PHARMAC
Pharmaceutical Management Agency

PHARMACEUTICAL SCHEDULE APPLICATION

From: Medical Director

Date: July 2015

Cannabidiol with tetrahydrocannabinol (Sativex) for Multiple Sclerosis (MS) spasticity, epilepsy, and pain, including pain associated with spasticity.

We are seeking PTAC's advice on Sativex for both its registered indication (moderate-severe spasticity due to multiple sclerosis (MS) and off-label use (spasticity and pain from other causes/palliative care, epilepsy).

This application involves funding for three different indications; therefore, this paper will begin with an introduction section that includes information common to all indications and will then be divided out with separate questions and specific information for each of the indications as follows:

Introduction: Information common to all indications

Indication 1: Sativex for spasticity due to multiple sclerosis (MS)

Indication 2: Sativex for pain, including pain associated with spasticity

Indication 3: Sativex for treatment-resistant epilepsy

Whether or not PTAC recommends that Sativex should progress to a Pharmaceutical Schedule listing we have a need for some robust clinical advice given that we receive NPPA applications for Sativex.

INTRODUCTION: INFORMATION COMMON TO ALL INDICATIONS

SUMMARY OF PHARMACEUTICAL			
Brand Name	Sativex	**Chemical Name**	Cannabidiol/Tetrahydrocannabinol
Indications	MS Spasticity, Pain & Spasticity. Epilepsy	**Presentation**	Oromucosal Spray 3 x 10 ml vials per pack
Therapeutic Group	Muscle relaxants (Musculoskeletal System)	**Dosage**	Max 12 sprays per day
Supplier	Novartis	**Application Date**	PHARMAC generated
MOH Restrictions	Ministerial approval required Prescription medicine	**Proposal type**	New listing
Current Subsidy	Nil		
Proposed Subsidy	$With per 3 x 10 ml vials	**Manufacturer's Surcharge**	Nil
OP	Yes	**Section F**	No

OP = Original pack

Background

We have received 11 Named Patient Pharmaceutical Assessment (NPPA) applications for Sativex since July 2013, either for spasticity due to MS, epilepsy or pain with/without spasticity. Details of the NPPA applications are described in each section of the paper relevant to the indication applied for. Due to the potentially large sizes of these patient groups, we consider that it would be more appropriate for Sativex to be assessed as a Pharmaceutical Schedule funding application as opposed to assessment through the NPPA pathway.

Sativex is registered with Medsafe as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to Multiple Sclerosis (MS) and, we are seeking PTAC's advice on this indication, in addition to epilepsy and pain, including pain associated with spasticity. We have asked Novartis if it would like to submit a funding application for this indication; however Novartis has informed us that it is unwilling to support this. Novartis, at our request, has provided us with references it has and also the cost of the product. Information provided by Novartis is attached in Appendix 1. Sativex was developed by GW Pharmaceuticals, however, Novartis has the NZ marketing and distribution rights. No product samples have been provided.

Novartis has highlighted to us that if Sativex was to become funded, the supplier may need to talk with the Ministry of Health (MoH) about re-classifying it due to the heavy administrative burden currently associated with delivery of Sativex. At present, Ministerial Approvals are required for every prescriber/patient, and only a Novartis Medical Advisor can sign the form from the supplier side. The Novartis Medical Advisor also has to authorise delivery of every prescription, and a copy of every prescription has to be sent to them. Novartis can only send the product to a specific named pharmacy for each patient, and has to hold proof of delivery for every delivery. Apparently the MoH recognises that the system would need to change if the volumes were to increase.

Novartis has informed us that since August 2009, there have been approximately 75 Ministerial Approvals, although there appear to have been more approvals than patients actually receiving treatment At present there are 19 active approvals (they have expiry dates), and product is delivered to approximately 2 3 patients per month. Novartis estimates that there are probably about 5 patients actually receiving it at present.

Of interest, every report to Novartis of off label use (for any pharmaceutical supplied by Novartis) is recorded as an adverse event and reported to Novartis' drug safety unit in Australia which then reports to the health authority.

Sativex

Presentation

Sativex is formulated as a solution for oromucosal use and comes in a 10 ml spray container. Each ml contains: 38-44 mg and 45-42 mg of two extracts from *Cannabis sativa* L., folium cum flore (Cannabis leaf and flower) corresponding to 27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol. Each 100 microlitre spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD). Each 100 mcl spray also contains up to 0.04g alcohol. The combination of THC plus cannabidiol may also be referred to as nabiximols. Each 10 ml pack allows delivery (after priming) of up to 90 sprays of 100 mcl. Sativex must be refrigerated and stored in a safe (Class B controlled drug).

Medsafe Registered Indication

Sativex is indicated as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to 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.

Dose

The Medsafe-registered dose recommends a titration of the dose beginning with 1 spray in the evening and gradually increasing to a maximum of 12 sprays per day taken in divided doses (morning and evening). Dosing will vary between patients. The median dose in clinical trials for patients with MS is eight sprays per day. The recommended titration table is available in in Medsafe datasheet (Appendix 2).

Pharmacokinetics

Following administration, Sativex is rapidly absorbed from the buccal mucosa and is widely distributed, particularly to fatty tissues (cannabinoids are highly lipophilic). Both THC and CBD appear in the plasma within 15 minutes after single oromucosal administration. There is a high degree of pharmacokinetic parameters between patients, however Time-to-peak plasma concentration is around 2 hours. Sativex exhibits extensive protein binding and is metabolised in the liver via CYP isoensymes (2C9, 2C19, 2D6 and 3A4) to THC metabolite 11-hydroxy-tetrahydrocannabinol (11-OH-THC, psycho-active) and CBD metabolite 7-hydroxy-cannabidiol. Elimination of oral cannabinoids is bi-phasic with an initial half-life of approximately four hours, and the terminal elimination half-lives are of the order of 24-36 hours or longer. 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.

Mechanism of action

Cannabinoids are derived from the cannabis (marijuana) plant, which contains over 400 compounds, including more than 60 cannabinoids The primary psychoactive cannabinoid is THC (also known as dronabinol). In vivo, cannabinoid molecules such as THC interact with an endogenous system that includes cannabinoid-like ligands (the endocannabinoids) as well as multiple receptors in both the periphery and central nervous system 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. Activation of the CB_1 receptor produces marijuana-like effects on psyche and circulation, whereas activation of the CB_2 receptor does not. THC acts as a partial agonist at both CB_1 and CB_2 receptors, mimicking the effects of the endocannbinoids, which may modulate the effects of neurotransmitters (eg 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 improved motor function.

It is thought that cannabinoid receptors in the pain pathways of the brain and spinal cord mediate cannabinoid-induced analgesia.

Contraindications

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.

Breastfeeding.

Adverse effects

The most commonly reported side effects reported include the following:

- CNS disorders: dizziness, amnesia, balance disorder, disturbance in attention, dysarthria, dysguesia, lethargy, memory impairment somnolence, vertigo
- Psychiatric disorders depression, disorientation, dissociation, euphoric mood
- Gastrointestinal disorders: constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, changes in appetite, oral pain, vomiting
- General: fatigue, asthenia, feeling abnormal, feeling drunk, malaise, application site pain, blurred vision, fall

Price

$With per 3 x 10 ml vials

Sativex regulatory information

The Medsafe website provides the following information:

1 Sativex and risk of diversion, abuse and misuse

Sativex is considered to be a desirable and divertible pharmaceutical due to the inherent nature of its active substances Because it is a cannabis preparation, Sativex is classified as a Schedule 2 Class B (1) drug product under Misuse of Drugs Act 1975.

It is unclear what proportion of patients who are chronically exposed to Sativex (cannabinoids) will develop either psychological or physical dependence. At therapeutic doses, Sativex may produce side-effects that are interpreted as a euphoria or cannabis-like "high"

As with all controlled drugs, prescribers should monitor patients who receive Sativex for signs of excessive use, abuse and misuse. Patients with a personal or family history of substance abuse (including drug or alcohol abuse) are at higher risk of addiction than other patients with chronic severe disease.

2. Approval required before prescribing

Ministerial approval is required before Sativex can be prescribed by a New Zealand registered medical practitioner, for any use, under regulation 22 of the Misuse of Drugs Regulations 1977.

As part of the approval process each application for approval must be signed by an appropriate vocationally registered practitioner ("specialist").

Application forms for approval to prescribe Sativex are available on the Medsafe website: http://www.medsafe.govt.nz/profs/riss/Sativex.asp

Clinical advice

We have not received any formal clinical advice from PTAC or its Subcommittees on Sativex; however, of interest the Analgesic Subcommittee, at its December 2014 meeting, provided the following comments as part of a Therapeutic Group review.

5.3 The Subcommittee noted that Sativex oral spray (delta-9-tetracannabinol/cannabidiol) is not funded and that PHARMAC has not received a funding application for this product. Members noted that the registered indication for use of Sativex was to treat muscle spasm associated with multiple sclerosis. The Subcommittee noted that clinicians wanting to prescribe Sativex have to apply for Ministerial approval for both approved and unapproved indications, and members considered that this seemed inconsistent when compared with the prescribing of other controlled drugs for approved and unapproved uses.

International Prices

Country	Source	Pack Size	Local Price	Exchange Rate July 2015	Price ($NZ)
New Zealand	Supplier	3 x 10 ml		-	$ Withheld
United Kingdom	BNF	3 x 10 ml	£375	0.52	$635.16

INDICATION 1: SATIVEX FOR SPASTICITY DUE TO MULTIPLE SCLEROSIS (MS)

QUESTIONS TO PTAC

1. What is the strength and quality of the evidence in support of this indication?
2. Does Sativex have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule? If so, which pharmaceutical (or therapeutic sub-group) and at what dose does it have the same or similar effect?
3. With which pharmaceuticals would Sativex be used in combination, and which pharmaceuticals would it replace?
4. Are there currently any problems with access to and / or availability of alternative treatments?
5. Does Sativex provide any additional health benefit or create any additional risks compared with other treatment options? If so, what benefits or risks are different from alternative treatments?
    a. Specifically what is the appropriate comparator for assessing cost-effectiveness?
    b. Would there be a cost offset due to a decrease in the use of physical therapy?
    c. Would it be appropriate to use the PHARMAC CUA model (calibrated for relapsing remitting multiple sclerosis) as a proxy for cost-effectiveness in this condition?
    d. What time horizon should be used to assess cost-effectiveness?
6. Which patient population would benefit most from Sativex?
    a. Does PTAC agree with our estimates for patient numbers?
    b. If not can what would be a more appropriate estimation for patient numbers?
7. Are there any other diseases/conditions with associated spasticity that the Committee considers there to be sufficient evidence to warrant investigating?
8. Is there any unmet health need in this population, or within a subset of this population (e.g. Maori / Pacific people)?
9. Would the use of Sativex create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?
10. What effects would the listing of Sativex in the Pharmaceutical Schedule have on the current market dynamics for the alternative treatments?
11. Should Sativex be listed in the Pharmaceutical Schedule?
    - Name the decision criteria particularly relevant to a positive or negative recommendation and explain why each is relevant.
12. Should any restrictions be placed on the use of Sativex? If so, for what reason should these restrictions be applied?
13. If listing is recommended, what priority rating would you give to this proposal? [low / medium / high / only if cost neutral]?
14 Does the Committee have any additional recommendations in relation to this indication?

DISCUSSION

Disease Targeted

Multiple sclerosis (MS) is an autoimmune condition in which the immune system attacks the central nervous system, leading to demyelination It may cause numerous physical and mental symptoms, and often progresses to physical and cognitive disability.

MS is one of the most common chronic diseases of the central nervous system. In New Zealand, about one in every 1,000 to 2,000 people develop MS with approximately 2,500 people affected.

MS rarely affects Maori, with Maori having 0.24 times the rate than non-Maori (Taylor et al, Prevalence of MS in NZ). http://www.msnz.org.nz/Document.Doc?id=6

In general, three typical patterns of MS can be recognised:

- Relapsing-remitting MS (RRMS): relapses with a flare-up of old symptoms or the development of new symptoms are followed by a remission with resolution or reduction of symptoms.

- Secondary-progressive MS (SPMS): after an initial course of relapsing/remitting MS there is the development of slowly progressive disability.

- Primary-progressive MS (PPMS): in about 10% of cases, from the beginning, there is progressive worsening of symptoms and disability without distinct attacks.

RRMS may get better for varying lengths of time (remission) and temporarily worse at others (relapse). Full recovery from each relapse will not always be the case. There is no cure for MS and treatment options are limited both in number and effectiveness.

Patients' annual relapse rate (ARR) and Expanded Disability Status Scale (EDSS) scores are measures used to assess disability and disease progression. Magnetic Resonance Imaging (MRI) of neural tissue helps to establish the damage and scarring that has been caused by the disease. Classic MS lesions are called T2 hyper-intensities (as they appear in images), and are most closely associated with relapse activity.

Decreased mobility is one of the most common problems in MS and around 85% of people with MS report a gait disturbance as their main problem. Gait is a complex function and many symptoms associated with MS, such as fatigue, weakness, spasticity and ataxia can impact on its quality (NICE).

Spasticity is a common symptom affecting up to 80% of people with MS. Many people with MS also experience spasms, which are sudden, involuntary, often painful movements affecting any part of the body. Spasticity can range from a sensation of tightness or stiffness in a limb, especially the legs, which can cause problems with gait, to a tightening of the muscles throughout the body which is so severe that the person is unable to move and is confined to a wheelchair or bed. Moderate (frequently affects activities), severe (daily forced to modify activities) or total spasticity (prevents daily activities) has been reported to affect around 34% of people with MS. (Rizo et al. Mult Scler 2004, 10(5):589-95) (Appendix 3). Left unmanaged in the severe stage, spasticity can lead to the secondary complications of muscle shortening, permanent contracture and pain

Health Benefits and Risks of Current Treatments

Muscle relaxants used for MS spasticity that are listed in Section B of the Pharmaceutical Schedule and on the HML include baclofen, dantrolene, orphenadrine citrate and diazepam, these are detailed below along with clostridium botulinum toxin Type A which is listed only on the HML. Gabapentin, mentioned in the NICE guidelines for MS (Appendix 3) is funded via Special Authority for neuropathic pain, epilepsy and uraemic pruritus Tizanidine, also mentioned in the NICE guidelines is not registered with Medsafe or funded in NZ.

The NICE guidelines for MS recommend the following pharmacological treatment management for spasticity associated with MS:

1. Baclofen or gabapentin as first line treatment.
    - A combination of baclofen and gabapentin if either drugs do not provide adequate relieve or side effects from individual drugs prevent the dose being increased.
2. Tizanidine or dantrolene as second line treatment.
3. Benzodiazepines as third line treatment.

Baclofen

Baclofen 10mg tablets and baclofen intrathecal injections are listed on the Pharmaceutical Schedule. Intrathecal baclofen is subsidised only for use in a programmable pump in patients where oral antispastic agents have been ineffective or have caused intolerable side effects and the prescription is endorsed accordingly.

Baclofen is an antispastic agent and is a derivative of gamma-aminobutyric acid (GABA). Baclofen's mechanism of action is via inhibition of the transmission of both monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarisation of primary afferent fibre terminals with resultant relief of muscle spasticity.

Recommended oral dosing is as follows: 5 mg three times daily with gradual titration to optimal response. Optimal dosage ranges from 30 mg to 80 mg daily.

Intrathecal baclofen involves a pump being surgically implanted and is linked to the spinal cavity by a tube inserted by a lumber puncture. An intrathecal pump allows delivery of baclofen directly into the CSF whilst bypassing some of the side effects of oral tablets and providing a more consistent effect using a much lower dose (approximately 100th of the dose). Maintenance dosage for long-term continuous infusion of intrathecal baclofen in patients with spasticity of spinal origin ranges from 10 micrograms /day to 1200 micrograms /day, most patients being adequately maintained on 300 - 800 micrograms/day.

Common side effects include muscular weakness, drowsiness, confusion, fatigue, dizziness, insomnia, nausea and vomiting.

Dantrolene

Dantrolene 25 mg and 50 mg capsules are listed on the Pharmaceutical Schedule. Dantrolene produces relaxation of the contractile state of the skeletal muscle by an effect beyond the myoneural junction and directly on the muscle itself Dantrolene uncouples the excitation and contraction of the skeletal muscle, probably by interfering with the release of calcium ions from the sarcoplasmic reticulum. A central nervous system effect occurs with

drowsiness, dizziness and generalised weakness in around 20% of cases. The extent of the involvement of the CNS in dantrolene-induced muscle relaxation is unknown

Recommended dosing is as follows: 25 mg once daily with gradual titration to optimal response. The maximum recommended dose is 200 mg/day. As most patients respond to this or a lower dose, and hepatotoxicity appears to be dose-related above 200 mg/day, higher doses should be used only rarely and with close monitoring

The most common adverse effects of dantrolene are drowsiness, dizziness, weakness, general malaise, fatigue and diarrhoea. These effects are generally transient, occurring early in treatment, and can be managed by beginning therapy with a low dose and using a slow titration.

Orphenadrine citrate

Orphenadrine citrate 100 mg tablets are listed on the Pharmaceutical Schedule. Orphenadrine citrate is an analgesic and a muscle relaxant. The exact mechanism of action is unknown although indirect skeletal muscle relaxant effects are thought to work by central atropine-like effects; it also possesses analgesic properties.

Recommend dosing is as follows: 100 mg twice daily.

The most common adverse effects are dryness of mouth, tachycardia, palpitation, urinary hesitancy or retention, blurred vision, dilation of pupils, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, purities, hallucinations, agitation, tremor and gastric irritation. These adverse effects are mainly due to the mild anticholinergic action of orphenadrine, and are usually associated with higher doses, most effects can usually be eliminated by reducing the dose.

Diazepam

Diazepam 2 mg and 5 mg tablets are listed on the Pharmaceutical Schedule. Diazepam is a benzodiazepine tranquilliser that is thought to act by facilitating the synaptic actions of GABA. GABA is one of the major inhibitory neurotransmitters of the CNS. Diazepam does not act at the same site as GABA, but at a presumably allosterically-linked site, called the benzodiazepine receptor. It is through this site that anticonvulsant, sedative, skeletal muscle relaxant and amnestic properties of diazepam are mediated.

The recommended oral dose for muscle spasm is 2 to 15 mg daily in divided doses.

Common adverse effects include drowsiness, fatigue, unsteadiness and feeling less alert.

Clostridium botulinum type A toxin

Botulinum toxin injections, also known as Botox or Dysport, are listed on the HML and are a treatment option for spasticity and spasms associated with MS where there is an isolated area. It is also used to treat bladder symptoms from MS where spasms in the muscle of the bladder wall cause urgency and incontinence.

Botulinum toxin type A is a neurotoxin produced by Clostridium botulinum, which appears to affect the presynaptic membrane of the neuromuscular junction, where it prevents calcium-dependent release of acetylcholine and produces a state of denervation. Muscle inactivation persists until fibrils grow from the nerve and form junction plates on new area of the muscle cell walls. The effects of treatment generally last around 4 months.

The exact dose and number of injection sites is recommended to be tailored to the individual based on the size, number and location of muscles involved, the severity, presence of local muscle weakness, and the patient response to previous treatment A recommended dosing range, specific to site, is available on the product datasheet http://medsafe.govt.nz/profs/datasheet/b/Botoxinj.pdf

Botulinum toxin A injections are generally well tolerated Common adverse effects include pain, bruising and oedema at the injection site and general weakness and clumsiness.

Non-pharmacological treatment

Non-pharmacologic interventions for spasticity in MS include physiotherapy and structured exercise programs.

Surgery may be indicated for severe cases if muscles have shortened and caused contracted joints.

Key Evidence

The supplier has provided three randomised controlled trials (RCTs), two review articles, two long term open label trials and one meta -analysis in support of Sativex for spasticity due to MS. Appendix 3. The supplier also provided four articles relating to cost-effectiveness/QOL for spasticity due to MS. (Appendix 3). One additional RCT was provided by a NPPA applicant and the remainder were identified by PHARMAC (Appendix 3). No head to head trials comparing Sativex with baclofen, dantrolene or diazepam appear to have been published. A literature search was conducted on 2 July 2015 via Pubmed. Search terms included multiple sclerosis and tetrahydrocannabidiol-cannabidiol. Full details of the search and results are attached in Appendix 3. Full articles can be ordered and provided on request from the PTAC secretary. Articles PHARMAC staff consider to be the most relevant have been summarised below, and the full articles are attached in Appendix 3.

Randomised controlled trials

Zajicek et al (Lancet 2003;362:1517-1526) conducted a randomised, placebo-controlled, multicentre trial to investigate cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study).

- 657 patients with MS and muscle spasticity (as defined as an Ashworth score of >2 in two or more lower limb muscle groups) were randomised to receive treatment with either oral cannabis extract (n = 219), delta-9-tetrahydrocannabinol (n=216), or placebo (n=222), for 15 weeks. The primary outcome measure was change in overall spasticity scores, using the Ashworth scale.

- Analysis was by Intention to treat and data was obtained for 611 patients; cannabis extract (n=207), delta-9-tetrahydrocannabinol (n=197) and placebo (n= 207). Demographics and baseline characteristics were similar across the groups, with the exception of fewer patients in the cannabis extract group having relapsing remitting MS compared to the other groups. The authors considered that since RRMS represents only 5% of the total sample, that this imbalance was unlikely to have greatly affected the results. The authors reported no treatment effect of cannabinoids on the primary outcome (p=0.40). The estimated difference in mean reduction in total Ashworth score for patients taking cannabis extract compared with placebo was 0.32 (95% CI 1.04 to 1.67), and for those taking delta-9 tetrahydrocannabidiol versus placebo it was 0 94 (-0 44 to 2 31)

Wade et al (Mult Scler 2004;10: 434-441) conducted a double blind, randomised, placebo-controlled, parallel group, study (with a subsequent open label extension) to investigate whether a cannabis-based medicinal extract (CMBE) benefits a range of symptoms due to MS.

- 160 patients with MS experiencing problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain were randomised to either an oromucosal spray containing placebo or CBME (Sativex) containing equal amounts of THC and cannabidiol at a dose of 2.5-120 mg (1-48 sprays) of each daily, in divided doses for six weeks. At the end of the six weeks all patients were then offered active treatment for an additional four weeks (results from the open–label extension are reported separately). The primary outcome at four weeks, was a Visual Analogue Scale (VAS) for each patient's most troublesome symptom; termed as the Primary Symptom Score (PSS). Other outcome measures included VAS scores of other symptoms, measures of disability (the Guy's Neurological Disability Scale, GNDS), cognition, mood, sleep, fatigue and the modified Ashworth Scale of Spasticity.

- Demographic and baseline characteristics were similar across the groups, with no statistically significant differences, although the active treatment group were slightly more disabled (difference in mean Barthel score 1.5/20). Mean number of sprays used per day at the end of the four weeks were approximately 15 for the treatment group and 26 for the placebo group. No statistically significant difference between the groups was reported for the PSS (the primary outcome); the PSS reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CMBE and from 74.31 (12.5) to 54.79 (26.3) following placebo (P=0.124). The authors reported that patients on active treatment whose primary symptom had been spasticity showed a significant reduction in their VAS in comparison with placebo; patients treated with CBME had an average difference in VAS improvement compared with the placebo group of -22.79 [95% CI -35.52, -10.07], (P=0.001). A difference in favour of the placebo group was reported in the GNDS scores (P=0.048). No statistically significant differences were reported between the groups on measure of change in spasticity (p=0.548) as measured by the modified Ashworth Scale of spasticity, cognition or mood.

- Adverse effects associated with the use of CBME were reported to be generally mild. Dose-limiting effects most commonly noted clinically with use of CBME were dizziness, fatigue, mouth ulceration, intoxication and excessive reduction in lower limb tone.

- Wade et al (Mult Scler 2006;12:639-645) then carried out the open-label phase, being a long-term follow-up (up to 82 weeks) involving those patients who had completed the randomised, double-blind phase.

    - 137 MS patients transitioned into this phase, and patients were assessed every 8 weeks using VAS and diary scores for an average of 434 days.

    - The authors reported that reductions in VAS score at entry (from the initial RCT) were maintained over one year of treatment for patients who completed at least one year's open label treatment and contributed with data at each visit (n=73). The average number of doses taken daily remaining relatively constant (around 10-12 doses daily).

    - A total of 58 patients (42 3%) withdrew due to lack of efficacy (n=24); adverse events (n=7); withdrew consent (n=6); lost to follow up (n=3); and other (n=8). The majority of adverse events reported were mild and similar to those described

in the RCT above, however, three patients had five 'serious adverse events' between them – two seizures, one fall, one aspiration pneumonia and one gastroenteritis Four patients were reported to have first ever seizures The authors reported that a planned sudden interruption of CBME for two weeks in 25 patients (of 62 approached) did not cause a consistent withdrawal syndrome, although 11 (46%) patients reported at least one of – tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional liability, intoxication or vivid dreams. 22 patients (88%) restarted CMBE treatment.

Colin et al (Eur J Neurol 2007;14:290-296) carried out a randomised controlled double blind study to investigate the efficacy, safety and tolerability of Sativex for spasticity in MS.

- 189 patients were randomised in a 2:1 ratio to receive either Sativex (n=124) or placebo (n = 65) for a 6 week period. Patients were instructed to titrate their doses to a maximum of 48 sprays per day.

- Originally the primary outcome measure was the Ashworth Scale but publication of the CAMS trials (described above), which used the Ashworth Scale as the primary outcome measure, did not demonstrate a beneficial effect on spasticity, therefore the authors of this trial changed the primary outcome to be change in Numerical Rating Scale (NRS) of spasticity. The Ashworth scale then became a secondary outcome along with a subjective measure of spasm.

- The mean daily dose used in the study was not clear from the information provided, due to an apparent discrepancy in one of the tables. For the primary outcome measure, the adjusted mean change in NRS spasticity scores for the Sativex treatment at the end of treatment showed a reduction of 1.18 points (from a mean baseline score of 5.49) compared with the placebo group that showed a reduction of 0.63 points (from a mean baseline score of 5.39); the difference, in favour of Sativex was statistically significant (p=0.048; 95% CI: -1.029, -0.004 points). Secondary efficacy measures were reported to not reach statistical significance.

Colin et al (Neurol Res 2010;32(5):451459) conducted another double-blind, randomised, placebo-controlled trial to compare Sativex with placebo in relieving symptoms of spasticity due to MS.

- 337 patients with MS spasticity not relieved with current antispasticity therapy were randomised to receive either Sativex or placebo, as add-on to all existing anti-spasticity therapies, for 15 weeks. Patients self-titrated their doses to a maximum of 24 actuations in any 24 hour period.

- The primary endpoint was the change in baseline in mean 0-10 Numerical Rating Scale (NRS) spasticity score. Secondary endpoints included responder analysis (defined as a 30% improvement from baseline in spasticity NRS score), timed 10-meter walk, Carer Global Impression of Change (GCIC), change in modified Ashworth scale, EQ-5D, MSQoL-54 and severity of the following symptoms: spasm, pain, fatigue, tremor, bladder symptoms and sleep quality, as per the NRS.

- Demographic and baseline characteristics were reported to be similar between the groups. For the intention to treat (ITT) analysis, the change in spasticity 0-10 NRS score for the Sativex group at the end of the study was a decrease of 1.05 points (from a mean baseline NRS score of 6 77) compared to a decrease of 0 82 points (from a mean baseline NRS score of 6.48 points) for placebo, this difference of -0.23 points, was not statistically significant (p=0.219). In the Per Protocol (PP) analysis (n=265) (73% of the Sativex group and 85% of the placebo group), the authors

reported the change in NRS score for the Sativex group as -1.30 points (baseline 6 84) compared with -0 84 points (baseline = 6 49) for placebo, with the difference between the groups of -0 46 points in favour of Sativex to be statistically significant (p=0.035). In the PP analysis, 44 (36%) Sativex patients achieved at least a 30% improvement in their 0 10 NRS spasticity score compared with 35 placebo subjects (24%); this difference was statistically significant (OR=1 74, p=0 04, 95% CI: 1 024 2 960). The difference for the responder analysis as per the intention to-treat (ITT) analysis was not statistically significant.

- The authors reported that Sativex was generally well tolerated, with most adverse events being mild to moderate in severity.

Novotna et al (Euro J Neurol 2011;18:1112-1131) investigated the efficacy of Sativex as add-on treatment, in patients with refractory MS spasticity, who were identified as responders to Sativex via a run-in phase.

- 572 patients were enrolled into a 4 week run-in phase, single blind treatment trial with Sativex to identify responders to treatment. Participants were blinded to whether they were taking placebo or treatment, however, investigators were aware that that all participants were allocated to treatment with Sativex. Responders (defined as those who achieved an improvement of $\geq$ 20% in spasticity, as measured by the NRS) then continued on to a 12 week randomised, placebo controlled phase. The primary endpoint was the difference between treatments in the mean spasticity NRS.

- Of the 572 patients recruited in the initial run-in phase, 272 achieved a $\geq$ 20% improvement in spasticity and 241 of these patients were then randomised to receive either Sativex (n=124) or placebo (n = 117).

- The authors reported that over the 12 week double-blind, randomised phase, the mean spasticity score improved in the Sativex group by 0.04 (from a baseline score of 3.87 points) and deteriorated in the placebo group by 0.81 (from a baseline score of 3.92 points); the difference between the groups was 0.84 points (95% CI: -1.29 to -0.40) (P=0.0002).

- The most common adverse events reported in the Sativex group were vertigo, fatigue, muscle spasms and urinary tract infection.

Aragona et al (Clin Neuropharmacol 2009;32(1):41-47) conducted a double-blind, placebo controlled, crossover study to investigate possible psychopathological and cognitive effects, as well as general tolerability, effects on quality of life, fatigue and motor function in patients treated with Sativex.

- 17 cannabis-naïve patients with MS were randomly assigned to 2 counter-balanced groups starting either with Sativex or placebo as the first drug. After 3 weeks, the first treatment was discontinued, and patients entered a washout phase of 2 weeks, before starting the second treatment phase of 3 weeks. Patients were assessed at baseline and at the end of the Sativex and placebo phases of the trial by means of Symptom Checklist-90 Revised, self-rating Anxiety Scale, Multiple Sclerosis Functional Composite, VAS on health related QOL, Multiple Sclerosis Impact Scale-29, and Fatigue Severity Scale.

- The authors reported that post placebo versus post-cannabinoid scores showed that no significant differences could be detected on all the variables under study

- No serious adverse events, abuse tendencies, or direct withdrawal symptoms were reported Increased desire for Sativex with secondary depression was reported in 1 participant.

Meta-analysis

A meta analysis was conducted by Wade et al (Mult Scler 2010;16(6):707 714) to determine the efficacy and safety of Sativex on spasticity in people with MS.

- Results from three randomised, placebo, double-blind parallel group studies were combined for analysis. These trials have been detailed above (Mult Scler 2004;10: 434-441; (Mult Scler 2006;12:639-645; Eur J Neurol 2007;14:290-296).

- The authors reported that the patient populations were similar. The adjusted mean change of the NRS from baseline in the Sativex group was -1.30 compared with -0.97 for placebo. The treatment difference was -0.32 (95% CI -0.61, -0.04; p=0.026). A statistically significant greater proportion of treated patients were responders (defined as those who achieved a ≥30% improvement from baseline in their spasticity) (OR = 1.62, 95% CI 1.15, 2.28; p = 0.0073) and treated patients also reported greater improvement (OR = 1.67, 95% CI 1.05, 2.65; p=0.030). No statistically significant differences were reported between treatments (p=0.75) in the analysis of the Ashworth Scale score results.

- High numbers of patients reported experiencing at least one adverse event, but most were mild to moderate in severity and all drug-related serious adverse events resolved.

NPPA applications

We have received two NPPA applications for Sativex for the treatment of spasticity due to MS since July 2013. Prescribers for both patients had obtained approval to prescribe Sativex from the MoH under Regulation 22 of the Misuse of Drugs Regulation 1977 prior to applying to PHARMAC and were applying for a dose of up to a maximum of 12 sprays per day. These applications were not progressed as there appeared to remain funded alternative treatments. One of the pre-requisite criteria for NPPA applications is that all funded treatments have been reasonably tried and failed or are contraindicated.

The first application, received from a neurologist in October 2013, was for a Withheld under [redacted] patient with advanced secondary progressive MS. The application detailed previous treatment with fampridine (not funded), prednisone, and baclofen. However, the application was withdrawn as other muscle relaxants were considered to remain appropriate funded treatment options available for this patient. (Note that an application is classified as withdrawn either when the applicant advises that it is withdrawn, or if we have queried the applicant about funded alternatives and have received no response after follow-up.)

The second application was submitted by a general practitioner in August 2013 for a We have [redacted] We patient with MS who had received previous treatment with diazepam, clonazepam, baclofen and dantrolene. The NPPA Advisory Panel considered there were few details provided as to the nature and severity of the patient's spasticity and their specific response to the trialled treatments. However, the Panel considered that the doses of both dantrolene and baclofen appeared to be low and that baclofen may be better tolerated when used in combination with other agents such as gabapentin, clonazepam, or carbamazepine. These points were conveyed to the applicant, but no further information was received in reply

International recommendations

Pharmaceutical Benefits Advisory Committee (PBAC) of Australia

Sativex is not reimbursed on the Pharmaceutical Benefits Scheme The PBAC reviewed an application in July 2013 and this was rejected on the basis of insufficient evidence to establish comparative effectiveness and safety compared with standard care alone in patients who are intolerant to anti-spasticity medication; and no evidence of efficacy and safety provided in comparison with high dose baclofen alone, or in combination with dantrolene or diazepam as the second-line therapy. Details of the review are available from the following link: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/nabiximols

NICE, United Kingdom

The NICE guidance for Multiple Sclerosis recommends the following: Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment. http://www.nice.org.uk/guidance/cg186/resources/guidance-multiple-sclerosis-pdf

All Wales Medicines Strategy Group

Sativex is recommended as an option for use within NHS Wales as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis 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. Details of the All Wales Medicines Strategy Group's (AWMSG) review are available from the following link: http://www.awmsg.org/awmsgonline/app/appraisalinfo/644

Canadian Agency for Drugs and Technologies in Health

Sativex for MS spasticity does not appear to have undergone a review by CADTH; however, in 2005 an Issues in Emerging Health Technologies bulletin was published (Appendix 3)

Scottish Medicines Consortium (SMC)

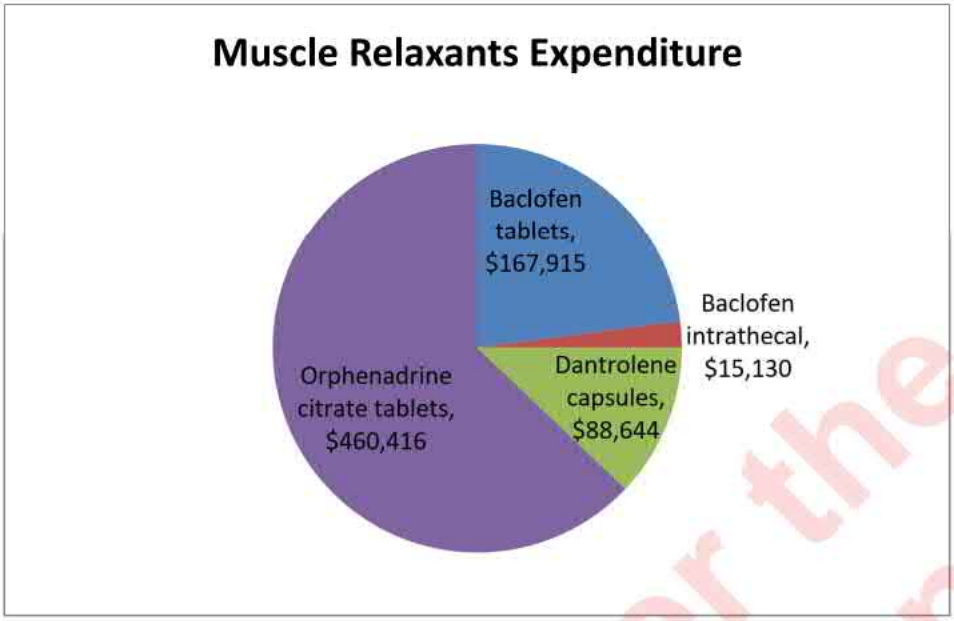
No submission has been assessed; therefore, Sativex is not recommended for use within NHS Scotland.

Cost of Current Treatments

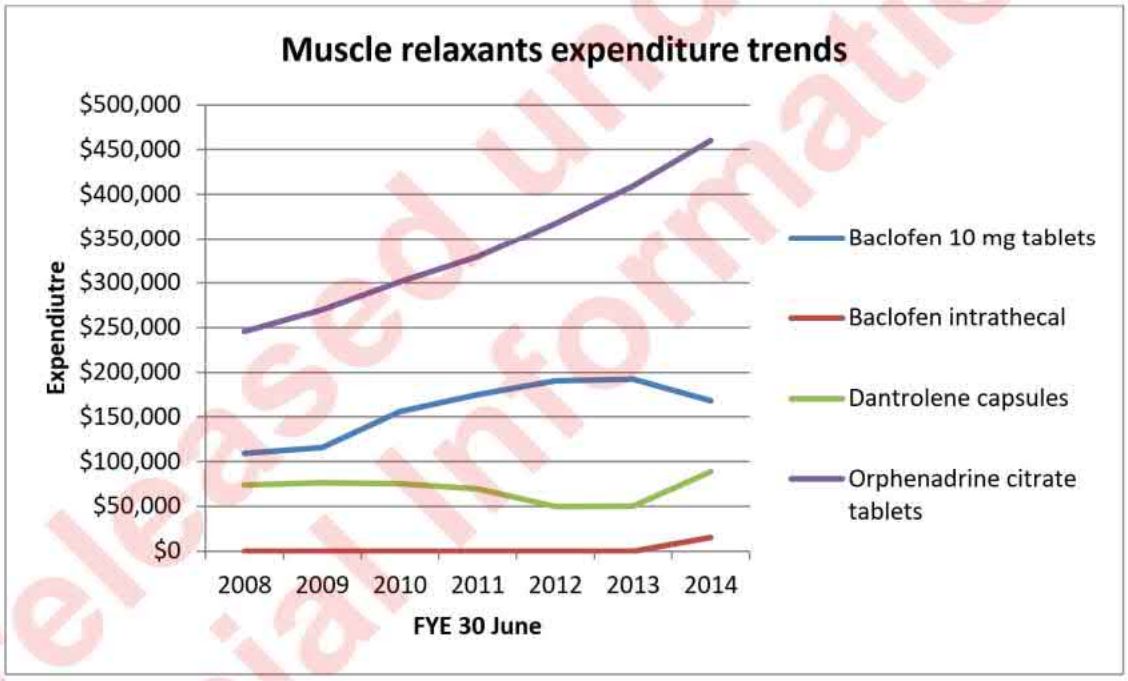
The cost of current oral treatments, based on the average daily dose in shown in the table below:

Treatment	Formulation	Average daily dose	Daily cost per patient	Annual cost per patient
Baclofen	tablet	20 mg tds	$ 0.2	$84
Baclofen	Intrathecal injection	550 mcg per day	$10.46	$3,820
Dantrolene	capsule	50 mg tds	$ 2.3	$843
Orphenadrine	tablet	100 mg bd	$ 0.4	$135
Diazepam	tablet	5 mg bd	$ 0.1	$20

Total annual expenditure for muscle relaxants for the FYE 30 June 2014 was ~$700,000. Current annual treatment costs for FYE 2014, for muscle relaxants, by treatment, were as follows:



The trends in expenditure on current treatment are shown in the following graph:



Estimated Incremental Cost of Listing

The cost of Sativex is $[redacted] per pack of 3 x 10 ml bottles, with each bottle administering 90 doses, so the cost of Sativex is $[redacted] per dose. If we assume that the average daily dose of Sativex is approximately 8 doses per day, as reported by Novotna et al (Euro J Neurol 2011;18:1112-1131), then the annual cost of Sativex per person would be ~ $[redacted].

If we assume that moderate to severe spasticity affects approximately 34% of patients with MS, as reported by Rizzo et al (Mult Scler 2004,10(5):589-95), with approximately only 38% of patients who respond to Sativex (Mult Scler 2010;16(6):707 714) and there are around 2500 patients with MS, then the first year of listing CPB expenditure could be ~$[redacted] million,

with a 5 year NPV of ~$[redacted] million, see table below. We have not included any cost offsets in this estimate as we seek PTAC's advice on what these could be

	Year 1	Year 2	Year 3
Patient numbers	323	355	391
Net cost to the schedule	$[redacted] million	$[redacted] million	$[redacted] million
Net cost to DHBs (NPV)	$[redacted] million		

Notes: NPV = Net Present Value

Cost-effectiveness

The supplier has not provided a cost-utility analysis for Sativex. PHARMAC staff have undertaken an initial review of a published cost effectiveness analysis reported by Lu et al (Pharmacoeconomics 2012;30(12):1157-1171). The authors of this study estimated a gain over 5 years of 0.15 QALYs at an incremental cost of £7,600. This resulted in an incremental cost-effectiveness ratio of £49,000 per QALY (approximately NZ$115,000 per QALY, ie 8.7 QALYs per $1 million net health sector spend). The model was mainly sensitive to dosage and price of Sativex, and utility gains from treatment. The population modelled was adults with moderate to severe spasticity due to MS who did not respond adequately to oral anti-spasticity medication (ie Sativex as add-on treatment in addition to oral anti-spasticity medication). The model did not include potential use of botulinum toxin injections or intrathecal baclofen as standard of care.

The model chosen by Lu et al. was a trial period of 4 weeks followed by ongoing treatment restricted to responders. The model assumed 57% of patients withdrew after a trial with 4% of the remaining patients withdrawing each month after a longer trial. PHARMAC staff note that although the model chosen seems reasonable it uses a 5 year time horizon, whereas PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA) outlines that a time horizon of modelling should extend far enough into the future to capture all the major clinical and economic outcomes. We seek PTAC's advice on the time horizon that should be used. PHARMAC staff note that our MS model, which is a life time model, is only targeted at relapse remitting MS, not secondary progressive MS or primary progressive MS.

If we were, rapidly, to use the PHARMAC MS model, and modelled a cohort of patients with an EDSS of 5, but assumed that the patients in the model had spasticity and that only those with an adequate response continued to receive treatment, the model produces a gain of 0.09 QALYs as the improvement in all health states. This modelling assumes that all other treatment options have been exhausted and no cost offsets exist. The results of this modelling estimate a gain of 1.64 QALYs over a patient's life time at a cost of $[redacted]. This gives a cost-effectiveness estimate of around [redacted] QALYs per million ($[redacted] per QALY). This appears to be [redacted] as cost-effective compared to that reported by Lu et al.

If PTAC recommended listing Sativex for spasticity due to MS, we would likely conduct a full CUA. To conduct this CUA, we seek PTAC's advice on the appropriate comparator for the analysis, the size of the health gains, the appropriateness of using a relapsing remitting multiple sclerosis model as a surrogate for all MS patients and the time horizon that should be modelled.

INDICATION 2: SATIVEX FOR PAIN, INCLUDING PAIN ASSOCIATED WITH SPASTICITY

QUESTIONS TO PTAC

1. What is the strength and quality of the evidence supplied in support of this indication?
2. Does Sativex have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule? If so, which pharmaceutical (or therapeutic sub-group) and at what dose does it have the same or similar effect?
3. With which pharmaceuticals would Sativex be used in combination, and which pharmaceuticals would it replace?
4. Are there currently any problems with access to and / or availability of alternative treatments?
5. Does Sativex provide any additional health benefit or create any additional risks compared with other treatment options? If so, what benefits or risks are different from alternative treatments?
    a. What is the appropriate comparator for assessing cost-effectiveness?
    b. What are the size of the health gains, Sativex would provide for patients with pain, including pain associated with spasticity?
6. Which patient population would benefit most from Sativex?
    a. Can PTAC provide an estimation of patient numbers for this population?
7. Is there any unmet health need in this population, or within a subset of this population (e.g. Maori / Pacific people)?
8. Would the use of Sativex create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?
9. What effects would the listing of Sativex in the Pharmaceutical Schedule have on the current market dynamics for the alternative treatments?
10. Should Sativex be listed in the Pharmaceutical Schedule?
    - Name the decision criteria particularly relevant to a positive or negative recommendation and explain why each is relevant.
11. If listing is recommended, what priority rating would you give to this proposal? [low / medium / high / only if cost-neutral]?
12. Should any restrictions be placed on the use of Sativex? If so, for what reason should these restrictions be applied?
13. Does the Committee have any additional recommendations in relation to this indication?

DISCUSSION

Disease Targeted

Pain can be classified by its pathophysiology into two major types: nociceptive and neuropathic, and can be classified as acute or chronic Nociceptive pain involves the normal neural processing of pain that occurs when free nerve endings are active by tissue damage or inflammation. Neuropathic pain involves the abnormal processing of stimuli from the peripheral or central nervous system.

Pain is common in advanced and progressive disease. Pain is estimated to be the most prevalent symptom preceding all deaths occurring in a palliative care setting in NZ.[1] Strong opioids, particularly morphine, are an effective treatment for moderate to severe pain, and as many as two-third of adults with terminal cancer will require treatment with a strong opioid.[2] A similar need for opioids is also observed in patients with other advanced and progressive illnesses, eg heart failure, kidney and liver disease and neurodegenerative conditions.

Nociceptive pain is often due to musculoskeletal conditions, inflammation, or mechanical/compressive problems.

Neuropathic pain has a number of different aetiologies. Diseases such as diabetes, infections with herpes zoster or HIV, medical interventions (e.g. chemotherapy, surgery) and injury can all damage the central or peripheral nervous system.

Neuropathic pain is often difficult to treat, because it is resistant to many medications and because of the adverse effects associated with effective medications. A number of classes of pharmaceuticals are used to manage neuropathic pain, including antidepressants, anti-epileptic (anticonvulsant) drugs, opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and topical treatments such as capsaicin cream. Many people require treatment with more than one medicine, but the correct choice of medicines, and the optimal sequence for their use, is patient specific.

A number of non-pharmacological treatments are often used as an adjunct to the management of chronic pain. These include: cognitive behavioural therapy, acupuncture, nerve stimulation techniques, massage and exercise therapy. Access to, and cost of, these treatments in NZ varies throughout the country and can be a significant barrier to treatment.

Current Treatments

Neuropathic pain

As described above a number of classes of pharmaceuticals are used to manage neuropathic pain:

- Antidepressants: These include tricyclic antidepressants (TCA), serotonin noradrenaline reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI); and all possess analgesic qualities. TCA's are associated with anticholinergic side effects such as constipation, urinary retention and dry mouth which can limit tolerability for some patients. The following relevant antidepressants are funded:
    - TCAs: amitriptyline, nortriptyline, clomipramine.

[1] Palliative Care Council of New Zealand National health needs assessment for palliative care. Phase 1 report: Assessment of palliative care need. Caner Control New Zealand: Wellington; 2011.
[2] National Institute for Health and Clinical Excellence (NICE). Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults: NICE clinical guideline 140, NICE: Manchester; 2012. Available from: www.nice.org.uk

- SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, sertraline.
- SNRIs: venlafaxine

- Gabapentin is funded via Special Authority for patients with neuropathic pain. Sleepiness can be a limiting side effect.

- Antiepileptics: carbamazepine, sodium valproate, lamotrigine, topiramate and phenytoin are funded without restrictions and can be used in the management of neuropathic pain.

Nociceptive pain

Treatment for nociceptive pain is generally based on a stepwise approach; nonopioid analgesics first followed by the used of opioids.

- Nonopioid analgesics that are funded include the following: paracetamol, aspirin, nefopam and nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac, ibuprofen, naproxen, ketoprofen, sulindac and tenoxicam). The main adverse effects of NSAIDs are inhibition of platelets, (with potential promotion of bleeding), gastrointestinal insult, renal insult and adverse cardiovascular effects and therefore may not be suitable for some patient groups.

- Opioid analgesics that are funded include the following: codeine, dihydrocodeine, tramadol, fentanyl, methadone, morphine, oxycodone and pethidine. Common adverse effects associated with opioids include nausea and vomiting, constipation and sedation.

Pain associated with spasticity

A wide variety of pain conditions, both acute and chronic, may be accompanied by painful muscle spasm. Commonly used muscle relaxants are described earlier in this paper.

NPPA applications

We have received six NPPA applications for Sativex for the treatment of pain, including pain associated with spasticity, since July 2013. Five were withdrawn as the pre-requisites of the NPPA Policy were not met. One application was declined.

Only one patient's doctors had obtained approval to prescribe Sativex from the MoH under Regulation 22 of the Misuse of Drugs Regulation 1977 prior to applying to PHARMAC. Most applications were seeking funding for a dose of up to a maximum of 12 sprays per day according to therapeutic response. A summary of the NPPA applications received for pain, including pain with spasticity, is detailed in the table below. A detailed description of the application that was declined is provided following the table.

Indication	Alternative treatments trialled	Outcome
Intractable pain or spasm +/- tetraplegia	diclofenac, codeine, paracetamol, clonazapam, amitriptyline, pregabalin, gabapentin, baclofen, dantrolene.	Withdrawn
Pain	gabapentin, nortriptyline, metoprolol, diclofenac, ibuprofen, carbamazepine, baclofen, paracetamol, citalopram, tramadol, omeprazole, nadolol, topiramate, codeine, indomethacin, carbamazepine,	Withdrawn

	beclomethasone, sodium valproate	
Acute pain resulting in hospital admission	tramadol/fentanyl, morphine/oxycodone, methadone, ketamine, nitrous oxide, paracetamol, NSAIDs, and TENS	Withdrawn
*Terminal disease reaching end of life (defined as 12 months or less) with severe spasticity and pain, Withheld under section 9(2) Withheld under section 9(2)(a) Withheld under section . Details of this application are provided below.	plasmapheresis, IV Ig, methylprednisone, diazepam, clonazepam, baclofen, gabapentin, morphine, rituximab	Declined
Pain	nortriptyline and venlafaxine	Withdrawn
Severe spasticity and pain	morphine, methadone, fentanyl, gabapentin, baclofen, amitriptyline, dexamethasone, NSAIDs, radiotherapy, epidural block, clonidine, ongoing chemotherapy (cisplatin and etoposide)	Withdrawn

**Patient with terminal disease with severe spasticity and pain* Withheld under section 9(2)

This application was first submitted in Withheld under by a palliative care physician for a patient with muscle spasms and pain resulting from Withheld under section 9(2)(a) Withheld under section 9(2)(a). The original application detailed a large number of funded alternative treatments that had been trialled; plasmapheresis, IVIG, methylprednisone, diazepam, clonazepam, baclofen, gabapentin, morphine, and currently on rituximab therapy. The applicant considered in their application that all funded alternatives to be too sedating, ineffective or inappropriate due to the patient's advanced disease. This application was not progressed as clinical advice indicated that intrathecal baclofen, either alone or in combination with dantrolene, remained the funded alternative treatment available to the patient.

However, In Withheld under reconsideration was requested for this patient as their disease had progressed Withheld under section 9(2)(a) Withheld. The application was progressed for a decision under PHARMAC's nine decision criteria (DC) and ultimately declined by PHARMAC due to the lack of evidence for the use of Sativex in this setting (DC4), and as clinical advice indicated that there was a potentially large group of patients with terminal disease who are reaching the end of their lives (defined as 12 months or less) who have severe spasticity and pain (DC6). When considering NPPA applications for individual patients PHARMAC also considers the size of the potential patient population, because we recognise that patients with similar clinical circumstances expect the same outcome from the NPPA application process.

Cost of Current Treatments

There are a large number of nonopioid and opioid analgesics, in various formulations, funded on the Pharmaceutical Schedule Below are examples of the costs associated with some of these.

Treatment	Formulation	Average daily dose	Daily cost per patient	Annual cost per patient
Amitriptyline	Tablet	75mg	$0.02	$6.13
Citalopram	Tablet	20mg	$0.03	$10.17
Venlafaxine	Tablet	150mg	$0.32	$115.50
Gabapentin	Capsule	3600mg	$1.24	$451.69
Paracetamol	Tablet	1000mg	$0.07	$24.73
Diclofenac	Tablet	150 mg	$0.10	$35.80
Tramadol	Capsule	400mg	$0.20	$73.00
Morphine	Tablet	80mg	$2.21	$805.92
Oxycodone	Tablet	40mg	$1.12	$407.34
Fentanyl	Patch	75mg	$1.84	$670.14

Key Evidence

The supplier has provided six RCTs in support of Sativex for pain with or without spasticity, and one long term open label trial. Appendix 4. A literature search was conducted on 3 July 2015 via Pubmed. Search terms included pain AND tetrahydrocannabidiol-cannabidiol. Full details of the search and results are attached in Appendix 4. Full articles can be ordered and provided on request from the PTAC secretary. Articles PHARMAC staff consider to be the most relevant have been summarised below, and the full articles are attached in Appendix 4.

Portenoy et al (J pain 2012;13(5):438-439) conducted a randomised placebo-controlled graded dose trial to investigate the efficacy of nabiximols (Sativex), in opioid-treated cancer patients with poorly-controlled chronic pain.

- 360 patients with advanced cancer and opioid-refractory pain were randomised to receive placebo or Sativex at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day) for a duration of 5 weeks. Participants were asked to continue their scheduled opioid dose without change during the study and were allowed to use their breakthrough opioid analgesic as required.

- Participants received a daily call from an interactive voice recording system (IVRS), at which time they were asked to grade their average pain during the past day using a 0-10 numeric rating scale (NRS). The same scale was also used to measure sleep disruption. Additional questionnaires were used to measure quality of life and mood. The primary efficacy endpoint was pain response status, with a positive response defined as a 30% or greater reduction in the mean 11-point NRS pain score for average pain during the last 3 days of week 5 compared with the mean during the 3-day baseline period.

- The authors reported that there were no baseline differences across the groups. The 30% responder rate primary endpoint was not significant for Sativex versus placebo (p=0.59). An improvement in sleep disturbance was reported for the low dose group with a treatment difference of 0.88 points in favour of Sativex (p=0.003 95% CI: 1.45, 0.31 points). In the medium dose group there was a non-significant treatment difference of 0 33 points in favour of Sativex (P = 0 260 95% CI: 0 90, 0 24), and there were no differences between the high-dose group and placebo. Neither the use of regularly scheduled opioids nor the number of opioid doses taken as needed for

breakthrough-pain varied significantly between treatment groups. The authors reported that there was a dose-related incidence of adverse events, with the high dose group comparing unfavourably with placebo and the two lower dose groups showing little difference from placebo.

Selvarajah et al (Diabetes Care 2010;33(1):128 130) conducted a randomised placebo controlled double blind trial to investigate the efficacy of Sativex, as an adjunctive treatment in painful diabetic peripheral neuropathy.

- 30 patients with chronic painful diabetic peripheral neuropathy were randomised to receive either Sativex or placebo administered sublingually in divided doses up to four times a day. Three modalities of pain (superficial, deep, and muscular pain) were assessed daily using a 100-mm visual analogy scale (VAS). Depression was assessed using the seven-term depression subscale of the Hospital Anxiety and Depression Scale (HADS-D). Patients were permitted to continue their neuropathic pain treatment during the study. Improvement in pain, as assessed by the pain diary and Neuropathic Pain scale (NPS) questionnaire, was used as the primary outcome measure. Secondary outcome measures were quality of life (QOL) assessed by McGill Pain and QOL, SF-36 Health Survey and EuroQOL Questionnaires.

- The authors reported there was significant improvement in pain scores in both groups, but mean change between groups was not significant. There were no significant differences in secondary outcome measures. The authors also reported that patients with depression had significantly greater baseline pain scores that improved regardless of intervention.

Langford et al (J Neurol 2013;260:984-997) conducted a double-blind, randomised, placebo-controlled, parallel-group trial of Sativex in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with MS.

- Patients who had failed to gain adequate analgesia from existing medication were treated with Sativex or placebo as an add-on treatment, in a double blind manner for 14 weeks to investigate the efficacy of Sativex in MS-induced neuropathic pain. This parallel-group phase of the study was then followed by an 18 week randomised withdrawal study (14-week open-label treatment period plus a double-blind 4-week randomised-withdrawal phase) to investigate time to treatment failure and maintenance of efficacy.

- 339 patients were randomised to phase A (167 received Sativex and 172 received placebo). Of those who completed phase A, 58 entered the randomised-withdrawal phase. The primary endpoint of responder analysis at the 30% level at week 14 of phase A of the study was not met, with 50% of patients on Sativex classed as responders at the 30% level compared to 45% of patients on placebo (p =0.234).

Johnson et al (J Pain Symptom Manage 2010;39(2):167-179) conducted a multicentre, double-blind, randomised, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain.

- 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week trial and were randomised to receive either THC:CBD extract (n=60), THC extract (n=58), or placebo (n=59).

- The primary endpoint measure was the change from baseline in mean pain Numerical Rating Scale (NRS) score. The authors reported the adjusted mean

reduction in NRS for the THC:CBD, THC and placebo groups at the end of the treatment were 1 37, 1 01, and 0 69 points respectively The adjusted mean treatment difference from placebo was statistically significant for a reduction in pain with the THC:CBD extract (0.67 points, p=0.014) but not the THC extract (0.32 points, p=0.245). No change from baseline was reported for the median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups No significant group differences were reported for the NRS sleep quality or nausea scores or the pain control assessment.

Berman et al (Pain 2004; 112:299-306) conducted a randomised, double-blind, placebo controlled crossover trial to investigate the efficacy of two cannabis based extracts for relief of central neuropathic pain from brachial plexus avulsion.

- 48 patients with at least one avulsed root, a baseline pain score of 4 or more on an 11-point ordinate scale with intractable symptoms regardless of current analgesic therapy entered a baseline period of 2 weeks, followed by three, 2 week treatment periods during each of which they received one of three oromucosal spray preparations. The three preparations were placebo, Sativex and THC. The primary outcome measure was the mean pain severity score during the last 7 days of treatment. An eleven point Box Scale (BS-11) was used as the primary measure of efficacy. Based on previously published work the authors assumed a priori that a difference of at least two points in the BS-11 pain score between the active and placbo phases would represent a clinically significant change. Secondary outcome measures included pain related quality of life assessments. The primary outcome measure was not met. The authors reported that the difference in the mean diary BS-11 pain score between both study medications and placebo was statistically significant but did not reach the *a priori* assumed level for clinical significance of two points; Sativex compared with placebo equalled a reduction of 0.58 points (p=0.005, 95% CI: -0.98, -0.18 points) and THC compared with placebo gave a reduction of 0.64 points (p=0.002, 95% CI: -1.03, -0.24).

Whiting et al (JAMA 2015; 313(24):2456-73) conducted a systematic review and meta-analysis of the benefits and adverse events of cannabinoids. All of the five RCTs described above were included in this review.

- Randomised clinical trials of cannabinoids for the following indications were included: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDs, chronic pain, spasticity due to MS or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma or Tourette syndrome.

- A total of 79 trials involving 6462 participants were included. The authors reported that most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with greater average number of patients showing complete nausea and vomiting response (47% vs 20%; OR, 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR,1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10 point scale; weighted mean difference, -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.36 [95% CI, -0.69 to -0.05]; 7 trials).

- The authors reported that common adverse events included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance and hallucination

International Recommendations

Canadian Agency for Drugs and Technology in Health

The Canadian Agency for Drugs and Technology in Health issued the recommendation 'do not list' in September 2007, in response to a reconsideration of Sativex as an adjunctive treatment for the symptomatic relief of neuropathic pain in MS. Details of the reasons for the recommendations are available from the following link https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Sativex_September-26-2007.pdf and are attached in Appendix 4.

No other international recommendations were located after a search of the following websites:

- National Institute for Health and Care Excellence (UK): http://www.nice.org.uk/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/
- The Pharmaceutical Benefits Advisory Committee (Australia): http://www.pbac.pbs.gov.au/home.html

Estimated Incremental Cost of Listing

We have not completed a budget impact analysis for funding Sativex for pain and pain associated spasticity given the potential wide indications; we seek PTAC's advice on the potential patient numbers.

If Sativex was funded for patients with terminal disease who are reaching the end of their lives (defined as 12 months or less) who have severe spasticity and pain, the budget impact for this group alone is estimated to be between $Withheld and $Withheld 5 year NPV (8%). We estimate this group to be around 10 patients per year. However, we consider this group may be extremely difficult to differentiate from other patients with similar clinical circumstances (who are not end of life) and other patient groups with similar health need. Therefore, the actual group size and the budget impact if Sativex was funded may be much greater.

Cost-effectiveness

No cost-utility analysis (CUA) has been completed for Sativex as a treatment for pain with or without spasticity. If PTAC recommends listing Sativex for this indication we would likely conduct a CUA on the patient group it recommends. To conduct this CUA, in addition to information mentioned above, we seek PTAC's advice on the appropriate comparator for this analysis. We also seek PTAC's advice on the size of the health gains Sativex would provide for patients with pain and spasticity.

INDICATION 3: SATIVEX FOR TREATMENT REFRACTORY EPILEPSY

QUESTIONS TO PTAC

1. What is the strength and quality of the evidence supplied in support of this indication?
2. Does Sativex have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule? If so, which pharmaceutical (or therapeutic sub-group) and at what dose does it have the same or similar effect?
    a. What would be the appropriate comparator
3. With which pharmaceuticals would Sativex be used in combination, and which pharmaceuticals would it replace?
4. Are there currently any problems with access to and / or availability of alternative treatments?
5. Does Sativex provide any additional health benefit or create any additional risks compared with other treatment options? If so, what benefits or risks are different from alternative treatments?
    a. Specifically what is the appropriate comparator for assessing cost-effectiveness?
    b. What reduction in seizure frequency would be associated with treatment with Sativex?
    c. Are there any other health gains that Sativex would provide for patient with epilepsy?
    d. What proportion of patients would not respond to Sativex due to a lack of efficacy or intolerability and therefore cease treatment?
    e. Are there any cost offsets associated with reduced medical management costs from reduced seizure activity due to the use of Sativex?
6. Which patient population would benefit most from Sativex?
7. Is there any unmet health need in this population, or within a subset of this population (e.g. Maori / Pacific people)?
8. Would the use of Sativex create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?
9. What effects would the listing of Sativex in the Pharmaceutical Schedule have on the current market dynamics for the alternative treatments?
10. Should Sativex be listed in the Pharmaceutical Schedule?
    - Name the decision criteria particularly relevant to a positive or negative recommendation and explain why each is relevant.
11. Should any restrictions be placed on the use of Sativex? If so, for what reason should these restrictions be applied?
12. If listing is recommended, what priority rating would you give to this proposal? [low / medium / high / only if cost-neutral]?
13. Does the Committee have any additional recommendations in relation to this indication?

DISCUSSION

Disease Targeted

Epilepsy is a group of neurological disorders characterised by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking. In epilepsy, seizures tend to recur, and have no immediate underlying cause while seizures that occur due to a specific cause are not deemed to represent epilepsy.

There are currently a number of antiepileptic drugs (AEDs) fully funded in New Zealand; described in the next section. Patients whose seizures do not successfully respond to AED therapy are considered to have treatment-refractory epilepsy. As many as 20% to 40% of patients with epilepsy are estimated to have treatment-refractory epilepsy, and these patients also have the greatest burden of epilepsy-related disabilities.[3]

Traditionally therapeutic failure of three AEDs has defined intractability, as with each AED failure the likelihood of successful treatment with other drugs diminishes. Also included in this patient group are those with a high burden of adverse effects with AED's, ie. if seizures can be controlled but only at medication doses that produce severe side effects, then it may be reasonable to consider that patient is actually treatment-refractory.

Patients with treatment-refractory epilepsy have an increased mortality rate, compared with individuals who become seizure free, who have no increased mortality. Some deaths are related to the underlying cause of epilepsy (e.g. cerebral neoplasm, neurodegenerative disease); other deaths are directly seizure-related, such as those that occur in the context of status epilepticus and in seizure-related accidents. Sudden unexplained death in epilepsy patients (SUDEP) is 40 times more likely among patients who continue to have seizures than in those who are seizure free. Treatment-refractory epilepsy is also associated with disability and diminished quality of life.

Current Treatments

There are several funded treatments for the control of epilepsy: older agents (carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbitone, phenytoin sodium, primidone and sodium valproate) and newer agents (gabapentin, lamotrigine levetiracetam, topiramate, stiripentol, lacosamide and vigabatrin).

Total annual net expenditure on these treatments is approximately $29 million; however, it is difficult to estimate the total epilepsy expenditure because many of the agents are used for multiple indications other than epilepsy (eg, neuropathic pain, mood disorders and migraine prophylaxis) and funded access to all but stiripentol, lacosamide and vigabatrin and is unrestricted.

Non-pharmacological treatments

Non-pharmacological treatments may include epilepsy surgery and the ketogenic diet.

PTAC advice

PTAC had not previously considered Sativex for the indication of epilepsy. PHARMAC staff note that in 2010 the Committee considered a funding application for lacosamide for the

[3] Evaluation and management of drug-resistant epilepsy on UpToDate website: http://www.uptodate.com/contents/evaluation-and-management-of-drug-resistant-epilepsy?source=search_result&search=refractory+epilepsy&selectedTitle=1%7E72

treatment of epilepsy in patients with inadequate control with current treatments. At that time the Committee considered that there was a reasonably large range of funded anti epilepsy treatments and that there were generally few problems with access to these treatments; however, the Committee noted that there would always be a small proportion of patients who continue to have seizures despite having tried all suitable funded options. The Committee noted that the evidence suggests that there may be a higher prevalence of epilepsy among Māori compared with the overall population. (Minutes attached in Appendix 5)

NPPA applications

We have received three NPPA applications for Sativex for the treatment of epilepsy since July 2013. One application was declined, one was not progressed as suitable funded treatments remained, and one was withdrawn as NPPA funding for zonisamide was approved instead.

The first application was received from a paediatric neurologist in July 2014 for an Withheld Wit child with refractory epilepsy, Dravet syndrome[4] (severe myoclonic epilepsy of infancy (SMEI)), and global developmental delay. The application was for a dose of one spray mane, two nocte and provided detail of previous treatment with stiripentol, clobazam, carbamazepine, lamotrigine, and levetiracetam. The application was withdrawn as it was considered that not all other treatment avenues had been trialled. Other funded anti-epileptic drugs appropriate in the treatment of Dravet syndrome were noted, such as sodium valproate, and topiramate, The NPPA panel noted that zonisamide, potassium bromide and rufinamide appeared not to have been explored, although these were also unfunded. It was noted there appeared not to be evidence that Sativex or other cannabinoids would be efficacious in the treatment of Dravet syndrome, epilepsy, or seizures.

The second application was submitted by a neurologist in September 2014 for a Withheld under patient with a progressive severe epilepsy syndrome with features of progressive myoclonic epilepsy. The dose regimen was not clearly stated but application was for a volume of 3 bottles per month as needed. The application provided details of previous treatment with lacosamide, zonisamide, sodium valproate, lamotrigine, clobazam, acetazolamide, topiramate, ethosuximide, phenytoin, levetiracetam, clonezepam, carbamazepine, phenobarbitone, gabapentin, and rufinamide. Although this patient had trialled a large number of funded and unfunded alternative treatments without success, this application was declined by PHARMAC due to the lack of evidence for the use of Sativex in patients with treatment-refractory epilepsy, and clinical advice indicating that the potential patient group (those with intractable epilepsy) could be large. When considering NPPA applications for individual patients we also consider the size of the potential eligible patient population because we recognise that patients with similar clinical circumstances can rightly expect the same outcome from a NPPA application process.

A third application for a patient with intractable epilepsy, myoclonic seizures, tonic clonic seizures, behaviour disorder, and intellectual disability was received in June 2015. The application was submitted by a general practitioner with support from a neurologist. Approval to prescribe Sativex had been granted from the MoH under Regulation 22 of the Misuse of Drugs Regulation 1977 prior to application to PHARMAC. The dose of Sativex requested was not clearly stated. Previous treatments tried by this patient include sodium valproate, clobazapam, carbamazepine, phenytoin, midazolam, diazepam, lamotrigine and topiramate. The applicant stated that previous treatment had largely been ineffective but their current treatment regimen of phenobarbitone, ethosuximide, lacosamide and levetiracetam had achieved partial control of grand mal seizures. The neurologist applicant indicated that zonisamide would be considered an appropriate treatment option for this patient and

[4] http://www dravetfoundation org/dravet-syndrome/what-is dravet-syndrome

therefore the application for Sativex was withdrawn and NPPA funding for zonisamide was approved instead

Another application for a patient with epilepsy was received but as the application was primarily for pain; this has application been detailed in the previous section.

Cost of Current Treatments

Annual cost of treatment with newer antiepileptics based on recommended adult maintenance dosing for add-on therapy from the Medsafe datasheet and UpToDate, is detailed in the following table:

Pharmaceutical	Average daily dose	Annual gross cost per patient
Lamotrigine	300 mg per day	$113
Gabapentin	1,200 mg per day	$161
Topiramate	300 mg per day	$584
Vigabatrin	2 g per day	$1,742
Levetiracetam	2,000 mg per day	$699
Lacosamide	300 mg per day	$3,915*
Stiripentol	250 mg per day	$3,098

*Rebate exists, based on patient numbers.

Figure should read $1,113

Total annual net expenditure for epilepsy agents for the FYE June 2014 was $[redacted] million. Current annual treatment costs for FYE 2014, for epilepsy agent, by treatment, were as follows:

Key Evidence

A literature search was conducted on 3 July 2015 via Pubmed Search terms included pain AND [tetrahydrocannabidiol-cannabidiol OR cannabidiol] Full details of the search and results are attached in Appendix 6. Full articles can be ordered and provided on request from the PTAC secretary. Articles PHARMAC consider to be the most relevant have been summarised below, and the full articles are attached in Appendix 6

In addition, a search of the clinicaltrials.gov website was undertaken and did not identify any trials for Sativex and epilepsy, although it appears that there are several trials that are either recruiting or are planned to investigate cannabidiol oral solution for epilepsy.

A Cochrane review by Vickrey and Gloss (Cannabinoids for epilepsy. The Cochrane Library 2014, Issue 3) assessed the efficacy and safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy.

- The authors independently selected trials, whether blinded or not, for inclusion and extracted the data, The primary outcome investigated was seizure freedom at one year or more, or three times the longest interseizure interval. Secondary outcomes included responder rate at six months or more, objective quality of life data, and adverse events. The authors identified reports for four randomised trial that included a total of 48 patients, each of which used cannabidiol as the treatment agent and antiepileptic drugs were continued in all studies. One report was an abstract and another was journal correspondence published as a letter.

- The authors reported that details of randomisation were not included in any study report, there no investigations of whether the control and treatment participant groups were the same or different, and all reports were low quality. The authors stated that the four reports only reported the secondary outcome of adverse effects, with none of the patients in the treatment groups suffering any reported adverse effects. The authors concluded no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. They also considered that as the dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients generally for short periods of time, the safety of long term cannabidiol treatment cannot be reliably assessed.

As part of assessing one of the above NPPA applications, PHARMAC staff sought clinical advice from a neurologist member of the Neurological Subcommittee. This is provided in Appendix 7. In summary, it says:

- There were a few AED's with reported efficacy in Dravet syndrome (the type of intractable epilepsy detailed in the NPPA application) that appeared to not have been explored for use in the particular patient, and in addition a ketogenic diet should be attempted.
- The strength and quality of evidence to support the use of Sativex for treatment of epilepsy and seizures is poor.
- There is no evidence either way that Sativex helps in the treatment of epilepsy or seizures. Appropriate clinical trials are needed.
- Sativex cannot currently be recommended as a therapeutic option for any type of epilepsy.
- If Sativex was approved for refractory, treatment resistant epilepsy, there may be 1200-2000 such people in NZ, or at least there may be that many people whose doctors might think they were suitable candidates for such therapy.

- If Sativex was to be used for refractory treatment resistant epilepsy as a "last resort" there might be 1000 people on treatment at any time, with growth of approximately 60 people per year.

International recommendations

No international recommendations for Sativex and epilepsy or cannabinioids and epilepsy appear to have been published. The following websites were searched:

- National Institute for Health and Care Excellence (UK): http://www.nice.org.uk/
- Canadian Agency for Drugs and Technology in Health: http://www.cadth.ca/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/
- The Pharmaceutical Benefits Advisory Committee (Australia): http://www.pbac.pbs.gov.au/home.html

Estimated Incremental Cost of Listing

The NPPA panel has previously advised that, should Sativex be funded in NZ, there is potentially a large number of patients in New Zealand (excess of 1000) who would potentially seek access to this treatment, which would result in a potentially large budget impact. If there were 1000 patients who accessed treatment the cost in the first year of listing could be around $Wit million with a 5year NPV of approximately $Wit million.

We consider that it would be unlikely that there would be 1000 patients with refractory epilepsy who have tried all other funded treatments, although there is a significant amount of uncertainty. We seek PTAC's advice; to assist in estimating the cost, on the following:

- Should Sativex be funded for epilepsy, where would it be in an epilepsy treatment algorithm and what would be the patient numbers for this group?
- What reductions in seizure frequency would be likely if Sativex was funded?
- What proportion of patients would not respond to Sativex and therefore cease treatment?

If we assume that Sativex is funded as a last line treatment and used at a dose of around 12 sprays per day, the cost per patient per day would be approximately $Wit and the cost per year would be approximately $Withheld per patient.

If we assume that the group is limited to those patients who have tried all funded alternatives, we estimate there could be around 20 new patients per year, with around 10 continuing treatment. It is also likely that there is already a pool of patients who have tried all funded alternatives and therefore there could be an additional a number of patients who would try this option in the first couple of years of listing. There does not appear to be any supporting evidence to inform us of the number of patients who would have success with Sativex for the treatment of epilepsy, so we have assumed that approximately 50% of patients who try Sativex for epilepsy would cease treatment after a 3 month trial due to lack of efficacy or intolerability. We seek PTAC's advice on these assumptions. Based on these assumptions we have estimated the following gross costs to the Combined Pharmaceutical Budget:

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients numbers (new)	100	70	40	20	20
Patient numbers (chronic usage)	50	85	105	115	125
Gross cost to the schedule	$[redacted]m	$[redacted]m	$[redacted]m	$[redacted]m	$[redacted]m
Gross cost to DHBs (NPV)	$[redacted]m				

Notes: NPV = Net Present Value

These estimates do not include any offsets associated with reduced medical management costs from reduced seizure frequency, as we seek PTAC's advice on the efficacy of Sativex.

Cost effectiveness

No cost-utility analysis (CUA) has been completed for Sativex as a treatment for epilepsy. If PTAC recommends listing Sativex we will likely conduct a CUA on the patient group it recommends. To conduct this CUA, in addition to information mentioned above, we seek PTAC's advice on the appropriate comparator for this analysis. We also seek PTAC's advice on the size of the health gains Sativex would provide for patients with epilepsy.

Appendices

Appendix 1: Sativex information provided by Novartis

Appendix 2: Sativex Medsafe Datasheet

Appendix 3: References (Spasticity due to MS); alphabetically ordered by name of author.

Appendix 4: References (Pain); alphabetically ordered by name of author.

Appendix 5: Relevant PTAC minutes regarding lacosamide.

Appendix 6: References (Epilepsy); alphabetically ordered by name of author.

Appendix 7: Clinical Advice received from Neurologist.

DECISION CRITERIA

1. The health needs of all eligible people within New Zealand;
2 The particular health needs of Maori and Pacific peoples;
3 The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;
4. The clinical benefits and risks of pharmaceuticals;
5. The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;
6. The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;
7. The direct cost to health service users;
8. The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
9. Such other criteria as PHARMAC thinks fit.

INFORMATION FOR

PHARMAC
PHARMACEUTICAL MANAGEMENT AGENCY

Sativex® Oromucosal Spray
(Cannabidiol / Tetrahydrocannabinol)

Novartis New Zealand Limited
Address: Private Bag 65904
Mairangi Bay, Auckland 0754

Contact: Withheld under section 9(2)(a)
Phone: (09) 523 8500
Fax: (09) 361 8181

May 2015

Table of Contents

Summary

This document provides current pricing and background clinical information about SATIVEX for PHARMAC

Current Ex-Manufacturer Price

The current selling price (exclusive of GST) for SATIVEX:

Dosage Form/Strength	Pack Size	Selling Price
Glass vial w. metered pump	3 x10mL	$Withheld

Overview of Publications

The table below provides a brief overview of the publications provided for Sativex.

Further summaries are provided below, with copies of the references provided with this submission (Note: Also included on a data CD).

Table. Summary of key publications of Sativex

Reference	Study objective, population	Randomised patients	Duration	Treatment groups/ dosage	Primary efficacy variable
• **Reviews**					
Syed 2014	Review MS Spasticity	-	-	Sativex Placebo (or open label)	-
Wade 2010	Meta-analysis MS Spasticity	666	6-14 weeks	Sativex Placebo	Spasticity
Garriga 2011	Expert Review MS Spasticity	-	-	Sativex Placebo (or open label)	Various
• **Controlled Trials (placebo-controlled) in MS Spasticity:**					
Collin 2010	MS Spasticity	337	15 week	Sativex Placebo	Spasticity rating scale
Novotna 2011	MS Spasticity	572	19 week	Sativex Placebo	Spasticity rating scale
Notcutt 2012	MS Spasticity	36	5 week	Sativex Placebo	Time to treatment failure
• **Long Term Open Label Trials in MS Spasticity:**					
Serpell 2013	Evaluate long term safety tolerability	146	334 days	Sativex	Safety / Tolerability
Flachenecher 2014	Long term clinical outcomes, tolerability, QOL	52	12 months	Sativex	Clinical outcomes, tolerability, QOL
• **Controlled Trials (placebo-controlled) in Other Indications:**					
Lynch 2014	Chemotherapy Induced Neuropathic Pain	18	6 months	Sativex Placebo	Pain scores
Langford 2013	Neuropathic Pain in MS	339	18 week	Sativex Placebo	Pain scores
Portenoy 2012	Poorly controlled Cancer related pain	360	5 weeks	Sativex Placebo	Pain scores
Selvarajah 2010	Painful Diabetic Neuropathy	30	10 weeks	Sativex Placebo	Pain scores
Johnson 2010	Intractable Cancer –related Pain	177	2 week	Sativex Placebo	Pain scores
Berman 2004	Neuropathic Pain- brachial plexus avulsion	48	8 weeks	Sativex Placebo	Pain scores
• **Cost Effectiveness/QOL:**					
Lu 2012	Cost effectiveness in MS Spasticity	-	-	UK payer perspective	ICER QALY
Slof 2012	Cost effectiveness in MS Spasticity	-	-	German and Spanish payer perspective	ICER QALY
Iskedjian 2009	Willingness to Pay Pain in MS	-	-	Canadian payer perspective	WTP
Arroyo 2014	QOL	-	-	European perspective	QOL

Brief Summaries of the Publications

1. Reviews:

Syed et al Drugs 2014

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Wade et al Multiple Sclerosis 2010.

Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Withheld under section 18(d)

Sastre-Gariga et al 2011.

Withheld under section 18(d)

2. Controlled Trials (placebo-controlled) in MS Spasticity:

Collin et al Neurol Res 2010

Withheld under section 18(d)

Novotna et al Eur J Neurol 2011

Withheld under section 18(d)

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Notcutt et al Multiple Sclerosis J 2012

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

3. Long Term Open Label Trials in MS Spasticity:

Serpell et al J Neurol 2013

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Flachenecker et al Eur Neurol 2014

Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

4. Controlled Trials (placebo-controlled) in Other Indications:

Lynch et al J Pain 2014

Withheld under section 18(d)

Langford et al 2013

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Selvarajah et al Diabetes Care 2010

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Johnson et al Cancer Pain 2010

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Berman et al 2004

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

5. Cost Effectiveness/QOL:

Lu et al Pharmacoeconomics 2012

Withhel
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Slof et al Expert Reviews Pharmacoecon Res 2012.

Withhel
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)

Iskedjian et al Pharmacoeconomics 2011.

Withhel
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

Arroyo et al J Comp Eff Res 2014

Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under
Withheld under section 18(d)
Withheld under section 18(d)
Withheld under section 18(d)

New Zealand Data Sheet

Sativex® Oromucosal Spray.

Presentation

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.
Extraction solvent: Liquid carbon dioxide.

Each 100 microlitre spray contains:
2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).
Each 100 microlitre spray also contains up to 0.04 g alcohol.

Uses

Actions

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 significant superiority 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 risk with continued treatment.

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. Higher doses of Sativex of 8 to 16 sprays taken at one time 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.

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_{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-τ = 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-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_{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 to show 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. 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 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.

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 fetal 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.

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.

Dosage and Administration

Sativex 5.5 ml / 10ml Solution in a Spray Container.
Sativex is for oromucosal use only.

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

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 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.

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 "clinical experience" on page 1). 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.

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).

Warnings and Precautions

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.

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.

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. No specific studies have been carried out in patients with significant hepatic or renal impairment. In such individuals the effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in this patient population.

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.

Although no effect has been seen on fertility, independent research in animals found that cannabinoids affected spermatogenesis. Female patients of child-bearing potential and male patients with a partner of childbearing potential should ensure that reliable contraceptive precautions are maintained for the duration of therapy and for three months after discontinuation of therapy.

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.

Pregnancy and lactation

There is insufficient experience in humans regarding the effects of Sativex on reproduction. Therefore men and women of child bearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

Pregnancy

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

Lactation

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.

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. 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.

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" page 6). 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 the following table (some of these adverse events may be part of the underlying condition).

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:

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.

Interactions

Interaction with other medicinal products and other forms of interaction

The two main components of Sativex, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P_{450} enzyme system. In clinical trials where Sativex has been taken concomitantly with other drugs metabolised by the cytochrome P_{450} enzyme system, no clinically apparent drug-drug interactions have been seen at clinical doses.

The inhibitory effects of Sativex on the cytochrome P_{450} system seen *in vitro* and in animal models were only seen at exposures 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).

No clinically relevant changes in levels of THC and CBD have been observed following food interaction and drug-drug interaction studies with Sativex.

When Sativex is co-administered with food there is a mean increase in C_{max}, AUC and half life. The magnitude of this increase was less than the between subject variability in these parameters.

Concomitant treatment with the CYP3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC and its primary metabolite and of CBD. The extent of this increase was substantially less than the between subject variability. Following treatment with the CYP3A4 inducer rifampicin a reduction in the C_{max} and AUC of THC and its primary metabolite and CBD were observed. The magnitude of this reduction for THC and CBD was substantially less than the between subject variability. However, small and sometimes, statistically significant changes were observed, but these were within the limits of natural between-subject variability.

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

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.

Overdose

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.

Further Information

List of excipients

Ethanol anhydrous.

Propylene glycol.

Peppermint oil.

Pharmaceutical Precautions

Incompatibilities

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

Shelf life

18 months (inclusive of in-use period).
In use:

5.5 mL: 4 weeks from date of opening.

10 mL: 6 weeks from date of opening.

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.

Nature and contents of container

A Type I amber glass spray container 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.

Special precautions for disposal

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

Package Quantities

Pack Size: 5.5 mL or 10 mL.
5.5 mL pack size allows delivery after priming of up to 48 actuations (sprays) of 100 microlitres.

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

1, 2, 3, 4, 5, 6, 10 or 12 glass sprays containers per carton.
Not all pack sizes may be marketed.

Medicine Classification

Controlled Drug B1 - Prescription Only

Name and Address

Novartis New Zealand Limited
Private Bag 65904
Mairangi Bay
Auckland 0754
Building G, 5 Orbit Drive
Rosedale
Auckland 0632

Telephone: 09 361 8100

Date of Preparation

18 April 2011

Appendix 3: References (Spasticity due to MS)

Sativex in MS related spasticity Literature search

Search conducted 02 July 2015 via PubMed complete Search terms:
Multiple Sclerosis AND tetrahydrocannabinol-cannabidiol[1]

Search retrieved 50 hits. We applied the filters of Human and English language. This reduced the list to 42 papers. The abstracts for these are included below.

A separate search for Pain and tetrahydrocannabinol-cannabidiol was conducted, and it is possible that some relevant references were included on that list.

Finally, a free text search for sativex was conducted in Pubmed. This was again restricted to English language and Humans. The title of papers were reviewed for inclusion in literature searches relating to either pain or spasticity. This yielded 10 additional papers of which 4 were considered useful for spasticity, 5 for pain and 1 for both literature searches.

1. Evaluation of the tolerability and efficacy of Sativex in multiple sclerosis.
   Moreno Torres I, Sanchez AJ, Garcia-Merino A.
   Expert Rev Neurother. 2014 Nov;14(11):1243-50. doi: 10.1586/14737175.2014.971758. Review.
2. Clinical case reviews and poster sessions in multiple sclerosis spasticity: main outcomes and highlights.
   Trojano M, Celius EG, Donzé C, Izquierdo G, Patti F, Pöhlau D.
   Eur Neurol. 2014;72 Suppl 1:15-9. doi: 10.1159/000367619. Epub 2014 Sep 26.
3. Advances in the management of MS spasticity: recent observational studies.
   Fernández O.
   Eur Neurol. 2014;72 Suppl 1:12-4. doi: 10.1159/000367618. Epub 2014 Sep 26.
4. Advances in the management of multiple sclerosis spasticity: recent clinical trials.
   Fernández O.
   Eur Neurol. 2014;72 Suppl 1:9-11. doi: 10.1159/000367616. Epub 2014 Sep 26.
5. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity nervous pathways.
   Centonze D.
   Eur Neurol. 2014;72 Suppl 1:6-8. doi: 10.1159/000367615. Epub 2014 Sep 26.
6. Drug-resistant MS spasticity treatment with Sativex(®) add-on and driving ability.
   Freidel M, Tiel-Wilck K, Schreiber H, Prechtl A, Essner U, Lang M.
   Acta Neurol Scand. 2015 Jan;131(1):9-16. doi: 10.1111/ane.12287. Epub 2014 Sep 11.
7. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis.
   Syed YY, McKeage K, Scott LJ.

---

[1] Search term ((("tetrahydrocannabinol-cannabidiol combination" [Supplementary Concept]) AND "Multiple Sclerosis"[Mesh])

Appendix 3: References (Spasticity due to MS)

Drugs 2014 Apr;74(5):563-78 doi: 10 1007/s40265-014-0197 5 Review

8. Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice results of a multicenter, non interventional study (MOVE 2) in patients with multiple sclerosis spasticity
   Flachenecker P, Henze T, Zettl UK.
   Eur Neurol. 2014;71(5-6):271-9. doi: 10.1159/000357427. Epub 2014 Feb 12.
9. Who benefits most from THC:CBD spray? Learning from clinical experience.
   Koehler J.
   Eur Neurol. 2014;71 Suppl 1:10-5. doi: 10.1159/000357743. Epub 2014 Jan 22.
10. THC:CBD spray and MS spasticity symptoms: data from latest studies.
    Rekand T.
    Eur Neurol. 2014;71 Suppl 1:4-9. doi: 10.1159/000357742. Epub 2014 Jan 22. Review.
11. Overview of MS spasticity.
    Pozzilli C.
    Eur Neurol. 2014;71 Suppl 1:1-3. doi: 10.1159/000357739. Epub 2014 Jan 22. No abstract available.
12. Clinical case reviews in multiple sclerosis spasticity: experiences from around Europe.
    Koehler J, Amato MP, Oreja-Guevara C, Lycke J.
    Expert Rev Neurother. 2013 Dec;13(12 Suppl):61-6. doi: 10.1586/14737175.2013.865881. Review.
13. A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany.
    Flachenecker P.
    Expert Rev Neurother. 2013 Feb;13(3 Suppl 1):15-9. doi: 10.1586/ern.13.1. Review.
14. Endocannabinoid system modulator use in everyday clinical practice in the UK and Spain.
    García-Merino A.
    Expert Rev Neurother. 2013 Feb;13(3 Suppl 1):9-13. doi: 10.1586/ern.13.4. Review.
15. Multiple sclerosis spasticity symptoms management. Endocannabinoid system modulator data beyond clinical trials. Foreword.
    Trojano M.
    Expert Rev Neurother. 2013 Feb;13(3 Suppl 1):1. doi: 10.1586/ern.13.2. No abstract available.
16. What place for ▾ cannabis extract in MS?
    [No authors listed]
    Drug Ther Bull. 2012 Dec;50(12):141-4. doi: 10.1136/dtb.2012.11.0150. Review.
17. Cost effectiveness of oromucosal cannabis-based medicine (Sativex®) for spasticity in multiple sclerosis.
    Lu L, Pearce H, Roome C, Shearer J, Lang IA, Stein K.
    Pharmacoeconomics. 2012 Dec 1;30(12):1157-71. doi: 10.2165/11598470-000000000-00000.

Appendix 3: References (Spasticity due to MS)

18 Assessment of blinding to treatment allocation in studies of a cannabis based medicine (Sativex®) in people with multiple sclerosis: a new approach

Wright S, Duncombe P, Altman DG

Trials. 2012 Oct 9;13:189. doi: 10.1186/1745-6215-13-189.

19. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis.

Serpell MG, Notcutt W, Collin C.

J Neurol. 2013 Jan;260(1):285-95. doi: 10.1007/s00415-012-6634-z. Epub 2012 Aug 10.

20. A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine.

Notcutt WG.

Prim Health Care Res Dev. 2013 Apr;14(2):192-9. doi: 10.1017/S1463423612000333. Epub 2012 Jul 12.

21. Sativex® in multiple sclerosis spasticity: a cost-effectiveness model.

Slof J, Gras A.

Expert Rev Pharmacoecon Outcomes Res. 2012 Aug;12(4):439-41. doi: 10.1586/erp.12.40. Epub 2012 Jun 8.

22. Evaluation of the safety and tolerability profile of Sativex: is it reassuring enough?

Wade D.

Expert Rev Neurother. 2012 Apr;12(4 Suppl):9-14. doi: 10.1586/ern.12.12. Review.

23. Clinical efficacy and effectiveness of Sativex, a combined cannabinoid medicine, in multiple sclerosis-related spasticity.

Oreja-Guevara C.

Expert Rev Neurother. 2012 Apr;12(4 Suppl):3-8. doi: 10.1586/ern.12.11. Review.

24. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols).

Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R.

Mult Scler. 2012 Feb;18(2):219-28. doi: 10.1177/1352458511419700. Epub 2011 Aug 30.

25. Evaluate symptomatic therapy in MS: can clinical trials be fine-tuned?

Solaro C.

Eur J Neurol. 2011 Sep;18(9):1113-4. doi: 10.1111/j.1468-1331.2011.03425.x. Epub 2011 Jul 5. No abstract available.

Comment on
A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. [Eur J Neurol. 2011]

26. Abuse potential and psychoactive effects of δ-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine.

Robson P.

Expert Opin Drug Saf 2011 Sep;10(5):675-85 doi: 10 1517/14740338 2011 575778 Epub

Appendix 3: References (Spasticity due to MS)

2011 May 4 Review

27. THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis

Sastre-Garriga J, Vila C, Clissold S, Montalban X.

Expert Rev Neurother. 2011 May;11(5):627-37. doi: 10.1586/ern.11.47. Epub 2011 Apr 1. Review.

28. Sativex(®) (tetrahydrocannabinol + cannabidiol), an endocannabinoid system modulator: basic features and main clinical data.

Vermersch P.

Expert Rev Neurother. 2011 Apr;11(4 Suppl):15-9. Review.

29. Pathophysiology, assessment and management of multiple sclerosis spasticity: an update.

Haas J.

Expert Rev Neurother. 2011 Apr;11(4 Suppl):3-8. Review.

30. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis.

Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P; Sativex Spasticity Study Group.

Eur J Neurol. 2011 Sep;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x. Epub 2011 Mar 1.

31. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis.

Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ.

Mult Scler. 2010 Nov;16(11):1349-59. doi: 10.1177/1352458510378020. Epub 2010 Sep 9.

32. Cannabis-based treatment induces polarity-reversing plasticity assessed by theta burst stimulation in humans.

Koch G, Mori F, Codecà C, Kusayanagi H, Monteleone F, Buttari F, Fiore S, Bernardi G, Centonze D.

Brain Stimul. 2009 Oct;2(4):229-33. doi: 10.1016/j.brs.2009.03.001. Epub 2009 Apr 3.

33. Cannabis based drug is licensed for spasticity in patients with MS.

Kmietowicz Z.

BMJ. 2010 Jun 22;340:c3363. doi: 10.1136/bmj.c3363. No abstract available.

34. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis.

Wade DT, Collin C, Stott C, Duncombe P.

Mult Scler. 2010 Jun;16(6):707-14. doi: 10.1177/1352458510367462.

35. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis.

Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, Notcutt W, O'Leary C, Ratcliffe S, Nováková I, Zapletalova O, Piková J, Ambler Z

Neurol Res 2010 Jun;32(5):451-9 doi: 10 1179/016164109X12590518685660 Epub 2010 Mar 19.

36 Lack of effect of cannabis based treatment on clinical and laboratory measures in multiple sclerosis.

Centonze D, Mori F, Koch G, Buttari F, Codecà C, Rossi S, Cencioni MT, Bari M, Fiore S, Bernardi G, Battistini L, Maccarrone M.

Neurol Sci. 2009 Dec;30(6):531-4. doi: 10.1007/s10072-009-0136-5. Epub 2009 Sep 19.

37. Willingness to pay for a treatment for pain in multiple sclerosis.

Iskedjian M, Desjardins O, Piwko C, Bereza B, Jaszewski B, Einarson TR.

Pharmacoeconomics. 2009;27(2):149-58. doi: 10.2165/00019053-200927020-00005.

38. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial.

Rog DJ, Nurmikko TJ, Young CA.

Clin Ther. 2007 Sep;29(9):2068-79.

39. Cannabis; adverse effects from an oromucosal spray.

Scully C.

Br Dent J. 2007 Sep 22;203(6):E12; discussion 336-7. Epub 2007 Aug 17.

40. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain.

Barnes MP.

Expert Opin Pharmacother. 2006 Apr;7(5):607-15. Review.

41. Conditional okay for cannabis prescription drug.

Sibbald B.

CMAJ. 2005 Jun 21;172(13):1672. No abstract available.

42. GW-1000. GW Pharmaceuticals.

Smith PF.

Curr Opin Investig Drugs. 2004 Jul;5(7):748-54.

43. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study.

Aragona M, Onesti E, Tomassini V, Conte A, Gupta S, Gilio F, Pantano P, Pozzilli C, Inghilleri M.

Clin Neuropharmacol. 2009 Jan-Feb;32(1):41-7. doi: 10.1097/WNF.0B013E3181633497.

44. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain.

Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR.

Curr Med Res Opin. 2007 Jan;23(1):17-24.

45. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis.

Wade DT, Makela PM, House H, Bateman C, Robson P.

Appendix 3: References (Spasticity due to MS)

Mult Scler 2006 Oct;12(5):639-45

46. Sativex for the management of multiple sclerosis symptoms.
Perras C.
Issues Emerg Health Technol. 2005 Sep;(72):1-4.

47. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients.
Wade DT, Makela P, Robson P, House H, Bateman C.
Mult Scler. 2004 Aug;10(4):434-41.

Additional papers sorted by author surname:

1. Aragona_Clin Neuropharm 2009
2. Arroyo_J Comp Eff Res 2014
3. CADTH emerging technologies 2005 310_sativex_cetap_e
4. Colin_EuroJNeurol_2007
5. Collin_Neurol Res 2010
6. Flachenecker_Eur Neurol 2014
7. Flachenecker_Eur Neurol 2014b
8. Gold_Exp Rev 2013
9. Iskedjian_Pharmacoecon 2009
10. Kavia_MS 2010
11. Koehler_Eur Neurol 2014
12. Lu_Pharmacoecon 2012
13. NICE_ guidance-multiple-sclerosis_2014
14. Notcutt_MS J 2012
15. Novotna_Eur J Neurol 2011
16. Oreja-Guevara_exp Rev 2012
17. Pozzilli_Exp Rev 2013
18. Rekand_Eur Neurol 2014
19. Rizzo_Mult Scler_2004
20. Sastre-Garriga_Exp Rev 2011
21. Serpell_J Neurol 2013
22. Slof_Exp Rev 2012
23. Syed_Adis Drug Evaluation_Drugs 2014
24. Torres_Exp Rev 2014
25. Wade_MS 2010
26. Wade_Mult Scler_2004
27. Wade_MultScler_2006
28. Zajicek_Lancet_2003 (sativex CAMS study)

Appendix 4: References (Pain)

Sativex in Pain Literature search

Search conducted 03 July 2015 via PubMed complete Search terms:
Pain AND tetrahydrocannabinol-cannabidiol[2]

Search retrieved 23 hits. We applied the filters of Human and English language. This reduced the list to 18 papers. Abstracts reviewed to determine if the papers were previously included in literature search relating to MS spasticity. If included in that literature search, then they were excluded here. This left 10 items remaining. The remaining abstracts for these are included below.

Finally, a free text search for sativex was conducted in Pubmed. This was again restricted to English language and Humans. The title of papers were reviewed for inclusion in literature searches relating to either pain or spasticity. This yielded 10 additional papers of which 4 were considered useful for spasticity, 5 for pain and 1 for both literature searches.

1. New pain drugs in pipeline, but challenges to usage remain.
   Brower V.
   J Natl Cancer Inst. 2012 Apr 4;104(7):503-5. doi: 10.1093/jnci/djs199. Epub 2012 Mar 22. No abstract available.
   Link to full (free) text http://jnci.oxfordjournals.org/content/104/7/503.long
2. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor.
   Selvarajah D, Gandhi R, Emery CJ, Tesfaye S.
   Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. Epub 2009 Oct 6.
3. Managing neuropathic pain with Sativex: a review of its pros and cons.
   Perez J, Ribera MV.
   Expert Opin Pharmacother. 2008 May;9(7):1189-95. doi: 10.1517/14656566.9.7.1189. Review.
4. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial.
   Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D.
   Pain. 2007 Dec 15;133(1-3):210-20. Epub 2007 Nov 7.
5. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine.
   Russo EB, Guy GW, Robson PJ.
   Chem Biodivers. 2007 Aug;4(8):1729-43. Review.
6. Latest pain relief a combination of new and old.
   D'Arcy Y.
   Nurse Pract. 2007 Jan;32(1):11-2. Review.

---

[2] Search term ("tetrahydrocannabinol-cannabidiol combination" [Supplementary Concept]) AND "Pain"[Mesh]

Appendix 4: References (Pain)

7 New pain management options: drugs

D'Arcy Y.

Nursing. 2007 Jan;37(1):18-9.

8. The use of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis.

Wright S, Ware M, Guy G.

Rheumatology (Oxford). 2006 Jun;45(6):781; author reply 781-2. Epub 2006 Apr 18.
No abstract available.

Link to free text http://rheumatology.oxfordjournals.org/content/45/6/781.1.long

9. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS.

Rheumatology (Oxford). 2006 Jan;45(1):50-2. Epub 2005 Nov 9.

10. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial.

Berman JS, Symonds C, Birch R.

Pain. 2004 Dec;112(3):299-306.

11. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial.

Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT.

J Pain. 2012 May;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003. Epub 2012 Apr 5.

12. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use.

Schoedel KA, Chen N, Hilliard A, White L, Stott C, Russo E, Wright S, Guy G, Romach MK, Sellers EM.

Hum Psychopharmacol. 2011 Apr;26(3):224-36. doi: 10.1002/hup.1196.

13. Using cannabinoids in pain and palliative care.

Peat S.

Int J Palliat Nurs. 2010 Oct;16(10):481-5.

14. A treatment algorithm for neuropathic pain: an update.

Namaka M, Leong C, Grossberndt A, Klowak M, Turcotte D, Esfahani F, Gomori A, Intrater H.

Consult Pharm. 2009 Dec;24(12):885-902. Review.

15. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside.

Rahn EJ, Hohmann AG.

Neurotherapeutics. 2009 Oct;6(4):713-37. doi: 10.1016/j.nurt.2009.08.002. Review.

16. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain.

Appendix 4: References (Pain)

Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR
Curr Med Res Opin 2007 Jan;23(1):17 24

Additional papers sorted by author surname:

1. Berman_Pain 2004
2. CADTH Sativex for MS associated neuropathic pain_2007
3. Iskedjian_Pharmacoecon 2009
4. Johnson_J Pain 2010
5. Johnson_J Pain 2013b
6. Langford_J Neurol 2013
7. Lynch_J Pain 2014
8. Nurmikko_Pain_2007
9. Portenoy_J Pain 2012
10. Selvarajah_Diabetes 2010
11. Whiting_JAMA Systematic_2015

Relevant minutes regarding lacosamide

From the **Record of the Pharmacology and Therapeutics Advisory Committee Meeting Held on 5 & 6 August 2010**

11 Lacosamide (Vimpat) for treatment resistant epilepsy

Application

11.1 The Committee reviewed an application from UCB Australia for the listing of lacosamide (Vimpat) on the Pharmaceutical Schedule as an add-on treatment for patients with partial onset epilepsy who have received inadequate control from at least one first-line anti-epileptic treatment and two second-line adjunctive anti-epileptic treatments.

Recommendation

11.2 The Committee **recommended** that the application for the funding of lacosamide (Vimpat) as an add-on treatment for patients with partial onset epilepsy who have received inadequate control from at least one first-line anti-epileptic treatment and two second-line adjunctive anti-epileptic treatments be declined, on the basis that there are cheaper alternative options that it would be reasonable to try at that point in the treatment paradigm.

11.3 The Committee **recommended** that lacosamide (Vimpat) be funded as an add-on treatment for patients with partial onset epilepsy who have received inadequate control from previous treatments, subject to the following Special Authority criteria, with a medium priority:

> Initial application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:
> All of the following:
> 1 Patient has partial onset epilepsy; and
> 2 Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from an optimal treatment with all of the following; sodium valproate, carbamazepine, phenytoin sodium, lamotrigine, topiramate and levetiracetam (see Notes); and
> 3 Patient is currently taking at least two antiepilepsy treatments.
> Notes: "Optimal treatment" is defined as treatment which is indicated and clinically appropriate for the patient, given adequate doses for the patient's age, weight and other features affecting the pharmacokinetics of the drug with good evidence of compliance. Women of childbearing age are not required to have a trial of sodium valproate.
>
> Renewal from any relevant practitioner. Approvals valid for 2 years where the patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting lacosamide treatment (see Note).
> Note: As a guideline, clinical trials have referred to a notional 50% reduction in seizure frequency as an indicator of success with anticonvulsant therapy and have assessed quality of life from the patient's perspective.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule*.

Discussion

11.4 The Committee noted that lacosamide is a functionalised amino acid (D-serine) anti-epileptic. Its precise mechanism of action is not known but *in vitro* lacosamide selectively enhances slow inactivation of voltage-gated sodium channels resulting in stabilisation of hyperexcitable neuronal membranes. It is indicated as an add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients 16 years or older. The Committee noted that the supplier was seeking funding for lacosamide in patients who had tried at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents.

11.5 The Committee considered that there was a reasonably large range of funded antiepilepsy treatments and that there were generally few problems with access to these treatments; however, the Committee noted that there would always be a small proportion of patients who continue to have seizures despite having tried all suitable funded options. The Committee noted that the evidence suggests that there may be a higher prevalence of epilepsy among Māori compared with the overall population.

11.6 The Committee considered that the evidence provided by the supplier in support of the application was of good quality, consisting of three medium-sized randomised controlled pivotal trials (one phase 2b study and two phase 3 studies), which have been published in peer reviewed journals. In addition, the supplier provided long-term safety data from clinical trial extensions and a meta-analysis of the randomised controlled trials.

11.7 All the pivotal trials were randomised, double-blind, multicentre, placebo-controlled, parallel-group trials investigating the efficacy and safety of lacosamide 200 mg, 400 mg and/or 600 mg (depending on the trial) as adjunctive therapy in patients with partial seizures with or without secondary generalisation (Ben-Menachem et al. Epilepsia 2007;48(7):1308-17; Chung et al. Epilepsia 2010;51(6):958-67; Halasz et al. Epilepsia 2009;50(3):443-53). All patients were adults over the age of 16 who had uncontrolled epilepsy despite prior treatment with at least two anti-epileptics. Patients were taking one, two or three concomitant anti-epileptic treatments. In each trial, patients were entered into an eight-week baseline phase and only those who reported ≥4 partial-onset seizures per 28 days, with seizure-free period no longer than 21 days during the baseline phase, were randomised. After randomisation, patients were titrated up to the randomised dose of lacosamide or placebo over four or six weeks, followed by a 12-week maintenance phase. Patients then transitioned to 200 mg/day prior to entry into an extension study or entered a three-week taper phase. In all trials the primary outcome measures were change in seizure frequency per 28-days and proportion of patients with ≥50% reduction of seizure frequency from baseline to the maintenance phase.

11.8 The Committee considered that the results of the trials supported the efficacy of lacosamide 400 mg and 600 mg in reducing seizure frequency in patients with refractory epilepsy compared with placebo for both primary outcome measures, noting that the outcomes for patients on lacosamide 200 mg were not statistically

significantly greater than those in the placebo groups. However, the Committee noted that even in the lacosamide 400 mg and 600 mg groups the response rates were not high (approximately 38%–41% of lacosamide 400 mg or 600 mg patients had ≥50% reduction in seizure frequency compared with 18%–26% of placebo patients) and very few patients were seizure free over the 28-day period

11.9 The Committee noted that the supplier had provided a *post-hoc* analysis of the clinical trials to examine the efficacy of lacosamide in patients that would be targeted by the proposed Special Authority criteria. The Committee noted that the results of this analysis suggested that more lacosamide-treated patients in this subgroup achieved a ≥50% reduction in seizure frequency compared to placebo patients in the subgroup, and that the supplier concluded that the responder rate observed in the randomised controlled trials was representative of the response that would be achieved in patients meeting the proposed criteria.

11.10 The Committee noted that although the recommended daily dose of lacosamide on the Medsafe datasheet is 400 mg per day, it appeared from the clinical trials that patients on the 600 mg dose may have a better response than those on the 400 mg dose, and given that a reasonable proportion of patients were able to tolerate this dose (600 mg) in the clinical trials it was likely that in clinical practice higher doses would be used. The Committee noted that this was occurring with patients taking levetiracetam through Levetiracetam Special Access, where doses considerably higher than the Medsafe-recommended doses were sometimes being used.

11.11 The Committee noted that the main side effects of lacosamide reported in the clinical trials were dizziness and vertigo, unsteady gait, headache, nausea, vomiting and diplopia, and that a relatively high proportion of patients in the clinical trials withdrew because of side effects (19% in the lacosamide 400 mg group and 30% in the 600 mg group, compared with 5% in the placebo group). Other side effects subsequently reported and added to the datasheet included rash, bradycardia, confusional state, suicidal ideation, suicide attempts and syncope. The Committee considered that the results of the extension studies suggest that lacosamide has an acceptable long-term safety profile; however, the Committee considered that it would be important to continue to monitor for emerging side effects given that this was still a relatively new treatment.

11.12 The Committee noted that the supplier had not provided a cost-utility analysis (CUA) but had instead provided a cost-effectiveness analysis (CEA). The Committee considered that the supplier should have provided a CUA as this would be required in order to compare the cost-effectiveness of lacosamide with other pharmaceuticals under consideration for funding, noting that this was stated in PHARMAC's funding application guidelines.

11.13 The Committee noted that the supplier considered that the appropriate comparator for lacosamide in cost-effectiveness analyses was no treatment, because no other treatment had demonstrated clinical trial efficacy in the patient group for whom lacosamide funding was sought. The Committee considered that the evidence supported the use of lacosamide as a last-line add-on treatment and from that perspective it was reasonable to use placebo as the comparator. However, the Committee noted that there would be multiple other funded treatment options for patients meeting the Special Authority criteria proposed by the supplier, many of which would be reasonable to try at that point in the treatment paradigm. The Committee noted that it would be difficult to compare the efficacy of lacosamide with other possible funded options because there were no comparative trials available. However, the Committee considered that if a CUA was to be performed for

lacosamide under the criteria proposed by the supplier, it would be reasonable to use levetiracetam as a comparator as this was the treatment currently being used at that point in the treatment paradigm

11.14 The Committee noted that in a rapid CUA performed by PHARMAC staff, which assumed that lacosamide would be used as a last line add on treatment; lacosamide at a dose of 300 mg per day was associated with a cost per quality adjusted life year (QALY) of approximately $60,000 to $100,000. The Committee noted that the cost per QALY was likely to be higher if higher doses (eg 400 mg–600 mg per day) were used in the analysis.

11.15 The Committee noted the large cost differential between lacosamide and all other funded treatments, including generic levetiracetam (which is due to be funded from 1 November 2010).

11.16 For the above reasons, the Committee considered that, at a minimum, patients should be required to have a trial of sodium valproate carbamazepine, phenytoin sodium, lamotrigine, topiramate and levetiracetam, and should be taking at least two current treatments, before accessing funded lacosamide. The Committee noted that sodium valproate has a high risk of teratogenic effects and, therefore, women of childbearing age should not be required to have a trial of sodium valproate prior to accessing lacosamide.

11.17 The Committee considered that if it were funded following the treatments outlined in the paragraph above, lacosamide would be used purely as an add-on treatment and would not replace the use of, or delay the use of, any funded treatments.

11.18 The Committee considered that the patient numbers estimated by PHARMAC staff was reasonable (being approximately double the patient numbers suggested by the supplier) and that no cost-offsets should be included in the budget impact analysis.

11.19 The Committee considered that it would be useful to know whether lacosamide was effective in the subgroup of patients in the clinical trials that had previously received inadequate benefit from levetiracetam, noting that these data should be available because a relatively high proportion of patients in the trials had tried levetiracetam. The Committee considered that this information could help determine whether lacosamide is efficacious following failure of treatment with levetiracetam.

Appendix 6: References (Epilepsy)

Sativex in epilepsy Literature search

Search conducted 03 July 2015 via PubMed complete Search terms:
Epilepsy AND tetrahydrocannabinol-cannabidiol[3]
Search retrieved 0 hits.

Second search for Epilepsy AND cannabidiol
This returned 34 hits
Filtered for clinical trials. This returned 1 hit. 1 phase 1 study.

We included a filter to include systematic reviews. This expanded our search results by 3 hits of which one was a duplicate and one a case report.

1. Chronic administration of cannabidiol to healthy volunteers and epileptic patients.
   Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R.
   Pharmacology. 1980;21(3):175-85.
2. Hypnotic and antiepileptic effects of cannabidiol.
   Carlini EA, Cunha JM.
   J Clin Pharmacol. 1981 Aug-Sep;21(8-9 Suppl):417S-427S.
3. Cannabinoids for epilepsy.
   Gloss D, Vickrey B.
   Cochrane Database Syst Rev. 2012 Jun 13;6:CD009270. doi: 10.1002/14651858.CD009270.pub2. Review. Update in: Cochrane Database Syst Rev. 2014;3:CD009270.
4. The case for medical marijuana in epilepsy.
   Maa E, Figi P.
   Epilepsia. 2014 Jun;55(6):783-6. doi: 10.1111/epi.12610. Epub 2014 May 22.

Additional papers sorted by author surname:

1. Cilio_Epilepsia_2014
2. Devinsky_Epilepsia_2014
3. Hill_Pharmacol Ther_2012
4. Maa_Epilepsia_2014
5. Vickrey_ Cochrane_2014

[3] Search term ("Epilepsy"[Mesh]) AND "tetrahydrocannabinol-cannabidiol combination" [Supplementary Concept]