Attachment 1: Product information for AusPAR Nabiximols Sativex Novartis Pharmaceuticals Australia Pty Limited PM-2011-00150-3-1 Final 27 September 2013. This Product Information was approved at the time this AusPAR was published.

SATIVEX®

nabiximols

WARNING

The maximum recommended dose of Sativex should not be exceeded. High doses of Sativex increase the risk of serious psychiatric adverse events including psychosis, hallucinations, delusions, and homicidal and suicidal ideation.

NAME OF THE MEDICINE

Active ingredient: nabiximols (AAN)

Each mL Sativex oromucosal spray contains:

80 mg of extracts (nabiximols) from *Cannabis sativa* L., folium cum flore (Cannabis leaf and flower), corresponding to 27 mg delta-9-tetrahydrocannabinol (THC) and 25 mg cannabidiol (CBD) and lesser amounts of other cannabinoids (56 mg total cannabinoids).

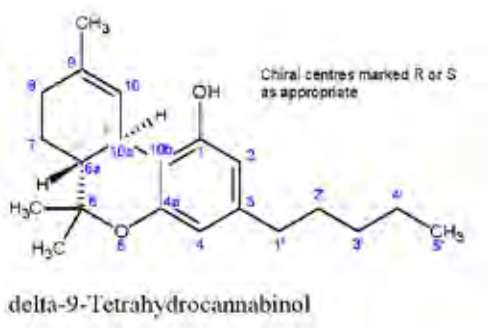
The name 'dronabinol' is used for pure, synthetically-derived delta-9-tetrahydrocannabinol rather than the extracted delta-9-tetrahydrocannabinol present in Sativex.

Extraction solvent: Liquid carbon dioxide.

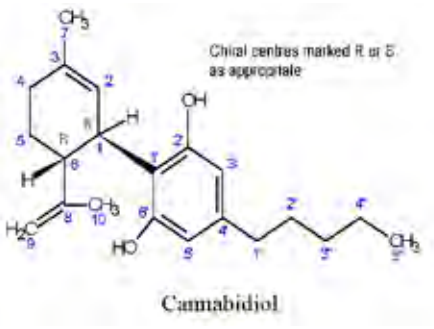
Each 100 microlitre spray contains 2.7 mg THC and 2.5 mg CBD.

Each 100 microlitre spray also contains up to 0.04 g alcohol.

THC is trans-delta[9]-tetrahydrocannabinol. The molecular formula of THC is $C_{21}H_{30}O_2$, its molecular weight is 314.47, and it is assigned CAS Number 1972-08-3. CBD is cannabidiol. The molecular formula of CBD is $C_{21}H_{30}O_2$, its molecular weight is 314.47 and it is assigned CAS Number 13956-29-1. The chemical structures of THC and CBD are shown below:



delta-9-Tetrahydrocannabinol



Cannabidiol

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DESCRIPTION

Sativex is supplied as a solution in a spray container and is for use as an oromucosal spray only.

The drug substances are produced from cultivated *Cannabis sativa* L. plants. The drug substances are partially purified extracts, therefore botanical drug substances (BDS). The plants have been specifically bred to produce two separate chemotypes, expressing their cannabinoid content as high delta-9-tetrahydrocannabinol (THC) or high cannabidiol (CBD) chemotypes. The physical descriptions of both THC BDS and CBD BDS are brown, viscous, semi-solid (soft) extracts with a characteristic odour of cannabis and are almost insoluble in water, but exhibit good solubility in most organic solvents.

Sativex contains ethanol absolute, propylene glycol and peppermint oil as inactive ingredients.

PHARMACOLOGY

Pharmacodynamic Properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics

ATC Code: N02BG10

Mechanism of Action and Pharmacodynamic Effects

There are at least two types of cannabinoid (CB) receptors as part of the human endocannabinoid system. CB_1 is found mainly in nerve terminals in the CNS where it modulates neurotransmitter release and CB_2 is found primarily in cells of the immune system. THC, the main psychotropic constituent of cannabis, acts as a partial agonist at both CB_1 and CB_2 receptors.

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.

CBD has little activity at cannabinoid receptors, but does have neuroprotective properties, most likely mediated by its ability to modulate intra-cellular calcium. It is also able to modulate the course of the disease in animal models of MS. The key pharmacology of CBD in MS probably relates to its ability to inhibit microglial activity and T-cell proliferation. It is unknown whether CBD in Sativex has a facilitating or antagonising effect on the anti-spasticity action of THC.

Pharmacokinetics

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 $C_{\mathbf{max}}$ (range 0.97-9.34 ng/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% ($C_{\mathbf{max}}$ range = 0.92-6.37) and 37.4% (AUC_0-τ = 5.34-15.01 h*ng/mL) for THC and 75.7% ($C_{\mathbf{max}}$ range 0.34-3.39 ng/mL) and 46.6% (AUC_0-τ = 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 $C_{\mathbf{max}}$ after nine days of multiple dosing, whilst three had increases (1 drop-out). For CBD, seven had reductions in $C_{\mathbf{max}}$ 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 1 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.

Metabolism:

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-Δ^9-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 oxidised metabolite identified is CBD-7-oic acid containing a hydroxyethyl side chain.

See INTERACTIONS WITH OTHER MEDICINES for information on drug interaction and metabolism by the cytochrome P_{450} enzyme system.

Excretion:

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.

CLINICAL TRIALS

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 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 not great. 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 second 14-week Phase 3 study failed to show a significant treatment effect. The difference from placebo on the NRS score was 0.2 points.

It was postulated that a clinically useful treatment effect in some patients might be 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 predictive 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. Of these, 272 subjects (48%) responded with a reduction of at least 20% on the spasticity symptom NRS, with a mean change from the start of treatment of -3.0 points on the 10 point NRS. Of these, 241 patients were eligible to be 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 mean NRS scores for patients receiving Sativex generally remained stable (mean change from randomisation in NRS score -0.19), while the mean NRS score for patients switched to placebo increased 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).* Thus, the primary outcome measure was highly statistically significantly in favour of Sativex (p=0.0002).

Of those patients who had at least a 20% reduction from screening in NRS spasticity score at week 4 and who continued in the trial to receive randomised treatment, 74% (Sativex) and 51% (placebo) achieved a 30% reduction at week 16. Thus, the attributable response rate was 23% in the randomised cohort (which equates to around 10% of the original cohort).

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:	Sativex -0.25 ; Placebo +0.59 ;
(0 to 10 NRS)	Adjusted Difference -0.88 (95% CI -1.25, -0.51)
Timed 10 metre walk (seconds):	Sativex -2.3; Placebo +2.0;
	Adjusted Difference -3.34 (95% CI -6.96, 0.26)
Motricity index (arm and leg):	No differences between treatment groups were seen.
Barthel Activities of Daily Living:	Odds ratio for improvement: 2.04

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

The benefit of continued treatment in the long-term was studied in a placebo controlled, parallel group, randomised withdrawal trial, in subjects taking long-term Sativex. Thirty-six patients with a mean duration of Sativex use prior to the trial of 3.6 years 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, hazard ratio 0.335 (95% CI 0.16, 0.69). The primary efficacy endpoint was significantly in favour of Sativex (p=0.013). It is possible that some treatment failures on placebo could have reflected temporary factors associated with drug withdrawal. It is not known whether such patients would have improved again if they had remained off Sativex.

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INDICATIONS

Sativex is indicated as 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.

CONTRAINDICATIONS

Sativex is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients.
- 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. See PRECAUTIONS – Use in Lactation).

PRECAUTIONS

Individual response to Sativex varies widely and patients being considered for treatment with Sativex should therefore be assessed by a neurologist or rehabilitation physician. Patients who then commence a trial of Sativex should be reassessed by a neurologist or rehabilitation physician after 4 weeks of treatment. Patients who do not show a clinically significant improvement in spasticity on reassessment should not continue Sativex.

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

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

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.

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.

Psychiatric adverse events

Psychiatric adverse events including disorientation (4.1% vs 0.8%), depression (2.9% vs 2.0%), euphoric mood (2.2% vs 0.9%), and dissociation (1.7% vs 0.1%) occurred more frequently in patients given Sativex than in those given placebo in clinical trials. Approximately 10% more patients given Sativex experienced a psychiatric adverse event than those given placebo (17.6% vs 7.8%). Patients with a personal or family history of psychotic illness should not receive Sativex. Patients with a history of depression should be closely monitored and Sativex discontinued if clinically significant worsening of symptoms occurs on therapy.

In a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In this circumstance, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved.

The maximum recommended dose should not be exceeded. Serious psychiatric adverse events including transient psychosis occurred in 4/41 healthy volunteers given 18 actuations of Sativex twice daily.

No specific studies have been carried out in patients with significant hepatic or renal impairment. 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. Thus, the systemic exposure and the effects of Sativex are dependent on both renal and hepatic function and in patients with significant impaired hepatic or renal function the effects of Sativex may be exaggerated or prolonged (see PHARMACOKINETICS - Metabolism). Frequent clinical evaluation by a clinician is recommended in these patient populations.

Sativex contains approximately 50% v/v of ethanol. Each actuation contains up to 0.04g of ethanol. A small glass of wine (125 mL) of nominal ethanol content 12% v/v would contain approximately 12g ethanol. Most patients respond at doses up to and including 12 sprays a day which would contain less than 0.5 g of ethanol.

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.

Patients who have a history of substance abuse may be more prone to abuse Sativex as well (see CLINICAL TRIALS).

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.

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.

Genotoxicity

Sativex or a mixture of its component extracts was not genotoxic in *in vitro* tests for bacterial reverse mutation and *in vivo* micronucleus tests for clastogenicity in mice and rats, or in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes. No consistent genotoxicity was seen in an *in vitro* test for forward mutation in mouse L5178Y cells.

Carcinogenicity

A long-term carcinogenicity study has been conducted in rats with CBD BDS using dietary doses of 5-50 mg/kg/day, with no oncogenic response being observed. The highest dose resulted in estimated CBD and THC exposures (based on AUC) that were respectively 350 and 40 times that expected in humans with the maximum recommended dose. No studies were conducted with Sativex or its other component, THC BDS, but results were available from a published source for mouse and rat studies with oral administration of THC. Doses of THC used in the mouse were 125, 250 and 500 mg/kg/day (17, 35 and 70 times the maximum recommended human dose in terms of body surface area). There was an increase in thyroid follicular cell adenomas in males and females, but only with the lowest dose and the significance of this finding is uncertain. No oncogenic responses were seen in rats with THC doses of 12.5-50 mg/kg/day (3-14 times the maximum recommended human dose based on body surface area), associated with estimated exposures (AUC) of 90-550 times that expected in humans with the maximum recommended dose.

Effects on Fertility

Fertility in rats was unaffected by oral treatment with a 1:1 mixture of THC BDS and CBD BDS, at doses up to 12.5 mg/kg/day or each active component. This dose resulted in estimated exposures that were well in excess of that expected in humans with the maximum recommended dose (>300 fold based on AUC). Effects on various male reproductive parameters have been reported with cannabinoids in some animal studies, but findings were inconsistent or observed at high/toxic doses and their clinical significance is uncertain.

Use in Pregnancy (Category B2)

There is insufficient experience in humans regarding the effects of Sativex on reproduction. 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.

There was no evidence for teratogenicity in rats and rabbits treated with oral doses of a 1:1 THC BDS and CBD BDS mixture of up to 12.5 mg/kg/day of each active component. This dose resulted in respective THC and BDS exposures (based on AUC) that were approximately 490 and 320 fold (rats) or 12.5 and 3 fold (rabbits) those expected in humans with the maximum recommended dose. The highest dose was maternotoxic in rabbits and resulted in a slightly lower foetal weight and impaired skeletal ossification. Reduced foetal weights and increased incidences of skeletal variants were seen in rabbits, associated with maternal toxicity which was apparent with all doses tested.

Oral treatment of rats with 4 mg/kg/day of a 1:1 THC BDS and CBD BDS mixture from the time of implantation to weaning of the offspring resulted in a lower pup body weight gain and slightly impaired righting reflex on day 5 of lactation. The NOEL for these findings (2 mg/kg/day) was below the maximum recommended human dose in terms of body surface area.

Use in Lactation

High concentrations of THC and CBD were measured in the milk of lactating rats after oral treatment with a 1:1 mixture of THC BDS and CBD BDS, as may be expected due to the lipophilic nature of cannabinoids. Oral treatment of rats with a 1:1 THC BDS and CBD BDS mixture from the time of implantation to weaning was associated with impaired nursing behaviour and pup survival at doses of 5 mg/kg/day or greater (less than the maximum recommended human dose in terms of body surface area).

Following repeat dosing, high levels of cannabinoids are concentrated in breast milk. Doses in excess of normal clinical doses may affect growth rates of breast-fed infants.

In view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants, Sativex is contraindicated in breast feeding mothers (see CONTRAINDICATIONS).

Paediatric Use (<18 years)

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

Use in the Elderly (> 65 years)

No specific studies have been carried out in elderly patients, although patients up to 90 years of age have been included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks. In clinical trials patients aged over 65 years were three times more likely to have a CNS adverse event on Sativex than on placebo, and more than a third of all elderly subjects on active treatment had a CNS adverse event.

Effect on Laboratory Tests

During clinical trials with Sativex, no clinically relevant effects on laboratory tests were observed.

Effects on Ability to Drive and Use Machines

Sativex may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Therefore, given the combination of existing disability from MS plus the common effects of Sativex, patients taking Sativex should not drive, operate dangerous machinery or engage in hazardous activities.

INTERACTION WITH OTHER MEDICINES

The two main components of Sativex, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P_{450} enzyme system.

The inhibitory effects of Sativex on the cytochrome P_{450} system seen *in vitro* were only seen at concentrations significantly higher than the maximum observed in clinical trials.

In an *in vitro* study with 1:1% (v/v) THC botanical drug substance (BDS) and CBD BDS, no relevant induction of cytochrome P_{450} enzymes was seen for human CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes in human hepatocytes, at doses of up to 1µM (314 ng/mL).

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 figures for CBD were 3.3- and 5.1-fold.

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. ketoconazole, ritonavir, clarithromycin) is started or stopped during treatment with Sativex, a new dose titration may be required.

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, if concomitant drug treatment with strong enzyme inducers (e.g.rifampicin, carbamazepine, St John's Wort) is started or stopped during treatment with Sativex, a new dose titration may be required.

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

Based on *in vitro* data an inhibition of p-glycoprotein at the intestinal level by CBD cannot be excluded. Therefore, caution is recommended upon concomitant treatment with digoxin and other drugs being substrates for p-glycoprotein.

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 additive CNS effects could increase the risk of falls and other accidents.

ADVERSE EFFECTS

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 DOSAGE AND ADMINISTRATION). When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced.

Treatment emergent all-causality adverse events with an incidence of at least 1% for Sativex in placebo controlled trials in patients with MSare given below (some of these adverse events may be part of the underlying condition).

	All-Causality			Treatment-related		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	**Sativex Total (n=805)**	**Placebo Total (n=741)**	**Sativex Total (n=1016)**	**Sativex Total (n=805)**	**Placebo Total (n=741)**	**Sativex Total (n=1016)**
Overall Subjects with an Event	628 (78.0%)	492 (66.4%)	686 (67.5%)	532 (66.1%)	330 (44.5%)	599 (59.0%)
Cardiac Disorders						
Tachycardia	8 (1.0%)	3 (0.4%)	4 (0.4%)	5 (0.6%)	1 (0.1%)	4 (0.4%)
Ear and Labyrinth Disorders						
Vertigo	52 (6.5%)	15 (2.0%)	34 (3.3%)	48 (6.0%)	14 (1.9%)	32 (3.1%)
Eye Disorders						
Vision blurred	15 (1.9%)	3 (0.4%)	16 (1.6%)	13 (1.6%)	2 (0.3%)	8 (0.8%)
Gastrointestinal Disorders						
Nausea	77 (9.6%)	42 (5.7%)	98 (9.6%)	62 (7.7%)	27 (3.6%)	70 (6.9%)
Dry Mouth	49 (6.1%)	23 (3.1%)	60 (5.9%)	49 (6.1%)	22 (3.0%)	56 (5.5%)
Diarrhoea	44 (5.5%)	29 (3.9%)	84 (8.3%)	25 (3.1%)	14 (1.9%)	64 (6.3%)
Vomiting	28 (3.5%)	16 (2.2%)	57 (5.6%)	17 (2.1%)	11 (1.5%)	28 (2.8%)
Constipation	19 (2.4%)	4 (0.5%)	47 (4.6%)	8 (1.0%)	3 (0.4%)	27 (2.7%)
Oral Pain	17 (2.1%)	16 (2.2%)	48 (4.7%)	17 (2.1%)	16 (2.2%)	45 (4.4%)
Oral Discomfort	15 (1.9%)	14 (1.9%)	20 (2.0%)	14 (1.7%)	14 (1.9%)	20 (2.0%)
Mouth Ulceration	12 (1.5%)	6 (0.8%)	28 (2.8%)	11 (1.4%)	5 (0.7%)	26 (2.6%)
Dyspepsia	11 (1.4%)	12 (1.6%)	26 (2.6%)	8 (1.0%)	9 (1.2%)	17 (1.7%)
Abdominal pain upper	11 (1.4%)	2 (0.3%)	11 (1.1%)	3 (0.4%)	1 (0.1%)	8 (0.8%)
Glossodynia	9 (1.1%)	10 (1.3%)	32 (3.1%)	9 (1.1%)	10 (1.3%)	31 (3.1%)
General Disorders and Administration Site Conditions						
Fatigue	101 (12.5%)	62 (8.4%)	99 (9.7%)	89 (11.1%)	49 (6.6%)	77 (7.6%)
Asthenia	45 (5.6%)	23 (3.1%)	63 (6.2%)	37 (4.6%)	16 (2.2%)	40 (3.9%)
Feeling drunk	24 (3.0%)	3 (0.4%)	19 (1.9%)	23 (2.9%)	3 (0.4%)	19 (1.9%)
Feeling abnormal	19 (2.4%)	4 (0.5%)	25 (2.5%)	19 (2.4%)	4 (0.5%)	25 (2.5%)
Application site pain	16 (2.0%)	17 (2.3%)	27 (2.7%)	16 (2.0%)	17 (2.3%)	27 (2.7%)
Pain	10 (1.2%)	17 (2.3%)	29 (2.9%)	3 (0.4%)	7 (0.9%)	9 (0.9%)
Malaise	8 (1.0%)	3 (0.4%)	15 (1.5%)	8 (1.0%)	1 (0.1%)	8 (0.8%)
Infections and Infestations						
Urinary Tract Infection	71 (8.8%)	66 (8.9%)	164 (16.1%)	1 (0.1%)	5 (0.7%)	8 (0.8%)
Nasopharyngitis	22 (2.7%)	25 (3.4%)	74 (7.3%)	2 (0.2%)	0	2 (0.2%)
Pharyngitis	10 (1.2%)	8 (1.1%)	26 (2.6%)	6 (0.7%)	3 (0.4%)	15 (1.5%)
Viral infection	10 (1.2%)	2 (0.3%)	12 (1.2%)	0	0	2 (0.2%)
Lower respiratory tract infection	8 (1.0%)	10 (1.3%)	33 (3.2%)	1 (0.1%)	0	3 (0.3%)
Injury, Poisoning and Procedural Complications						
Fall	12 (1.5%)	4 (0.5%)	43 (4.2%)	8 (1.0%)	1 (0.1%)	14 (1.4%)
Metabolism and Nutrition Disorders						
Anorexia	17 (2.1%)	5 (0.7%)	30 (3.0%)	11 (1.4%)	4 (0.5%)	23 (2.3%)
Increased appetite	11 (1.4%)	3 (0.4%)	8 (0.8%)	11 (1.4%)	3 (0.4%)	8 (0.8%)
Musculoskeletal and Connective Tissue Disorders						
Muscle Spasms	24 (3.0%)	20 (2.7%)	48 (4.7%)	7 (0.9%)	3 (0.4%)	12 (1.2%)
Back Pain	19 (2.4%)	14 (1.9%)	37 (3.6%)	1 (0.1%)	1 (0.1%)	3 (0.3%)
Pain In Extremity	16 (2.0%)	19 (2.6%)	35 (3.4%)	2 (0.2%)	1 (0.1%)	6 (0.6%)
Muscular	11 (1.4%)	10 (1.3%)	30 (3.0%)	8 (1.0%)	4 (0.5%)	21 (2.1%)

	All-Causality			Treatment-related		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	**Sativex Total (n=805)**	**Placebo Total (n=741)**	**Sativex Total (n=1016)**	**Sativex Total (n=805)**	**Placebo Total (n=741)**	**Sativex Total (n=1016)**
Weakness						
Arthralgia	9 (1.1%)	3 (0.4%)	32 (3.1%)	3 (0.4%)	0	2 (0.2%)
Nervous System Disorders						
Dizziness	201 (25%)	61 (8.2%)	211 (20.8%)	200 (24.8%)	52 (7.0%)	200 (19.7%)
Somnolence	66 (8.2%)	17 (2.3%)	65 (6.4%)	65 (8.1%)	14 (1.9%)	64 (6.3%)
Headache	49 (6.1%)	56 (7.6%)	82 (8.1%)	41 (5.1%)	41 (5.5%)	48 (4.7%)
Disturbance in Attention	31 (3.9%)	1 (0.1%)	37 (3.6%)	30 (3.7%)	1 (0.1%)	36 (3.5%)
Dysgeusia	25 (3.1%)	6 (0.8%)	36 (3.5%)	25 (3.1%)	6 (0.8%)	34 (3.3%)
Muscle spasticity	26 (3.2%)	25 (3.4%)	21 (2.1%)	18 (2.2%)	15 (2.0%)	8 (0.8%)
Balance disorder	23 (2.9%)	13 (1.8%)	46 (4.5%)	20 (2.5%)	6 (0.8%)	26 (2.6%)
Multiple Sclerosis Relapse	20 (2.5%)	24 (3.2%)	46 (4.5%)	1 (0.1%)	3 (0.4%)	4 (0.4%)
Dysarthria	16 (2.0%)	3 (0.4%)	13 (1.3%)	13 (1.6%)	3 (0.4%)	11 (1.1%)
Lethargy	12 (1.5%)	5 (0.7%)	26 (2.6%)	10 (1.2%)	4 (0.5%)	21 (2.1%)
Paraesthesia	12 (1.5%)	12 (1.6%)	12 (1.2%)	8 (1.0%)	6 (0.8%)	9 (0.9%)
Memory Impairment	11 (1.4%)	1 (0.1%)	20 (2.0%)	11 (1.4%)	1 (0.1%)	19 (1.9%)
Amnesia	9 (1.1%)	2 (0.3%)	13 (1.3%)	8 (1.0%)	1 (0.1%)	10 (1.0%)
Tremor	9 (1.1%)	6 (0.8%)	10 (1.0%)	6 (0.7%)	3 (0.4%)	7 (0.7%)
Psychiatric Disorders						
Disorientation	33 (4.1%)	6 (0.8%)	21 (2.1%)	32 (4.0%)	4 (0.5%)	18 (1.8%)
Depression	23 (2.9%)	15 (2.0%)	47 (4.6%)	15 (1.9%)	6 (0.8%)	27 (2.7%)
Euphoric Mood	18 (2.2%)	7 (0.9%)	24 (2.4%)	18 (2.2%)	7 (0.9%)	24 (2.4%)
Dissociation	14 (1.7%)	1 (0.1%)	12 (1.2%)	14 (1.7%)	1 (0.1%)	11 (1.1%)
Insomnia	11 (1.4%)	16 (2.2%)	23 (2.3%)	5 (0.6%)	7 (0.9%)	13 (1.3%)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	11 (1.4%)	7 (0.9%)	20 (2.0%)	3 (0.4%)	3 (0.4%)	3 (0.3%)
Pharyngolaryngeal pain	8 (1.0%)	11 (1.5%)	1 (0.1%)	3 (0.4%)	4 (0.5%)	1 (0.1%
Vascular Disorders						
Hypertension	9 (1.1%)	4 (0.5%)	15 (1.5%)	5 (0.6%)	1 (0.1%)	3 (0.3%)

A single case of ventricular bigeminy has been reported though this was in the context of acute nut allergy.

Abuse potential

In a study designed to identify its abuse potential, Sativex at a dose of 4 sprays taken at one time, did not differ significantly from placebo. At 8 sprays there was a moderate effect, significantly different from placebo, and the results were more marked at 16 sprays. Sativex taken at the maximum recommended doses of up to twelve sprays per day sprays has moderate potential for abuse. Patients with a history of substance abuse may abuse Sativex and if Sativex is being considered for these patients close monitoring is recommended.

Psychiatric and cognitive adverse effects

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. 4/41 (9.7%) patients taking substantial multiples of the therapeutic dose experienced psychiatric adverse effects including hallucinations, delusions, and homicidal and suicidal ideation.

Please also refer to the PRECAUTIONS section.

DOSAGE AND ADMINISTRATION

Patients being considered for treatment with Sativex should be assessed by a neurologist or rehabilitation physician. Patients who then commence a trial of Sativex should be reassessed by a neurologist or rehabilitation physician after 4 weeks of treatment. Patients who do not show a clinically significant improvement in spasticity on reassessment should not continue Sativex.

Treatment must be initiated and supervised by a specialist neurologist or rehabilitation physician with expertise in treating patients with spasticity due to multiple sclerosis.

Sativex is for oromucosal use only.

Sativex is intended to be used in addition to the patient's current anti-spasticity medication.

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

Adults

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.

To minimise variability of bioavailability in the individual patient, administration of Sativex should be standardised as far as possible in relation to food intake (see INTERACTIONS WITH OTHER MEDICINES).

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 below. 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. The maximum number of consecutive sprays must not exceed 7 within a 3 hour period.

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 was 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 must not exceed 12 sprays in any 24-hour period.

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 CLINICAL TRIALS). The value of long term treatment should be re-evaluated periodically.

Children

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

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 of hot food and drinks.

Patients with significant hepatic or renal impairment

There are no studies in patients with impaired hepatic or 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 (see PRECAUTIONS).

Method of administration

Priming:

The spray container needs to be primed before first use and if not used for more than 21 days. To this end, the spray container should be shaken gently and the protective cap removed. The vial then needs to be held in an upright position while the actuator is pressed firmly and quickly for two or three times, directing into a tissue until a fine spray appears.

Normal use: The spray container should be shaken before use and the spray should be directed at different sites on the oromucosal surface changing the application site each time the product is used.

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation

Sativex is a yellow-brown oromucosal spray solution containing 27 mg/mL of THC and 25 mg/mL of CBD. The Type I amber glass spray container with brown plastic coating is fitted with a metering pump possessing a polypropylene dip tube and elastomer neck covered with a polyethylene cap. The metering pump delivers 100 microlitres per spray.

Pack Size: 10 mL.

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

1 or 3 glass spray containers per carton.

Not all pack sizes may be marketed.

Storage Conditions

Store below 8^{o}C (Refrigerate). Store upright. Keep away from heat and direct sunlight.

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

Use within 42 days from date of opening.

Special precautions for disposal

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

NAME AND ADDRESS OF SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

Sativex® is a registered trade mark of GW Pharma Limited, United Kingdom.

POISON SCHEDULE OF THE MEDICINE

Poison schedule: Controlled Drug - Schedule 8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 November 2012