX as well.

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

Excipients

Each 100 microlitre of Sativex contains up to 40 mg of ethanol, equivalent to 50% by volume ethanol, that is approximately 480 mg per maximal daily dose (for an adult weighing 70 kg) equivalent to around 10 mL of beer or 5 mL of wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 52 mg propylene glycol in each 100 microlitre spray.

4.5 Interaction with other medicinal products and other forms of interaction

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 with other CYP3A4 substrates may result in an increase in plasma concentration of the concomitant drug. 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 CYP3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite (3- and 3.6-fold, respectively) and of 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).

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.

General

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 second barrier method.

4.6 Fertility, pregnancy and lactation

There is insufficient experience in humans regarding the effects of SATIVEX on reproduction. Although no effect has been seen on fertility, independent research in animals found that cannabinoids affected spermatogenesis (see section 5.3).

Therefore, men and women of childbearing potential 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.

Fertility

In fertility studies in rodents, there was no effect of treatment with SATIVEX in males or females. There was no effect on fertility of the offspring from mothers treated with SATIVEX.

Pregnancy

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

Lactation

Available pharmacodynamics / toxicological data in animals have shown excretion of SATIVEX / metabolites in milk (for details see section 5.3).

A risk to the breastfed child cannot be excluded. SATIVEX is contraindicated during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

SATIVEX may produce undesirable effects such as dizziness and somnolence which may impair judgment and performance of skilled tasks. Patients should not drive, operate machinery or engage in any hazardous activity if they are experiencing any significant CNS effects such as dizziness or somnolence. Patients should be aware that SATIVEX has been known to cause a few cases of loss of consciousness.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

The medicine is likely to affect your ability to drive:

- Do not drive until you know how the medicine affects you
- Check national legislation to determine the requirements for driving while under the influence of this medicine.

4.8 Undesirable Effects

Summary of the safety profile

The SATIVEX clinical program has so far involved over 1500 patients with MS in placebo-controlled trials and long-term open label studies in which some patients used up to 48 sprays per day.

The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued (see section 4.2). When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced.

The frequency of adverse events with a plausible relationship to SATIVEX, from placebo-controlled trials in patients with MS, according to System Organ Classes (SOC) are given in Table 2 (some of these adverse events may be part of the underlying condition).

Table 2. The frequency of adverse events

MedDRa SOC	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100
Infections and infestations			pharyngitis
Metabolism and nutrition disorders		anorexia (including appetite decreased), appetite increased	
Psychiatric disorders		depression, disorientation, dissociation, euphoric mood	hallucination (unspecified, auditory, visual), illusion, paranoia, suicidal ideation, delusional perception*
Nervous system disorders	dizziness	amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment somnolence	syncope
Eye disorders		vision blurred	
Ear and labyrinth disorders		vertigo	
Cardiac disorders			palpitations, tachycardia
Vascular disorders			hypertension
Respiratory, thoracic and mediastinal disorders			throat irritation
Gastrointestinal disorders		constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort, oral pain, vomiting	abdominal pain (upper), oral mucosal discolouration*, oral mucosal disorder, oral mucosal exfoliation*, stomatitis, tooth discolouration
General disorders and administration site conditions	fatigue	application site pain, asthenia, feeling abnormal, feeling drunk, malaise	application site irritation
Injury, poisoning and procedural complaints		fall	

* reported in long-term open-label studies

Description of selected adverse reactions

Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with SATIVEX. These are likely to be the result of transient CNS effects and are generally mild to moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of SATIVEX medication.

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

completely resolved.

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

Adverse reactions have been reported which could be associated with the route of administration of the medicine. Application site type reactions consisted of mainly mild to moderate stinging at the time of application. Common application site reactions include application site pain, oral pain and discomfort, dysgeusia, mouth ulceration and glossodynia. Two cases of possible leukoplakia were observed but neither was confirmed histologically; a third case was unrelated. In view of this, patients who observe discomfort or ulceration at the site of application of the medicine are advised to vary the site of application within the mouth and should not continue spraying onto sore or inflamed mucous membrane. Regular inspection of the oral mucosa is also advised in long-term administration. If lesions or persistent soreness are observed, medication should be interrupted until complete resolution occurs.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdosage

There is no experience of deliberate overdose with SATIVEX in patients. However, in a Thorough QT study of SATIVEX in 257 subjects, with 18 sprays taken over a 20-minute period twice daily, signs and symptoms of overdose/poisoning were observed. These consisted of acute intoxication type reactions including dizziness, hallucinations, delusions, paranoia, tachycardia or bradycardia with hypotension. In three of 41 subjects dosed at 18 sprays twice a day, this presented as a transient toxic psychosis which resolved upon cessation of treatment. Twenty-two subjects who received this substantial multiple of the recommended dose successfully completed the 5-day study period.

In the case of overdose, treatment should be symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other Analgesics and Antipyretics, ATC Code: N02BG10

5.1 Pharmacodynamic properties

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

In animal models of MS and spasticity CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. These effects are prevented by CB antagonists, and

CB_1 knockout mice show more severe spasticity. In the CREAE (chronic relapsing experimental autoimmune encephalomyelitis) mouse model, SATIVEX produced a dose-related reduction in the hind limb stiffness.

Clinical experience

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population

The efficacy and safety of SATIVEX was evaluated in a 12-week randomised, double-blind, placebo-controlled study involving 72 children and adolescents aged from 8-18 years with cerebral palsy or traumatic central nervous system injury. The placebo-controlled phase was followed by a 24-week open label extension phase. The maximum permitted daily dose in this trial was 12 sprays and was titrated for 9 weeks. At baseline, most patients had severe impairment of motor function (Gross Motor Function Classification Scale level IV or V). The primary efficacy endpoint was the change in spasticity severity 0–10 numerical rating scale (NRS) score from baseline which is a carer reported outcome measure.

After 12 weeks of treatment, the mean change from baseline for SATIVEX-treated participants' spasticity severity NRS scores was −1.850 (SD 1.9275) and for placebo participants −1.573 (SD 2.0976). The least square mean difference between the two groups (−0.166, 95% CI −1.119, 0.787) was not statistically significant (p=0.7291).

No new safety findings were identified in this study.

No data are available in children below 8 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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.

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% ($AUC_{0-\tau}$ = 5.34-15.01 h*ng/mL) for THC and 75.7% (C_{max} range 0.34-3.39 ng/mL) and 46.6% ($AUC_{0-\tau}$ = 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.

When SATIVEX is administered oromucosally, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose. A dose of 8 mg of vaporised THC extract, administered by inhalation resulted in mean plasma C_{max} of more than 100 ng/mL within minutes of administration, with significant psychoactivity.

Table 3. PK parameters for SATIVEX, for vaporised THC extract and smoked cannabis

	C_{max} THC ng/mL	T_{max} THC minutes	$AUC_{(0-t)}$ THC ng/mL/min
SATIVEX (providing 21.6 mg THC)	5.40	60	1362
Inhaled vaporised THC extract (providing 8 mg THC)	118.6	17.0	5987.9
Smoked cannabis* (providing 33.8 mg THC)	162.2	9.0	No data

*Huestis et al, Journal of Analytical Toxicology 1992; 16:276-82.

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 primary 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 metabolised and excreted via the urine and faeces.

Biotransformation

THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, the primary metabolite of THC, and CBD similarly to 7-OH- CBD. Human hepatic P_{450} 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-Δ9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The P_{450}-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.

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.

In a specific hepatic impairment PK study a single oromucosal dose of 4 sprays of SATIVEX (10.8 mg THC and 10 mg CBD) showed no significant difference in THC or CBD clearance between subjects with mild hepatic impairment and healthy controls. However there was substantially reduced clearance and prolonged elimination half-life in the cohorts of subjects with moderate and severe hepatic impairment.

5.3 Preclinical safety data

Effects in preclinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Reprotoxicity studies carried out with the THC and CBD extracts present in SATIVEX showed no adverse effects on either male or female fertility in terms of numbers of animals mating, number of fertile males and females, or on copulation or fertility indices. There were reduced absolute weights of epididymides, with a "no-effect" dosage level of 25 mg/kg/day (150 mg/m^2)

for male fertility. The "no-effect" dosage levels for effects on early embryonic and foetal survival, in rat studies, were approximately 1 mg/kg/day (6 mg/m^2), which is close to or less than the likely maximum human dosage level of SATIVEX. There was no evidence to suggest any teratogenic activity in either rats or rabbits at dosage levels considerably in excess of likely human maximum dosage levels. However, in a rat pre- and post-natal study, pup survival and nursing behaviour were impaired at doses of 2 and 4 mg/kg/day (12 and 24 mg/m^2 respectively). Data from the literature have shown negative effects of THC and/or CBD on sperm number and motility.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol absolute
Propylene glycol
Peppermint oil

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months (inclusive of in-use period).

In use: 6 weeks from date of opening.

6.4 Special precautions for storage

Store in a refrigerator (2 to 8°C). Do not freeze.

Once the spray container is opened and in use, refrigerated storage is not necessary but do not store above 25°C.

Store upright. Keep away from heat and direct sunlight.

6.5 Nature and contents of container

A Type I amber glass spray container fitted with a metering pump possessing a polypropylene diptube and elastomer neck covered with a polypropylene cap. The metering pump delivers 100 microlitres per spray.

Pack size: 10 mL.

10 mL pack size allows delivery after priming of up to 90 actuations (sprays) of 100 microlitres.

1 or 3 glass sprays containers per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Class B1 Controlled Drug

8 SPONSOR

Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics
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10 DATE OF REVISION OF THE TEXT

13 March 2025

Summary Table of Changes

Section changed	Summary of new information
8	Updated sponsor information