MINISTRY OF HEALTH
MANATŪ HAUORA

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Russell Brown
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Ref: H201600082

Dear Mr Brown

Response to your request for official information

Thank you for your request of 11 January 2016 under the Official Information Act 1982 (the Act) for:

1. how the criteria were prepared for non-pharmaceutical grade medicinal cannabis products, by whom and on what advice? I'm also seeking any documents and communications that contributed to the final criteria.

2. what advice was considered in declaring in the Medsafe statement on Sativex that "Sativex is considered to be a desirable and divertible pharmaceutical due to the inherent nature of its active substances." Was the position of the British Government's Advisory Council on Misuse of Drugs (ACMD) considered? I would also like any advice or communication in which claims that Sativex has a low potential for diversion and abuse was considered.

The information relating to this request is itemised below, with copies of documents attached. Some of the information you request is already in the public domain. This information is available at the websites given or from an electronic search for the journal articles listed. No information has been withheld.

Response to question 1:

The criteria were developed for the consideration of the Associate Minister of Health by regulatory advisors within the Ministry of Health with input from Sector Policy and the Acting Director of Public Health.

Initial advice was developed in June 2015 to assist the Associate Minister in deciding whether to grant Ministerial approval under the Misuse of Drugs Regulations 1977 following an application to import and prescribe a non-pharmaceutical grade cannabis product for medicinal use

The criteria were then developed further to ensure that there was a consistent framework to evaluate any further applications for Ministerial approval of non-pharmaceutical grade products and align the criteria with those for pharmaceutical

grade cannabis products undergoing clinical trials and pharmaceutical grade products with consent for distribution in New Zealand (currently only Sativex). These criteria were provided to the Associate Minister for his approval in Health Report 20151078 titled Criteria for Access to Medical Products that require Ministerial Approval.

Documents and communications that contributed to the final criteria were:

1. Health Report 20150878, Ministerial Approval to Prescribe and Import Cannabidiol Oil. Please note that the family of the patient named in this report have been contacted and they do not require any of the patient's personal information to be withheld. This report includes, as appendices, further documents that contributed to the criteria:
    - "Rapid Assessment of application to prescribe Cannabidiol product", a review of international literature and advice prepared by Dr Stewart Jessamine, Acting Director of Public Health, following the application for a non-pharmaceutical grade product cannabidiol product Elixinol to be prescribed for a patient. It needs to be noted that due to the urgency of the situation, the review was completed and the application considered and approved within 24 hours of receipt
    - a copy of a Health Report 20150106 provided to the Minister and Associate Ministers of Health in February 2015 titled Medicinal Cannabis.
2. The criteria in place for approvals of Sativex, a pharmaceutical-grade medicinal cannabis product. http://www.medsafe.govt.nz/
3. The Victorian Law Commission Issues Paper March 2015, developed following a request from the Victorian Government for the Commission to review and report on options for legislative change to allow people to be treated with cannabis in exceptional circumstances. http://www.lawreform.vic.gov.au/projects/medicinal-cannabis/medicinal-cannabis-issues-paper
4. International literature published in peer reviewed journals including:
    - Cannabinoids for Medical Use. A systematic Review and Meta-analysis. Whiting et al. JAMA. 2015;313(24):2456-2473
    - Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems. A Clinical Review. Hill, Kevin P. JAMA2015;313(24):2474-2483
    - The case for assessing cannabidiol in epilepsy. Cilio et al, Epilepsia, 55(6);787-790, 2014

The criteria developed are detailed in Health Report 20151078, Criteria for Access to Medical Products that require Ministerial Approval that is attached and information provided on the Ministry of Health Website www.health.co.nz (search under 'medicinal cannabis').

Response to question 2

The statement of interest is located in 'Sativex Oromucosal Spray – Requirements for Prescribers' published on the Medsafe website. The document provides regulatory information for prescribers and links to the related applications for approval to prescribe Sativex Oromucosal Spray.

The advice that Sativex is desirable and divertible was provided by the National Drug Policy unit of the Ministry of Health in August 2007, a copy is attached. The advice was based on a number of references cited in the document.

The National Drug Policy document pre-dates the ACMD advice on Sativex published February 2013 that concluded that Sativex has a low abuse potential and low risk of diversion.

No other record of advice or communication claiming that Sativex has a low potential for diversion and abuse could be located.

The Ministry of Health will review and, if necessary, revise the information on the abuse potential of Sativex in the website document: Sativex Oromucosal Spray – Requirements for Prescribers, to ensure that it is fit for purpose.

Documents attached are:

1. Health Report 20150878, Ministerial; Approval to Prescribe and Import Cannabidiol Oil.
2. Health Report 20151078, Criteria for Access to Medical Products that require Ministerial Approval.
3. Sativex® (standardised cannabis pharmaceutical): Requirements for Physician Application-Approval, National Drug Policy, Ministry of Health, August 2007.

I trust this information fulfils your request.

Yours sincerely

Dr Don Mackie
Chief Medical Officer
Clinical Leadership, Protection and Regulation

MINISTRY OF HEALTH
MANATŪ HAUORA

Health Report number: 20151078
File number: PP05-08-0
Action required by: routine

Criteria for Access to Medicinal Products that require Ministerial Approval

To: Hon Peter Dunne (Associate Minister of Health)

Copy to: Hon Dr Jonathan Coleman (Minister of Health)

Purpose

This report provides criteria to support decisions on applications for Ministerial approval for non-pharmaceutical grade medicinal products under regulation 22 of the Misuse of Drugs Regulations 1977. Criteria for Ministerial approval of pharmaceutical grade products undergoing clinical trials and pharmaceutical grade products with consent for distribution in New Zealand are also provided for your information.

Key points

- In June 2015, Ministerial approval was given for the use of a non-pharmaceutical grade cannabis product, Elixinol.
- A need for criteria to support Ministerial decisions on whether to approve the use of non-pharmaceutical grade controlled drugs for medicinal purposes was identified.
- Under current legislation, medical practitioners can prescribe non-pharmaceutical grade products for patients under their care. In most cases this does not require approval prior to prescribing the product.
- A number of controlled drugs, including products containing cannabinoids and some substances more commonly used for illicit purposes are being investigated for specific medical purposes. The therapeutic use of these controlled drugs requires Ministerial approval under regulation 22 of the Misuse of Drugs Regulations 1977.
- Ministerial approval is delegated to Ministry of Health officials except when the application to prescribe is outside current government policy, for example a non-pharmaceutical grade cannabis product.
- The medicinal use of non-pharmaceutical grade products does not progress medical knowledge and evidence for the safety and efficacy of these products is lacking.
- It is recommended that Ministerial approval of applications for the use of non-pharmaceutical grade controlled drugs continues to be treated as an exceptional circumstance, outside government policy, and granted only under Ministerial direction rather than under delegation.
- Criteria to support Ministerial decision making in these exceptional circumstances are provided.
- Ministerial approval for the use of pharmaceutical grade controlled drug products, with or without approval for distribution, will continue to follow the normal delegation to Ministry of Health officials. The criteria used for these approvals are provided in Appendix 1.

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Health Report number: 20151078

Criteria for Access to Medicinal Products that require Ministerial Approval

Recommendations

The Ministry recommends that you:

a) **Agree** to the proposed decision making framework for Ministerial approval of controlled drugs regulated by Regulation 22 of the Misuse of Drugs Regulations1977 — Yes / No

b) **Agree** the proposed criteria should guide ministerial approval for the use of a non-pharmaceutical grade controlled drug — Yes / No

b) **Agree** that ministerial approval for the use of non-pharmaceutical grade controlled drugs will not be delegated to Ministry officials at this stage — Yes / No

c) **Note** ministerial approval for pharmaceutical grade controlled drugs with or without approval for distribution in New Zealand will continue to follow the normal delegation process.

Dr Don Mackie
Chief Medical Officer
Clinical Leadership Protection and Regulation

Minister's signature

Date: 8-09-15

Criteria for Access to Medicinal Preparations requiring Ministerial Approval

Introduction

1. Recently, Ministerial approval was given for the compassionate use in exceptional circumstances, of a non-pharmaceutical grade cannabis product containing cannabidiol (Elixinol).
2. Government policy in relation to cannabinoid products is that it supports the use of pharmaceutical grade cannabinoid products such as Sativex® but it does not support the use of unprocessed or partially processed cannabis preparations.
3. The use of the non-pharmaceutical grade Elixinol, a Class B1 controlled drug, fell outside government policy. Normal delegation processes for Ministerial approval to import, prescribe and administer Elixinol under regulation 22 of the Misuse of Drugs Regulations 1977 (MoDR) were suspended and approval sought directly from you.
4. This report proposes criteria to support future Ministerial decisions when requests are received for access to non-pharmaceutical grade controlled drugs in similar circumstances to Elixinol.
5. Criteria for Ministerial approval of pharmaceutical grade controlled drug products to be used in clinical trials, outside clinical trials and the use of pharmaceutical grade controlled drugs with approval (or consent) for distribution in New Zealand are also provided.

Requirements when prescribing unapproved and/or non-pharmaceutical grade products

6. Under the Medicines Act 1981 medical practitioners can prescribe any product for therapeutic purposes for patients under their care.
7. When prescribing a non-pharmaceutical grade product, a non-approved pharmaceutical product or an approved pharmaceutical product for a non-approved condition, the prescriber is required to take special care to ensure that the patient or their appointed guardian is fully informed so that they can make an informed choice. Informed consent must be documented.
8. A number of other jurisdictions allow access to unapproved products on compassionate grounds. Compassionate use in the United States and the European Union is intended to facilitate the availability of new pharmaceutical grade products under development. It is limited to patients where there is no satisfactory authorised therapy and who cannot enter a clinical trial.

Ministerial Approval under the Misuse of Drugs Act and Regulations

9. When the product is a controlled drug listed in Schedule A, Parts 1 and 2 of Schedule B and Part 1 of Schedule C of the Misuse of Drugs Act 1975 (MoDA), there are additional requirements for prescribing. Regulation 22 of MODR requires Ministerial approval to import, supply, prescribe and administer these controlled drugs with some exemptions, principally morphine.
10. Ministerial approval is generally delegated to the Director-General of Health, the Manager of Provider Regulation and the Team Leader Medicines Control.
11. Some medicines covered by regulation 22 have "blanket" approvals, for example the prescribing of methylphenidate (commonly known as Ritalin®) for attention deficit hyperactivity disorder (ADHD) and the prescribing of pseudoephedrine or ephedrine.
12. Other Ministerial approvals are considered on a case by case basis by Ministry of Health clinicians and regulators, for example pharmaceutical grade cannabis products for medicinal use such as Sativex®.

13. Individual Ministerial approvals are granted for a limited period of time and renewal of an approval is subject to evidence of efficacy and safety.

Categories for Ministerial approval under Regulation 22

14. The Ministry of Health (the Ministry) has defined three different categories of product use. Each category has its own criteria. The categories are:

    a) pharmaceutical grade products with approval for distribution in New Zealand, for both approved uses and unapproved (off-label) use, for example Sativex® (see Appendix 1 for criteria)

    b) pharmaceutical grade products that do not have approval for distribution in New Zealand, for example the use of the cannabinoid product Epidiolex® outside the clinical trial that is currently underway in the United States (compassionate use) or the clinical trial of pharmaceutically prepared Methylenedioxymethamphetamine (MDMA or Ecstasy) for the treatment of tinnitus (see Appendix 1 for criteria)

    c) use of non-pharmaceutical grade products, for example Elixinol (see below).

Considerations when granting Ministerial approval to prescribe non-pharmaceutical grade products

15. Important considerations and limitations on Ministerial approval to prescribe non-pharmaceutical grade products were noted in Dr Stewart Jessamine's Rapid Assessment of the application to prescribe Cannabidiol product (the Rapid Assessment) (Appendix 2). The Rapid Assessment was provided to assist the decision as to whether to provide Ministerial approval for the use of Elixinol for a named patient.

16. The Rapid Assessment was cognisant of the recent review, "The case for assessing cannabidiol in epilepsy" (Cillo et al 2014), considering the risks in epilepsy of using non-standardised cannabis treatments based on anecdotal information. They state:

    a) autonomy is a step backward for medical care if it becomes dissociated from rigorous and unbiased study

    b) patients need objective and unbiased data on safety and efficacy to endorse a new drug to treat epilepsy

    c) the best track record in medicine is with pure compounds and rigorous data.

17. The Victorian Law Reform Commission issues paper *Medical Cannabis*, released in March 2015 is also useful. The Commission was asked to review and report on options for changes to their legislation to allow people to be treated with medicinal cannabis in exceptional circumstances. They state:

    a) if strict criteria of evidence-based medicine are applied at this stage, the scope for the therapeutic prescription of cannabis product would be relatively confined

    b) it is important and humane that unrealistic expectations are not created

    c) departure from the principals of evidence-based medicine should only take place when the potential benefits outweigh potential risks, dangers and side effects.

Non-pharmaceutical grade products requiring Ministerial approval

18. The Ministry recommends that use of non-pharmaceutical grade products as medicines should only be considered in extremely limited circumstances.

19. The proposed criteria for Ministerial approval are:

    a) severe or life-threatening condition

    b) evidence that all reasonably applicable conventional treatments have been trialled and the symptoms are still poorly controlled

    c) evidence that the risk/ benefit of the product has been adequately considered by qualified clinical specialists – that is, the risk of treatment with an unproven product is less than the risk of non-treatment and account has been taken of any evidence of potential benefit and weighed against known adverse effects

    d) patient hospitalised when treatment is initiated

    e) patient or guardian has provided informed consent

    f) application from a specialist appropriate to the medical condition being treated or the Chief Medical Officer of a District Health Board

    g) applicant or specialist prescriber has sought adequate peer review eg, Hospital Ethics Committee approval, Drug or Therapeutics Committee review

    h) provision of a Certificate of Analysis, preferably from an accredited laboratory, so that the concentration of the active ingredient(s) is known

20. Ministerial approval in these circumstances should not be delegated as the use is outside government policy and use of the product will not contribute meaningful data to the pool of scientific research on the safety and efficacy of cannabis products in the condition being treated.

21. Products that are not pharmaceutical grade or not pharmaceutically prepared will not be approved for use in clinical trials.

END.

Appendix 1: Criteria for Access to Pharmaceutical Grade Products requiring Ministerial Approval

1. Pharmaceutical grade products approved for distribution in New Zealand for both approved and unapproved conditions (for example Sativex®)

   a) Application from an appropriate specialist, usually in conjunction with a general practitioner

   b) Evidence that there will be close follow up of patient by a prescriber

   c) Evidence that a wide range of conventional treatments have been trialled and symptoms are still poorly controlled

   d) Condition is an approved condition for use (for Sativex® this is multiple sclerosis), *or*

   e) Condition is one for which there is some evidence of efficacy, preferably in clinical trials, for example for Sativex®:

      i. chronic pain

      ii. neuropathic pain

      iii. cancer pain

   f) Ministry clinicians assess application is appropriate if for other non-approved use, for example the use of Sativex® for intractable childhood epilepsy

   g) No history of abuse or diversion of controlled drugs

   h) The patient has no known contraindication to the use of the product

   i) Initial approvals usually for 6 months

   j) Baseline clinical indicators generally required and evidence of improvement before a new approval is given.

   Ministerial approval is delegated to Ministry officials as per current process

2. Pharmaceutical grade products that do not have approval for distribution in New Zealand, for example the use of the product Epidiolex® currently undergoing clinical trials overseas (compassionate use) or pharmaceutically prepared MDMA (Ecstasy) for use in a clinical trial for the treatment of tinnitus.

   a) Application from an appropriate specialist

   b) A manufacturer has demonstrated a commitment to the development of the product as a pharmaceutical *or*

   c) The product has been prepared pharmaceutically and the characteristics and formulation are clearly described and defined

   d) The product has completed animal studies demonstrating proof of concept and potential clinical benefit

   e) The product is undergoing an appropriately designed Phase II clinical study *or*

   f) The product has completed clinical trials and is marketed overseas but is not approved for distribution in New Zealand

   g) The product is available for use

   h) Criteria b) to j) in 1. above are met where relevant.

   Ministerial approval will be delegated to Ministry officials as the use of these products is within Government policy.

Notes:

i. Access to trial products outside clinical trials may be difficult due to the liability or product protection concerns of the manufacturer.

ii. Ministerial approval of a pharmaceutical grade or pharmaceutically prepared product for a New Zealand clinical trial would occur only after Ethics Committee and Standing Committee on Therapeutic Trials (SCOTT) approval had been given. Ministerial approval would be given to the trial protocol rather than for administration to named individuals.

Appendix 2: Rapid Assessment of application to prescribe Cannabidiol product

This rapid assessment report reviews an application made by clinicians at Capital & Coast District Health Board to use a controlled drug containing cannabidiol. The Ministry of Health considers the review report and the advice it offers as confidential, free and frank advice to the Minister responsible for decisions made under the Misuse of Drugs Act 1975.

Conclusion

This application is essentially a request to allow compassionate use of Cannabidiol (CBD) in a patient with a life threatening condition in whom treatment options have been exhausted and where death is a highly likely outcome of his underlying condition. Despite the absence of clinical evidence supporting the efficacy of CBD in status epilepticus, the benefit:risk assessment for use of Elixinol in this particular patient is very weakly positive. This conclusion is driven by the severity of the underlying medical condition, the absence of any other treatment options, the low risk of significant adverse effects, and the very weak evidence supporting the use of CBD in animal studies. This conclusion is supported by reported verbal feedback from the hospital ethics committee and would be supported by the patient's family.

However, if a broader perspective is taken and use of CBD in patient management is required to make a positive contribution to the development of knowledge supporting the development of a new medical treatment, the benefit:risk assessment becomes negative once again. The product named in the application is not a pharmaceutical and its use in this patient will not add to the knowledge of the safety or efficacy of CBD in the management of refractory epilepsy.

I would support the concept that Ministerial approval of use of a medicine should take a broad perspective. In this analysis *"Autonomy, (even when supported by clinical opinion in a single case), is a backward step for medical care as it is disassociated from rigorous and unbiased study"*. The way forward for CPD as a potential treatment for refractory epilepsy is the classical pharmaceutical development model exploring the safety and efficacy. In this approach, compassionate use before proof of concept is even described for the product formulation is not supportable.

A decision to approve use of CBD for this patient does not necessarily set a precedent for approval of CBD or other cannabinoids, in the management of other medical conditions. A decision to approve use of CBD in this patient can include conditions that would limit the generalisability of the approval to exceptional cases. However, it will increase pressure on Ministerial approval to use CBD in the management of paediatric patients with refractory epilepsy.

Adoption of a clearer set of principles that include the requirement that approval of cannabinoids will only be considered when a product is on a pharmaceutical development pathway will relieve some pressure on this subject. In this approach compassionate use as proposed in this application would only be permitted after animal testing is complete and a phase one human safety study has been completed or a in a limited set of exceptional circumstances. The application as submitted fails to meet these criteria and therefore could not be supported.

What is being requested?

The application seeks permission to prescribe a product sold in the United States called Elixinol for compassionate use in an 18 year old male who has presented with New Onset Refractory Status Epilepticus (NORSE). Due to its cannabidiol content the product is a controlled drug in New Zealand and Ministerial approval to prescribe or administer the product under the Misuse of Drugs Act 1975 is required. As Elixinol is to be administered to a human being to treat or prevent refractory epilepsy, the product is also an unapproved medicine and its use is covered by the Medicines Act 1981. Section 25 of the Medicines Act allows a medical practitioner to import and administer an unapproved medicine for administration to a patient under their care without the need to obtain approval or any other licence.

What is Elixinol?

Elixinol is considered to be a food supplement in the United States of America. It is manufactured from low tetrahydrocannabinol (THC) strains of cannabis sativa organically grown in Europe. The manufacturer's website claims that it contains up to 18 percent CBD and very low levels of THC. As the strains of cannabis sativa utilised are low THC, the product is claimed to have no psychoactive effects.

The manufacturers make only general health claims for consumption of the product. There is no clinical evidence or clinical studies being undertaken with this product as far as can be ascertained. Note that Elixinol is not a form of medicinal cannabis and it can be freely sold and transported across state borders in the USA. The product is also distributed through agents in Europe and the United Kingdom. In New Zealand, however, it is considered to be a controlled drug as cannabis sativa and its active ingredients are included in the schedules of the Misuse of Drugs Act 1975.

Elixinol is not a pharmaceutical product in the USA and its quality is not assessed or assured by the US Food and Drug Administration (FDA). The manufacturing process is described on the manufacturer's website as being based on a method of super critical fluid extraction that uses no solvents. The manufacturing process claims to safely extract a wide range of cannabinoids and other active ingredients from low THC strains of cannabis sativa. I was unable to find any documentation concerning whether the manufacturing site was operating to GMP standards, however, as a food supplement it is more likely to be operating to a lesser quality standard than a pharmaceutical. It is likely that the manufacturer is subject only to state licensing and approval (as opposed to FDA approval required for a pharmaceutical). There is evidence on the website that the manufacturer is using some quality systems in its manufacturing process.

What does Elixinol contain?

The potency testing result available on the manufacturer's website indicates that Elixinol which is sold as a concentrated oil, contains approximately 18 percent CBD and <0.001 percent THC. Testing for residual solvents failed to detect anything at concentrations between 1ppm and 50ppm. These findings are consistent with the use of a Carbon Dioxide super critical fluid extraction methodology as described on the manufacturer's website.

Can we be assured by these test results?

The testing laboratory identified on the manufacturer's website is a company called Cannlabs Incorporated. The Cannlabs website describes the company as an industry leader in testing of cannabis products and its directors and scientific advisory panels and boards appear to be credible. The technical and investor material I can find on the company website states that the laboratory is providing testing and advice to several US states, and that its testing systems are validated. I could find no independent confirmation of these claims.

What is the proposed dose of Elixinol?

There are no data exploring the use of Elixinol in the management of epilepsy and I can find no clinical trial data on use of this product in the literature. The application proposes to use the dose of Elixinol described on the manufacturer's website as a food supplement of 0.5 millilitres placed under the tongue twice a day (equivalent to 180 milligrams of CBD a day). This dose is less than the 200-300 milligrams of CBD quoted in the limited number of studies published in the literature in refractory epilepsy.

What is New Onset Refractory Status Epilepticus (NORSE)?

The term NORSE is a syndromic description of a refractory status epilepticus occurring after a non-specific illness. The current clinical hypothesis is that the underlying mechanism of the condition is secondary to an underlying autoimmune mechanism ie, following a possible viral infection the patient's own immune system is mounting a response against brain tissue causing inflammation and electrical excitation leading to uncontrolled epilepsy.

Have conventional treatments been exhausted?

The patient, a previously healthy 18 year old man, first presented nearly two months ago with recurrent seizures which quickly developed into super-refractory status epilepticus. As a result he has been fully sedated and ventilated for several weeks. He has undergone aggressive treatment with a range of immunosuppressive medicines to try to decrease the auto-immune challenge and he has been tried on a number of anticonvulsant medications without sustained clinically significant effect. The consensus among clinicians and intensive care clinicians involved in looking after this patient is that all standard anticonvulsant treatments have been explored and the addition of Elixinol to the treatment the patient is receiving is worthy of exploration and will not interact with other medical treatments.

Is there evidence supporting the use of Elixinol, or CBD in NORSE?

There is anecdotal evidence of use of cannabis and high ratio CBD:THC extracts in treating refractory epilepsy. Very few well clinical trials exploring the use of well-defined and characterised cannabinoid containing products in the treatment of refractory epilepsy have been published. Studies in animals provide contradictory results. What human clinical research that has been published has tended to focus on products with ratios of CBD:THC around 20:1. These low THC studies reflect some of the animal trial data which indicates that THC also has an anticonvulsive effect and that the greatest effect is seen when both cannabinoids (CBD and THC) are present. It must be noted that use of Sativex has not been considered in this assessment as the concentrations of CBD and THC in Sativex are similar and therefore quite different from the 20:1 concentrations used in the few epilepsy studies that have been conducted.

The psychoactive nature of THC has inhibited its use in clinical trials in humans especially as the greatest clinical need was perceived to be in the management of refractory childhood epilepsy secondary to conditions such as Dravet's syndrome. While the mechanism of action of CBD on the brain remains largely unknown, its lack of psychomotor effects has led to its exploration as an anticonvulsant in refractory paediatric epilepsy. Most of this research appears to be using CBD and other actives extracted from high THC containing cannabis sativa, rather than CBD extracted from low THC strains of cannabis sativa. Currently, GW Pharmaceuticals is conducting a trial of Epidiolex a highly purified and formulated product that contains CBD and no THC in refractory paediatric epilepsy. I note that while I am unable to determine the formulation of Epidiolex, as this is a commercial secret, it appears to be derived from high THC strains of cannabis sativa, and it is highly likely to contain fixed proportions of selected substances that are active at the CBD receptor, rather than the raw mixture of all cannabidiols present in the low THC cannabis found in Elixinol. As far as can be ascertained from preliminary published results use of Epidiolex is associated with significant and prolonged seizure suppression, of up to 50 percent, across a number of the six treatment resistant variants of epilepsy included in the study population.

There is no clinical trial evidence exploring the use of cannabinoids, or CBD, in the treatment of NORSE or status epilepticus. The application refers to some animal studies exploring the use of cannabinoids in status epilepticus but the general perception from the literature appears to be that animal studies have not proven to be particularly good predictors of the effect of cannabinoids in epilepsy.

Is it ethical to use an untested food supplement to treat this patient?

The applicants have discussed the option of using Elixinol as a treatment for NORSE in this patient with the hospital ethics committee. The verbal feedback given is: given that no treatment has yet been successful in a sustained manner, the use of this kind of medication in other epilepsy syndromes and the family's strongly held belief and support for use of CBD, then the treatment could be considered ethically appropriate. The ethics advice however was stressed to be specific to this particular situation and not a wider endorsement of use of cannabinoids in a wider range of clinical situations.

Cillo et al 2014 in a recent review assessing cannabidiol in epilepsy (Epilepsia, 55(6):787-790, 2014) touches on the issue of compassionate or autonomous use of CBD in refractory epilepsy and states that supporting this position is not a compelling argument in her opinion. Indeed she states that "Autonomy is a backward step for medical care if it becomes disassociated from rigorous and unbiased study". She then strongly argues that "patients, families and medical community need objective and unbiased data on safety and efficacy to endorse a new drug to treat epilepsy". Cillo then sets out a classic framework for product development setting out the steps required to fully explore the safety and efficacy of CBD as an anticonvulsant. Compassionate use is not a feature of her development framework.

This issues raised by Cillo in her article are relevant with respect to this application as the product (Elixinol) is not being developed as a pharmaceutical, has no supportive evidence of its efficacy and it seems unlikely that its manufacturers will establish a clinical trial programme to support its clinical development. Use of Elixinol in the management of this patient is outside the scope of the clinical research currently being undertaken, and will not contribute meaningful clinical data to the pool of scientific research on the safety or efficacy of cannabinoids in epilepsy.

What is current Government policy on the medical use of cannabinoids?

The Misuse of Drugs Act requires prescribers to seek Ministerial approval to prescribe a cannabinoid to treat a patient under their care. Government policy over many years has been that the use of unprocessed or partially-processed cannabis is not permitted. The result of this policy position being that only cannabinoids that are approved as pharmaceuticals by a competent recognised medicines regulator, or which are being developed as pharmaceuticals and the application is to enrol the patient in a clinical trial, can be considered and potentially supported.

This application seeks Ministerial approval for a product that does not meet the current criteria that the product be a pharmaceutical. Approval of the application would therefore potentially be precedent setting. As I am aware that several parents and paediatricians have expressed interest in obtaining high CBD products for the management of paediatric patients with refractory epilepsy, it is highly likely that other applications for Elixinol, or similar products, for the management of epilepsy (and or other medical conditions) will be submitted in the near future, irrespective of the outcome of this application.

What is the benefit:risk assessment for this product?

From a narrow clinical perspective focussed on use in the patient in the application, there is:

a) no human evidence that Elixinol, or CBD, is an effective treatment for status epilepticus or NORSE. While there are some animal data, it is not clear whether these animal results can be applied to Elixinol as the concentrations and characterisation of the THC and CBD used in these animal studies appear to be significantly different from that found in Elixinol. Human research involving the use of CBD in refractory paediatric epilepsy is really only beginning and the safety and efficacy of CBD, including the optimum dose and which types of seizure respond to CBD treatment, remains largely unexplored. The best and highest quality research available is the Epidiolex research programme and compassionate use programme in the United States. The formulation of cannabinoids present in Epidiolex is likely to be significantly different from that found in Elixinol and the results of the research for Epidiolex probably cannot be extrapolated to provide support for efficacy of Elixinol. It should be noted, however, that previous attempts to obtain Epidiolex from its manufacturer for other paediatric refractory epilepsy have been unsuccessful;

b) evidence that the administration of CBD to humans at the doses proposed in the application is well tolerated and unlikely to produce significant adverse effects. The clinicians supporting the application state that they do not consider the addition of Elixinol to the patient's treatment regimen is likely to interact with the existing medicines being administered or cause any measurable harm. The clinical risk of commencing this medicine is therefore assessed as being low.

The initial benefit:risk assessment is therefore negative, as there is no evidence of benefit, and evidence of potential mostly minor adverse effects.

However, to make a more definitive benefit:risk assessment the clinical condition of the patient who has ongoing intractable status epilepticus and the failure of all other treatment options needs to be taken into consideration. When these factors along with the: clinical support to commence treatment with CBD (which is peer supported); positive ethical opinion, and the strong family support for exploring experimental treatments, are taken into consideration the overall benefit:risk assessment changes to being very weakly positive.

Despite the absence of clinical evidence supporting efficacy in status epilepticus, this change in benefit:risk is driven by the severity of the underlying medical condition, the absence of any other treatment options, the low risk of significant adverse effects, and the very weak evidence of anticonvulsant effects of cannabinoids and of CBD in animal studies. In line with the conclusion of the hospital ethics committee I think that from an individual patient perspective, Elixinol can be administered to this patient while complying with the principal of "non-maleficence".

However, the balance of evidence is very thinly in favour of use only when the decision to treat is considered from an individual patient perspective. When a broader clinical view is taken and consideration of the issues raised by Cillo et al is added the overall benefit:risk assessment becomes negative. This change occurs because the product proposed for use in this application is not a pharmaceutical in development, and its use in this case will not move the science forward or provide clinical trial evidence supporting the safety and efficacy of CBD in the treatment of epilepsy. I would support and extend the argument put forward by Cillo that *"Autonomy, (even when supported by clinical opinion in a single case), is a backward step for medical care if it becomes disassociated from rigorous and unbiased study"*. The way forward for CPD as a potential treatment for refractory epilepsy is the classical pharmaceutical development model exploring the safety and efficacy. In this model, compassionate use before proof of concept is even described for the product formulation is not supportable.

Is there sufficient evidence to change current Government policy on medicinal use of cannabis?

This application is essentially a request to allow compassionate use of CBD in a patient with a life threatening condition in whom treatment options have been exhausted and where death is a highly likely outcome of his underlying condition. Approval to use CBD in these circumstances does not necessarily set a precedent for approval of CBD, or other cannabinoids, in the management of other medical conditions. A decision to approve use of CBD in this patient can include conditions that would limit the generalisability of the approval to exceptional cases. However, it will increase pressure on the Ministerial approval system in some specific cases.

The most likely effect of approval of this application is the submission of other applications to use CBD in children with refractory epilepsy. These submissions will be for children with Dravet's Syndrome, and other refractory epilepsies, where treatment options have been exhausted, the children are suffering multiple seizures every day to the point that the quality of their life is severely affected and their risk of sudden death in epilepsy is significantly increased.

If the same benefit:risk assessment, described above, was to be applied to these applications, the assessment would also be positive. Indeed given there is more research supporting use of CBD in refractory paediatric epilepsy the outcome of the assessment would be more positive than that set out above for this patient with NORSE.

The challenge of expanding use of CBD and cannabinoid containing products can be managed to some extent by adopting a clear set of criteria for consideration. These criteria could include the principals that use of cannabinoids can only be approved: when the manufacturer has demonstrated a commitment to develop the product as a pharmaceutical; the product characteristics and formulation are clearly described and defined; the product has completed animal studies demonstrating proof of

concept and potential clinical benefit; and the proposed use of the product is within an appropriately designed clinical study. Compassionate use of a product that has not reached Phase II clinical studies would not be permitted.

Dr Stewart S Jessamine
Acting Director of Public Health

MINISTRY OF HEALTH
MANATŪ HAUORA

Health Report number: 20150878
File number: MC04-01-1
Action required by: urgent

Ministerial Approval to Prescribe and Import Cannabidiol Oil

To: Hon Peter Dunne, Associate Minister of Health

Copy to: Hon Dr Jonathan Coleman, Minister of Health

Purpose

This report requests your decision as to whether ministerial approval under the Misuse of Drugs Act 1975 is granted for an application to prescribe and import a cannabidiol oil product, Elixinol, following an application from the Deputy Chief Medical Officer, Capital and Coast District Health Board.

Key points

- The Ministry has received an application from Dr Grant Pidgeon, Deputy Chief Medical Officer, Capital and Coast District Health Board for ministerial approval to prescribe and import an oil containing a cannabis constituent cannabidiol for administration to a patient.
- Cannabidiol (CBD) is a Class B1 controlled drug.
- Ministerial approval is required to prescribe, administer and import CBD.
- CBD is a constituent of cannabis with little or no psychoactive effect that has been indicated to have anticonvulsant and other effects.
- No pharmaceutical grade products containing CBD alone are available commercially, though a clinical trial of a product is underway in the United States.
- Medical practitioners can prescribe non-pharmaceutical grade products for patients under their care but the Class B1 controlled drug classification of CBD means that ministerial approval must first be provided.
- Ministerial approval is also required for a licence to import CBD.
- A food grade product called Elixinol with a high CBD level and low THC level has been identified by the applicant. This is not a pharmaceutical grade product nor has it undergone clinical trials
- A Certificate of Analysis is available
- A Rapid Assessment of the application to prescribe Cannabidiol has been prepared by Ministry clinicians and the draft supplied to you. The final version is attached as appendix 1.
- Government policy has been that it does not support the use of unprocessed or partially processed cannabis preparations but supports the use of pharmaceutical grade cannabinoid products such as Sativex®.
- Ministerial approval to allow the administration of this product would be outside current stated government policy.
- We are aware of other potential applications to prescribe and import processed cannabis in particular for the treatment of intractable childhood epilepsy such as Dravet's syndrome.
- Criteria that can be used to define exceptional circumstances in which compassionate approval may be granted will be developed by the Ministry.

Contacts:	Dr Stewart Jessamine, Group Manager Medsafe and Acting Director of Public Health	021 650 278
	Michael Haynes, Team Leader, Medicines Control	027 274 4851

Health Report number: 20150878

Ministerial Approval to Prescribe and Import Cannabidiol Oil

Recommendations

The Ministry recommends that you:

a) **Note** the Rapid Assessment of application to prescribe cannabidiol product report in Appendix 1 — Yes / No

b) **Agree** that a broad perspective should be taken with respect to this application — Yes / No

c) **Agree** that approval should not be granted as the application will not make a positive contribution to the evidence base supporting the development of cannabinoids as a treatment for refractory epilepsy — Yes / No

d) **Agree** that a patient centred perspective to ministerial approval of this application is appropriate — Yes / No

e) **Agree** that the circumstances surrounding this application are very exceptional and compassionate use of this product can be given — Yes / No

f) **Agree** to grant ministerial approval to prescribe and administer Elixinol for Alex Renton for compassionate purposes. Ministerial approval to allow import of Elixinol is also granted. — Yes / No

Dr Stewart Jessamine
Acting Chief Medical Officer
Clinical Leadership, Protection & Regulation

Minister's signature

Date: 9.06.15

Health Report number: 20150878

Ministerial Approval to Prescribe and Import Cannibidiol Oil

Application

1. The applicant is Dr Grant Pidgeon, Deputy Chief Medical Officer, Capital and Coast District Health Board. The patient is Mr Alex Renton, a 18 year old male who had been otherwise healthy until he presented to Nelson Hospital two months ago with recurrent seizures. He subsequently developed super-refractory status epilepticus. He has the working diagnosis of New Onset Refractory Status Epilepticus (NORSE).
2. He is now fully sedated and ventilated. Treatments of the most likely autoimmune mechanism of the illness and with various antiepileptic medicines plus a ketogenic diet have been unable to establish any control over Alex's refractory multifocal seizures.
3. His family hold strong beliefs in the value of complementary healing mechanisms. They have researched cannabinoids and believe cannabidiol may be of use in Alex's situation.
4. DHB staff have consulted widely and believe that given the refractory nature of the seizures and the inability to attain adequate seizure control with the agents that have been trialled, an alternative and unproven treatment as requested by the family could be considered.
5. The DHB believe that Elixinol is not likely to cause harm and will not interfere with any other aspect of Alex's care in the Intensive Care Unit.
6. As with the administration of any non-approved product or the use of an approved product for a non-approved condition, the prescriber has taken responsibility for gaining informed consent from the guardian and takes responsibility for administering the product and subsequent care of the patient.

Ministerial Approval

7. CBD extract is classed as a B1 controlled drug under the Misuse of Drugs Act 1975 (the Act). Regulation 22 of the Misuse of Drugs Regulations 1977 requires ministerial approval to supply, prescribe, administer or import any substance listed in Parts 1 and 2 of Schedule B and Part 1 of Schedule C of the Act.
8. Ministerial approval is delegated to the Director-General of Health, the Manager Provider Regulation (currently vacant) and the Team Leader Medicines Control.
9. Applications for ministerial approval are assessed by Dr Stewart Jessamine and peer reviewed by other clinicians within the Ministry.
10. In the normal course of events for a medicine requiring ministerial approval, if a recommendation is made by Ministry clinicians that the application is clinically appropriate and justifed, ministerial approval to prescribe will be granted by the Ministry, usually with a requirement for baseline measures and for a limited period of time. Re-application at the end of the time frame will result in consideration of evidence of efficacy and safety and may result in an extended period of approval.
11. Following ministerial approval to prescribe, ministerial approval to issue an import licence, if necessary, would then follow.
12. The prescriber intends to import this product from the United States. Export documentation will have to be obtained from the United States however the Elixinol website states that it is approved under tariff codes as a directory supplement and can be shipped to other countries. In New Zealand an import licence will be required as it is a controlled drug.

The Cannabidiol Product

13. The Certificate of Analysis on the Elixinol website states that it has a CBD concentration of approximately 18% and a THC concentration of <0.001%. Testing for residual solvents failed to detect anything above the stated limits of 1ppm to 50ppm for the solvents tested.

14. The applicant proposes to use the dosage described on the website of 0.5ml placed under the tongue, twice daily which is equivalent to 180 mg of CBD daily.

15. The use of Sativex®, the only pharmaceutical grade cannabis preparation approved for distribution in New Zealand, has been discounted because of the sedative effects of the tetrahydrocannabinol (THC) that it contains. Sativex®, a spray applied to the oral mucosa, has a CBD concentration of 2.5% and a THC concentration of 2.7%.

16. GW Pharma Ltd is currently undertaking a trial of formulations of cannabidiol in children who have difficult to treat epilepsy. Results have not yet been published and it is not possible to obtain the trial formulations in New Zealand.

Risks of Providing Approval to Prescribe

17. If ministerial approval to prescribe, administer and import is granted this will be the first time that such approval has been given for a non-consented cannabis product for a medicinal purpose.

18. Ministerial approval would not be within current stated policy.

19. An approval is likely to result in pressure to approve the import, prescribing and administration of other similar non-consented, non-pharmaceutical grade cannabis preparations.

20. The Ministry is aware of a potential further potential application from a prescriber for a child with refractory generalised epilepsy (Dravet's syndrome).

Clinical Assessment of the Application

21. An assessment of the application by Ministry clinicians has been provided to you in a draft format. The final assessment is provided as Appendix 1.

Compassionate/Exceptional Circumstances Criteria

22. All applications for ministerial approval are considered on a case by case basis.

23. The Ministry will work to develop criteria against which further applications for the use of non-pharmaceutical grade, unapproved cannabis or other preparations can be assessed.

24. Circumstances of the patient that may be considered include whether:

    a. the patient is hospitalised in intensive care

    b. the condition is life threatening

    c. all other treatments have been explored.

25. The Victorian Law Reform Commission was asked to review and report on options for changes to their legislation to allow people to be treated with medicinal cannabis in exceptional circumstances.

26. In their issues paper Medical Cannabis, published in March 2015, they note that if strict criteria of evidence-based medicine be applied at this stage, the scope for the therapeutic prescription of cannabis product would be relatively confined. They state that it is important and humane that unrealistic expectations are not created and departure from the principles of evidence based medicine should only take place when the potential benefits outweigh potential risks, dangers and side effects.

27. The Commission has suggested the following considerations as to whether there are exceptional circumstances:

    a. the circumstances of the patient

    b. the state of clinical knowledge about the efficacy of using cannabis to treat the patient's condition.

Further Information on Medicinal Cannabis

28. Health Report, number 20150106A, previously provided to you in February 2014 is attached for further information as Appendix 2.

END.

Appendix 1

Rapid Assessment of application to prescribe Cannabidiol product

This rapid assessment report reviews an application made by clinicians at CCDHB to use a controlled drug containing cannabidiol. The Ministry of Health considers the review report and the advice it offers as confidential, free and frank advice to the Minister responsible for decisions made under the Misuse of Drugs Act 1975.

Conclusion

This application is essentially a request to allow compassionate use of CBD in a patient with a life threatening condition in whom treatment options have been exhausted and where death is a highly likely outcome of his underlying condition. Despite the absence of clinical evidence supporting the efficacy of Cannabidiol (CBD) in status epilepticus, the benefit:risk assessment for use of Elixinol in this particular patient is very weakly positive. This conclusion is driven by the severity of the underlying medical condition, the absence of any other treatment options, the low risk of significant adverse effects, and the very weak evidence supporting the use of CBD in animal studies. This conclusion is supported by reported verbal feedback from the hospital ethics committee and would be supported by the patient's family.

However, if a broader perspective is taken and use of CBD in patient management is required to make a positive contribution to the development of knowledge supporting the development of a new medical treatment, the benefit:risk assessment becomes negative once again. The product named in the application is not a pharmaceutical and its use in this patient will not add to the knowledge of the safety or efficacy of CBD in the management of refractory epilepsy.

I would support the concept that Ministerial approval of use of a medicine should take a broad perspective. In this analysis "Autonomy, *(even when supported by clinical opinion in a single case)*, is a backward step for medical care as it is disassociated from rigorous and unbiased study". The way forward for CPD as a potential treatment for refractory epilepsy is the classical pharmaceutical development model exploring the safety and efficacy. In this approach, compassionate use before proof of concept is even described for the product formulation is not supportable.

A decision to approve use of CBD for this patient does not necessarily set a precedent for approval of CBD, or other cannabinoids, in the management of other medical conditions. A decision to approve use of CBD in this patient can include conditions that would limit the generalisability of the approval to exceptional cases. However, it will increase pressure on Ministerial approval to use CBD in the management of paediatric patients with refractory epilepsy.

Adoption of a clearer set of principles that include the requirement that approval of cannabinoids will only be considered when a product is on a pharmaceutical development pathway will relieve some pressure on this subject. In this approach compassionate use as proposed in this application would only be permitted after animal testing is complete and a phase I human

safety study has been completed or a in a limited set of exceptional circumstances. The application as submitted fails to meet these criteria and therefore could not be supported.

What is being requested?

The application seeks permission to prescribe a product sold in the United States called Elixinol for compassionate use in an 18 year old male who has presented with New Onset Refractory Status Epilepticus (NORSE). Due to its cannabidiol content the product is a controlled drug in New Zealand and Ministerial approval to prescribe or administer the product under the Misuse of Drugs Act 1975 is required. As Elixinol is to be administered to a human being to treat or prevent refractory epilepsy, the product is also an unapproved medicine and its use is covered by the Medicines Act 1981. Section 25 of the Medicines Act allows a medical practitioner to import and administer an unapproved medicine for administration to a patient under their care without the need to obtain approval or any other licence.

What is Elixinol?

Elixinol is considered to be a food supplement in the United States of America. It is manufactured from low THC strains of cannabis sativa organically grown in Europe. The manufacturer's website claims that it contains up to 18% Cannabidiol (CBD) and very low levels of Tetrahydrocannabidiol (THC). As the strains of cannabis sativa utilised are low THC, the product is claimed to have no psychoactive effects.

The manufacturers make only general health claims for consumption of the product. There is no clinical evidence or clinical studies being undertaken with this product as far as can be ascertained. Note that Elixinol is not a form of medicinal cannabis and it can be freely sold and transported across state borders in the USA. The product is also distributed through agents in Europe and the United Kingdom. In New Zealand, however, it is considered to be a controlled drug as cannabis sativa and its active ingredients are included in the schedules of the Misuse of Drugs Act 1975.

Elixinol is not a pharmaceutical product in the USA and its quality is not assessed or assured by the US FDA. The manufacturing process is described on the manufacturer's website as being based on a method of super critical fluid extraction that uses no solvents. The manufacturing process claims to safely extract a wide range of cannabinoids and other active ingredients from low THC strains of cannabis sativa. I was unable to find any documentation concerning whether the manufacturing site was operating to GMP standards, however, as a food supplement it is more likely to be operating to a lesser quality standard than a pharmaceutical. It is likely that the manufacturer is subject only to state licensing and approval (as opposed to FDA approval required for a pharmaceutical). There is evidence on the website that the manufacturer is using some quality systems in its manufacturing process.

What does Elixinol contain?

The potency testing result available on the manufacturer's website indicates that Elixinol which is sold as a concentrated oil, contains approximately 18% CBD and <0.001% THC. Testing for residual solvents failed to detect anything at concentrations between 1ppm and 50ppm. These findings are consistent with the use of a Carbon Dioxide super critical fluid extraction methodology as described on the manufacturer's website.

Can we be assured by these test results?
The testing laboratory identified on the manufacturer's website is a company called Cannlabs Inc. The Cannlabs website describes the company as an industry leader in testing of cannabis products and its directors and scientific advisory panels and boards appear to be credible. The technical and investor material I can find on the company website states that the laboratory is providing testing and advice to several US states, and that its testing systems are validated. I could find no independent confirmation of these claims.

What is the proposed dose of Elixinol?
There are no data exploring the use of Elixinol in the management of epilepsy and I can find no clinical trial data on use of this product in the literature. The application proposes to use the dose of Elixinol described on the manufacturer's website as a food supplement of 0.5ml placed under the tongue twice a day (equivalent to 180mg of CBD a day). This dose is less than the 200-300mg of CBD quoted in the limited number of studies published in the literature in refractory epilepsy.

What is New Onset Refractory Status Epilepticus (NORSE)?
The term NORSE is a syndromic description of a refractory status epilepticus occurring after a non-specific illness. The current clinical hypothesis is that the underlying mechanism of the condition is secondary to an underlying autoimmune mechanism i.e following a possible viral infection the patient's own immune system is mounting a response against brain tissue causing inflammation and electrical excitation leading to uncontrolled epilepsy.

Have conventional treatments been exhausted?
The patient, a previously healthy 18yr old man, first presented nearly two months ago with recurrent seizures which quickly developed into super-refractory status epilepticus. As a result he has been fully sedated and ventilated for several weeks. He has undergone aggressive treatment with a range of immunosuppressive medicines to try to decrease the auto-immune challenge and he has been tried on a number of anticonvulsant medications without sustained clinically significant effect. The consensus among clinicians and intensive care clinicians involved in looking after this patient is that all standard anticonvulsant treatments have been explored and the addition of Elixinol to the treatment the patient is receiving is worthy of exploration and will not interact with other medical treatments.

Is there evidence supporting the use of Elixinol, or CBD in NORSE?
There is anecdotal evidence of use of cannabis and high ratio CBD:THC extracts in treating refractory epilepsy. Very few well clinical trials exploring the use of well-defined and characterised cannabinoid containing products in

the treatment of refractory epilepsy have been published. Studies in animals provide contradictory results. What human clinical research that has been published has tended to focus on products with ratios of CBD:THC around 20:1. These low THC studies reflect some of the animal trial data which indicates that THC also has an anticonvulsive effect and that the greatest effect is seen when both cannabinoids (CBD and THC) are present. It must be noted that use of Sativex has not been considered in this assessment as the concentrations of CBD and THC in Sativex are similar and therefore quite different from the 20:1 concentrations used in the few epilepsy studies that have been conducted.

The psychoactive nature of THC has inhibited its use in clinical trials in humans especially as the greatest clinical need was perceived to be in the management of refractory childhood epilepsy secondary to conditions such as Dravet's syndrome. While the mechanism of action of CBD on the brain remains largely unknown, its lack of psychomotor effects has led to its exploration as an anticonvulsant in refractory paediatric epilepsy. Most of this research appears to be using CBD and other actives extracted from high THC containing cannabis sativa, rather than CBD extracted from low THC strains of cannabis sativa. Currently GW Pharmaceuticals is conducting a trial of Epidiolex a highly purified and formulated product that contains CBD and no THC in refractory paediatric epilepsy. I note that while I am unable to determine the formulation of Epidiolex, as this is a commercial secret, it appears to be derived from high THC strains of cannabis sativa, and it is highly likely to contain fixed proportions of selected substances that are active at the CBD receptor, rather than the raw mixture of all cannabidiols present in the low THC cannabis found in Elixinol. As far as can be ascertained from preliminary published results use of Epidiolex is associated with significant and prolonged seizure suppression, of up to 50%, across a number of the six treatment resistant variants of epilepsy included in the study population.

There is no clinical trial evidence exploring the use of cannabinoids, or CBD, in the treatment of NORSE or status epilepticus. The application refers to some animal studies exploring the use of cannabinoids in status epilepticus but the general perception from the literature appears to be that animal studies have not proven to be particularly good predictors of the effect of cannabinoids in epilepsy.

Is it ethical to use an untested food supplement to treat this patient?
The applicants have discussed the option of using Elixinol as a treatment for NORSE in this patient with the hospital ethics committee. The verbal feedback given is: given that no treatment has yet been successful in a sustained manner, the use of this kind of medication in other epilepsy syndromes and the family's strongly held belief and support for use of CBD, then the treatment could be considered ethically appropriate. The ethics advice however was stressed to be specific to this particular situation and not a wider endorsement of use of cannabinoids in a wider range of clinical situations.

Cillo et al in a recent review assessing cannabidiol in epilepsy (Epilepsia, 55(6):787-790, 2014) touches on the issue of compassionate or autonomous

use of CBD in refractory epilepsy and states that supporting this position is not a compelling argument in her opinion. Indeed she states that "Autonomy is a backward step for medical care if it becomes disassociated from rigorous and unbiased study". She then strongly argues that "patients, families and medical community need objective and unbiased data on safety and efficacy to endorse a new drug to treat epilepsy". *Cillo* then sets out a classic framework for product development setting out the steps required to fully explore the safety and efficacy of CBD as an anticonvulsant. Compassionate use is not a feature of her development framework.

This issues raised by *Cillo* in her article are relevant with respect to this application as the product (Elixinol) is not being developed as a pharmaceutical, has no supportive evidence of its efficacy and it seems unlikely that its manufacturers will establish a clinical trial programme to support its clinical development. Use of Elixinol in the management of this patient is outside the scope of the clinical research currently being undertaken, and will not contribute meaningful clinical data to the pool of scientific research on the safety or efficacy of cannabinoids in epilepsy.

What is current Government policy on the medical use of cannabinoids?
The Misuse of Drugs Act requires prescribers to seek Ministerial approval to prescribe a cannabinoid to treat a patient under their care. Government policy over many years has been that the use of unprocessed or partially-processed cannabis is not permitted. The result of this policy position being that only cannabinoids that are approved as pharmaceuticals by a competent recognised medicines regulator, or which are being developed as pharmaceuticals and the application is to enrol the patient in a clinical trial, can be considered and potentially supported.

This application seeks Ministerial approval for a product that does not meet the current criteria that the product be a pharmaceutical. Approval of the application would therefore potentially be precedent setting. As I am aware that several parents and paediatricians have expressed interest in obtaining high CBD products for the management of paediatric patients with refractory epilepsy, it is highly likely that other applications for Elixinol, or similar products, for the management of epilepsy (and or other medical conditions) will be submitted in the near future, irrespective of the outcome of this application.

What is the benefit:risk assessment for this product?
From a narrow clinical perspective focussed on use in the patient in the application, there is:

- no human evidence that Elixinol, or CBD, is an effective treatment for status epilepticus or NORSE. While there are some animal data, it is not clear whether these animal results can be applied to Elixinol as the concentrations and characterisation of the THC and CBD used in these animal studies appear to be significantly different from that found in Elixinol. Human research involving the use of CBD in refractory paediatric epilepsy is really only beginning and the safety and efficacy of CBD, including the optimum dose and which types of seizure

respond to CBD treatment, remains largely unexplored. The best and highest quality research available is the Epidiolex research programme and compassionate use programme in the United States. The formulation of cannabinoids present in Epidiolex is likely to be significantly different from that found in Elixinol and the results of the research for Epidiolex probably cannot be extrapolated to provide support for efficacy of Elixinol. It should be noted, however, that previous attempts to obtain Epidiolex from its manufacturer for other paediatric refractory epilepsy have been unssucessful;

- evidence that the administration of CBD to humans at the doses proposed in the application is well tolerated and unlikely to produce significant adverse effects. The clinicians supporting the application state that they do not consider the addition of Elixinol to the patient's treatment regimen is likely to interact with the existing medicines being administered or cause any measurable harm. The clinical risk of commencing this medicine is therefore assessed as being low;

The initial benefit:risk assessment is therefore negative, as there is no evidence of benefit, and evidence of potential mostly minor adverse effects.

However, to make a more definitive benefit:risk assessment the clinical condition of the patient who has ongoing intractable status epilepticus and the failure of all other treatment options needs to be taken into consideration. When these factors along with the: clinical support to commence treatment with CBD (which is peer supported); positive ethical opinion, and the strong family support for exploring experimental treatments, are taken into consideration the overall benefit:risk assessment changes to being very weakly positive.

Despite the absence of clinical evidence supporting efficacy in status epilepticus, this change in benefit:risk is driven by the severity of the underlying medical condition, the absence of any other treatment options, the low risk of significant adverse effects, and the very weak evidence of anticonvulsant effects of cannabinoids and of CBD in animal studies. In line with the conclusion of the hospital ethics committee I think that from an individual patient perspective, Elixinol can be administered to this patient while complying with the principal of "non-maleficence".

However, the balance of evidence is very thinly in favour of use only when the decision to treat is considered from an individual patient perspective. When a broader clinical view is taken and consideration of the issues raised by Cillo et al is added the overall benefit:risk assessment becomes negative. This change occurs because the product proposed for use in this application is not a pharmaceutical in development, and its use in this case will not move the science forward or provide clinical trial evidence supporting the safety and efficacy of CBD in the treatment of epilepsy. I would support and extend the argument put forward by Cillo that "Autonomy, *(even when supported by clinical opinion in a single case)*, is a backward step for medical care if it becomes disassociated from rigorous and unbiased study". The way forward

for CPD as a potential treatment for refractory epilepsy is the classical pharmaceutical development model exploring the safety and efficacy. In this model, compassionate use before proof of concept is even described for the product formulation is not supportable.

Is there sufficient evidence to change current Government policy on medicinal use of cannabis?

This application is essentially a request to allow compassionate use of CBD in a patient with a life threatening condition in whom treatment options have been exhausted and where death is a highly likely outcome of his underlying condition. Approval to use CBD in these circumstances does not necessarily set a precedent for approval of CBD, or other cannabinoids, in the management of other medical conditions. A decision to approve use of CBD in this patient can include conditions that would limit the generalisability of the approval to exceptional cases. However, it will increase pressure on the Ministerial approval system in some specific cases.

The most likely effect of approval of this application is the submission of other applications to use CBD in children with refractory epilepsy. These submissions will be for children with Dravet's syndrome, and other refractory epilepsies, where treatment options have been exhausted, the children are suffering multiple seizures every day to the point that the quality of their life is severely affected and their risk of sudden death in epilepsy is significantly increased.

If the same benefit:risk assessment, described above, was to be applied to these applications, the assessment would also be positive. Indeed given there is more research supporting use of CBD in refractory paediatric epilepsy the outcome of the assessment would be more positive than that set out above for this patient with NORSE.

The challenge of expanding use of CBD and cannabinoid containing products can be managed to some extent by adopting a clear set of criteria for consideration. These criteria could include the principals that use of cannabinoids can only be approved: when the manufacturer has demonstrated a commitment to develop the product as a pharmaceutical; the product characteristics and formulation are clearly described and defined; the product has completed animal studies demonstrating proof of concept and potential clinical benefit; and the proposed use of the product is within an appropriately designed clinical study. Compassionate use of a product that has not reached Phase II clinical studies would not be permitted.

Dr Stewart S Jessamine
Acting Director of Public Health

MINISTRY OF HEALTH
MANATŪ HAUORA

DISPATCHED

Health Report number: 20150106
File number: AD10-05-1
Action required by: routine

Medicinal Cannabis

To:	Hon Dr Jonathan Coleman (Minister of Health)
Copy to:	Hon Peter Dunne (Associate Minister of Health)

Purpose

This paper responds to your request for a briefing on medicinal cannabis, international developments and possible next steps.

Key points

- Medicinal cannabis means one of two things: a pharmaceutical grade cannabinoid medicine; or an unprocessed or partially-processed cannabis product (eg. leaf cannabis) used for medicinal purposes.
- New Zealand regulates medicinal cannabis products as medicines and requires robust evidence of safety and efficacy. To date the only cannabinoid medicine available in New Zealand is Sativex. Approval to prescribe Sativex has been given for 48 patients.
- Of the patients who have been prescribed Sativex, two patients have been funded by ACC and the remainder are self-funding. Sativex is not currently funded by PHARMAC and costs approximately $1000 per month per patient.
- It is difficult to quantify the level of unmet need for access to Sativex by patients who would clinically benefit. Some patients whose prescribers have approval to prescribe Sativex have not filled the prescription it is likely that other patients' prescribers have not even applied due to the cost of the drug, and the administrative burden.
- Despite the lack of robust clinical data and evidence of patient benefit a number of jurisdictions permit personal use of unprocessed or partially-processed cannabis products on compassionate grounds.
- The Australian states of New South Wales and Victoria have announced initiatives which signal a move towards permitting personal use of unprocessed or partially-processed cannabis products for particular patient groups such as, adults with a terminal illness or AIDS.
- The Ministry's project to review legitimate uses of controlled drugs will review the current regulation of controlled drug therapies, potentially including cannabis-based medicines.

Contacts Paula Martin, Acting DDG, Policy Business Unit 021 825 691
Hannah Cameron, Manager, Sector & Services Policy 021 783 574

Paula Martin
Acting Deputy Director-General
Policy Business Unit

Minister's signature

Date: 4.2.15.

Minister's feedback on quality of report

Very poor (1)	Poor (2)	Neutral (3)	Good (4)	Very good (5)

Medicinal Cannabis

1. There are two approaches for regulation of cannabis products for medicinal purposes. The first is the approved medicines route where safety and efficacy standards are required, as for any pharmaceutical product.

2. A second approach is to permit personal use of unprocessed or partially-processed cannabis products (eg. leaf cannabis), for people with particular medical conditions. Unprocessed or partially-processed cannabis products do not meet the approved medicines requirements because of the lack of clinical data showing safety and efficacy, and the challenges with controlling the dose or potency.

3. Government policy is that the use of unprocessed or partially-processed cannabis is not permitted. Only a cannabinoid pharmaceutical such as Sativex could be approved for therapeutic use. This is consistent with the approach in the United Kingdom.

Approved medicines route

4. Approval and access to controlled drug products in New Zealand has three aspects.

   a. *Approval of the medicine by Medsafe.* This involves assessment of the safety and efficacy of medicines and compliance with a quality manufacturing process. Medicines are approved for a particular set of indications, but for many drugs there are other recognised indications not applied for in New Zealand. Controlled drug products require licences for import and supply (to protect the supply chain from diversion for illicit uses).

   b. *A prescriber who has the ability to prescribe the medicine.* Some controlled drugs require Ministerial approval prior to a prescription being written. For some drugs, a general permission has been issued to prescribe under certain conditions for example, pseudoephedrine can be prescribed by medical practitioners.

   c. *Funding* of the medicine via PHARMAC, ACC or privately by the individual patient.

Sativex

5. There is currently a very limited range of cannabinoid medicines being produced by pharmaceutical companies. To date Sativex, a medicine which contains a fixed combination of two of the active ingredients derived from cannabis, is the only approved cannabinoid medicine available in New Zealand. Sativex is approved to treat extreme spasticity linked with multiple sclerosis. Approval to prescribe Sativex is considered on a case-by-case basis.

6. To date, the Ministry has considered 49 applications to prescribe Sativex for multiple sclerosis and a variety of off-label conditions including chronic pain and Dravet Syndrome. Approval has been given for 48 patients, two of which are children (a third application for a child has been received and is currently being processed). Of the 48 approvals given to date, two of patients have been funded by ACC, all other patients are self-funding their treatment.

7. Sativex is not currently funded by PHARMAC and costs approximately $1000 per month per patient. Under PHARMAC's Named Patient Pharmaceutical Assessment (NPPA) policy applications can be made for funded treatment for an individual, outside of the Schedule decision-making process. PHARMAC has received eight NPPA applications for Sativex, none of which have been successful.

NZ requirements for clinical trials of medicinal cannabis

8. The Ministry of Health is not aware of any application to date to run a medicinal cannabis clinical trial in New Zealand. The rules to conduct a clinical trial of a medicinal cannabis in New Zealand are the same as that required for any clinical trial but with the additional requirements of licences and Ministerial approval.

9. The Law Commission's 2011 Report on the Misuse of Drugs Act recommended that the Government consider undertaking or supporting clinical trials into the efficacy of raw cannabis for pain relief. The Government's 2011 response stated that while it didn't oppose genuine research it

didn't believe it was the Government's role to actively initiate or support such trials. This response does not however, preclude researchers applying for funding for medicinal cannabis clinical trials from the Health Research Council and the Marsden Fund, or other entities, such as NGOs.

Findings from overseas medicinal cannabis clinical trials

10. To date clinical trials of unprocessed or partially-processed cannabis products have suffered from limited participant numbers and lack of data on long term effects. Results can't be compared across trials because they have used different products in different patient groups.

11. A 2013 review of randomised controlled trials of any cannabis intervention in adults with HIV or AIDS, compared with placebo or with a known effective treatment concluded that evidence for the efficacy and safety of cannabis and cannabinoids is lacking.

12. A 2012 review of medicinal cannabis research supported by the Center for Medicinal Cannabis Research at the University of California, concluded that evidence is accumulating that cannabinoids may be useful medicine for certain indications.

Access to unprocessed or partially-processed medicinal cannabis products overseas

13. The countries that allow the medicinal use of unprocessed or partially-processed cannabis include: Belgium, the Czech Republic, The Netherlands, Israel, Canada, and 20 States of the United States of America and the District of Columbia. In some cases, such as The Netherlands and Israel, provision is made for the prescription of a pharmaceutical grade leaf cannabis product. In other countries, such as the USA, people are allowed to join "compassion clubs" to buy small quantities of raw leaf cannabis or to cultivate a small number of plants.

14. These jurisdictions have, in one form or other, decriminalised use of unprocessed or partially-processed cannabis products for personal medicinal use. There are different parameters around the range of health conditions where cannabis use is permitted and different regulatory approaches to production, supply and possession.

Australian developments

15. There have been a number of recent developments in Australia signalling a move towards permitting the medicinal use of unprocessed or partially-processed cannabis.

16. A 2013 New South Wales Senate General Purpose Standing Committee report into the use of cannabis for medicinal purposes recommended that access to cannabis pharmacotherapies continue via the current regulatory regime (ie. through the Therapeutics Goods Administration) and that further clinical trials be conducted. It also recommended changing the law to allow people with a terminal illness or AIDS to be able to possess and use small quantities of unprocessed or partially-processed cannabis without prosecution. To date, no amendment to the State legislation has occurred.

17. In late 2014 the NSW Government announced it would invest $A9m over the next five years to support medicinal cannabis clinical trials examining the benefits for children with severe drug-resistant epilepsy, terminally ill adults, and chemotherapy patients who suffer nausea and vomiting as a result of their treatment.

18. In December 2014 the Victorian Government asked the Victorian Law Reform Commission to review and report on options for changes to the *Drugs, Poisons and Controlled Substances Act 1981* and associated Regulations to allow people with terminal or life-threatening illnesses to be treated with medicinal cannabis. The Commission will report by August 2015.

Next steps

19. Despite the lack of clinical data showing efficacy for unprocessed or partially-processed cannabis products some population groups strongly believe that they are effective and that access should be permitted. Allowing personal possession and use for patients with severe medical conditions where conventional treatments are not effective or with terminal illness would be based primarily on compassionate grounds.

20. The challenge jurisdictions face when permitting medicinal use of unprocessed or partially-processed cannabis is to develop a regulatory regime for production, manufacture, sale and supply that is robust, workable for patients and health professionals and efficient to run. This is a particular issue in jurisdictions which choose to retain restrictions around personal supply and use of cannabis.

21. While the medicines approval process is appropriate for the pharmaceutical grade products some of the Misuse of Drugs Act provisions which limit the use of controlled drugs have been designed to restrict illicit use rather than allow a potential legitimate medicinal use. The Ministry will be providing advice on regulation of legitimate uses of controlled drugs by June 2015, to allow some or all changes to be given effect through the new therapeutic products legislation. This work will provide advice on options for the future regulation of medicinal use of controlled drugs, potentially including cannabis-based medicines.

END.

SATIVEX® (standardised cannabis pharmaceutical): REQUIREMENTS FOR PHYSICIAN APPLICATION-APPROVAL

Under the provisions of the Misuse of Drugs Act 1975 (s8) and the Medicines Act 1981 (s109 and s29)

FOREWORD

The physician requirements for application and approval to administer Sativex® provides a framework for the effective, safe and responsive use of this standardised cannabis pharmaceutical as an adjunctive or alternative treatment in specific chronic disease states or terminal illness.

Sativex® is an unapproved medicine in New Zealand. The clinical safety, efficacy has been investigated in only a limited range of medical conditions and the long-term usefulness of this medicine has not been established.

These papers set out the patient management parameters that need to be addressed if Sativex® is to be permitted to be used in New Zealand. The detail required in Table III which sets out a proposal to use Sativex® in a specified patient, highlights that prescribers should consider they are initially prescribing this medication on a trail basis. An awareness of potential adverse drug reactions, the diagnosis of such events, and their reporting, is essential during the course of a patient's treatment with Sativex®.

The appendix to this document provides guidance for prescribing and should be used in conjunction with the Sativex® data-sheet and other relevant literature.

National Drug Policy, Ministry of Health

August 2007

CONTENTS

PRODUCT DESCRIPTION

Sativex® is a buccal (mouth) spray administering a metered, actuated dose containing the cannabis extracts Δ^9-THC (2.7 mg per spray) and cannabidiol (2.5 mg per spray).

Sativex® has gained tentative approval with *Health Canada,* and is available on a named patient basis in the UK. Sativex® is approved by *Health Canada* for use as an adjunct for the symptomatic relief of neuropathic pain in multiple sclerosis (MS) and moderate-severe cancer pain in adults.

Sativex® is not an approved drug in New Zealand, and therefore 'off-label' prescribing in the limited indications listed in this document (as per Table I) should be approached with caution, particularly during the inception of this drug to therapeutics in New Zealand.

The effectiveness of Sativex® in long-term use has not been evaluated in placebo-controlled clinical trials. Extended periods of treatment should be periodically re-evaluated to examine the long-term safety and efficacy of the drug for the individual patient.

RISK OF DIVERSION OF THIS DRUG SUBSTANCE

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

It is unclear what proportion of patients who are chronically exposed to Sativex® (cannabinoids) will develop either psychological or physical dependence. Evidence suggests that the long-term use of cannabis is associated with the development of psychosis, and disorders of motivation, judgment and cognition. 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.

INCLUSION CRITERIA

Table I: Eligibility criteria for the patient to receive Sativex®

Applicant	The applicant must be a general practitioner (GP) or specialist who "normally" provides medical care to the patient, either for general medical services or for care of the *specified condition*. The applicant should not have any previous complaints against them for drug or alcohol abuse, and Medicines Control (Ministry of Health) should have no outstanding investigations or concerns about their prescribing pattern of Drugs of Misuse.
Specific Chronic Disease States or Terminal Illness **'*specified condition*'**	In order to be eligible for permission to prescribe Sativex, a patient must have either: • nausea, anorexia and wasting (cachexia) associated to cancer and AIDS, or • chronic pain (including cancer pain) for which other pain relief treatments are ineffective, or have significant/severe adverse side-effects; or • neuropathic pain (associated with conditions including multiple-sclerosis, stroke, cancer, spinal cord injury, severe physical trauma and peripheral neuropathy resulting from diabetes) or • muscle spasm and spasticity associated with MS or spinal cord injury *Refer to the appendix, section: Indications and Dosing*
Failure of Other Prescription Medicines or Current Available Treatments	Adequate doses of standard treatments for the specified condition have either been trialled for appropriate periods of time without sufficient therapeutic benefit, or are contraindicated for the patient.
Specialist Endorsement	Specialist assessment and endorsement for the use of Sativex®, due to the inadequate response by the patient to standard treatments, must be issued by a practitioner who is registered with the New Zealand Medical Council as being competent in the scope of practice appropriate to the management of the *specified condition* to be treated. For example, treatment for cachexia related to cancer should be endorsed by a registered oncologist or palliative care specialist. Specialist endorsement is limited to oncologists, neurologists, anaesthetists and palliative care specialists
Patient Informed Consent	The patient should be advised that the use of Sativex® is on a trial basis and that the treatment protocol requires the dose to be adjusted over time, and if reassessment indicates no benefit the treatment will be stopped. The patient must sign an informed consent form (refer Table III). This indicates that the patient is willing to use Sativex® and they are aware of the potential danger associated with its use, and that if Sativex® is abused or diverted then the application and approval is no longer valid and that future applications will be declined.

PATIENT MANAGEMENT CRITERIA

Table III: Application form to prescribe *Sativex*®

Patient Details

• full name	

EXCLUSION CRITERIA

Table II: Potential exclusion criteria for Sativex®

Mental Illness	This is a potential exclusion criterion for the use of cannabis medicines. Increasing evidence suggests that excessive or chronic use of cannabis is linked to psychosis and that it may exacerbate the symptoms of schizophrenia or precipitate this condition. A history of psychosis or evidence of active psychosis is a contraindication to use of Sativex®.
Documented Abuse or Diversion	Approval may be declined if the patient has a documented history of abuse or diversion of controlled drugs, or that during the course of treatment with Sativex® such circumstance arise. Health professionals with a documented history of abuse or diversion of controlled drugs, or who have had their rights to prescribe controlled drugs limited under the Misuse of Drugs Act 1975 may be ineligible to prescribe.

• full street address		
• date of birth		NHI No.
• informed consent	*"I, the patient named above, am willing to use Sativex® and I am aware of the potential danger associated with its use. I am aware that that if Sativex® is abused or diverted then this application and approval is no longer valid and that future applications will be declined"* *Signed (above named patient):*	

Physician Contact Details

• full name		Medical Council No.
• full practice address		
• details of patient history with physician		

Details on Sourcing Sativex®

A copy of the agreement between GW Pharmaceutics Ltd (UK) to supply Sativex® to the above mentioned physician is included as an attachment with this application

Specialist Endorsement

Please refer to Table I: requirement for endorsement by a New Zealand Medical Council registered specialist

• full name of specialist		Medical Council No.
• full practice address		

Conditions and Symptoms to be Controlled by Administration of Sativex®

Refer to the appendix, section: Indications and Dosing & Precautions

• *Identify the specific condition(s) and symptoms to be treated/controlled by the administration of Sativex®*	
• *Identify other medical conditions the patient is known to be suffering from at the time of consideration of prescribing Sativex®*	

Evidence of Failure of Other Current Available Treatments

• *Outline the previous drug regimen(s) used by this patient to control the specified conditions and symptoms* • *Provide a time-line during which the previous regimen(s) were used.* • *Confirm that the patient complied with all of the requirements of the previous regimen(s)*	

Treatment Protocol (a detailed outline and specialist endorsement is required)

Refer to the appendix, section: Indications and Dosing & Precautions. Also refer to requirements for Concomitant Disease and Drug Interaction below

• The starting dose *Detail the treatment protocol including setting out the starting dose, and guidance for patient titration up and down (how dose adjustments would be made)* • Assessment of efficacy (I) *Outline and explain suitable diagnostic and measurement technique(s) to assess the safety and efficacy of the recommended regimen* • Assessment of efficacy (II) *Outline a plan to reassess the condition and determine over time if the desired effect has not been obtained and maintained* • Cessation of treatment *Outline a plan to stop treatment at a particular dose if no significant effect has been seen, or if side effects have occurred, or if abuse/diversion has been identified* *Confirm a protocol for returning unwanted or unused Sativex®*	

Reducing or Tailing of Current Treatments

• *Describe the procedure for reducing or tailing-off current and/or concurrent medicines and treatments that maybe considered, or become, redundant for the treatment of the specified condition(s) if Sativex® is found to be efficacious*	

Concomitant Disease and Drug Interaction

Refer to appendix, section: Precautions- drug interaction & concomitant disease, risk-benefit analysis and Table IV: potential therapeutic drug interactions

• Drug interaction *Examine the nature and/or describe the effect of (potential) drug-drug interactions within the overall proposed treatment regimen* *Discuss how interactions with drugs and concomitant disease will be identified* • Poly-pharmacy *Examine poly-pharmacy; this is considered within the context of the inclusion of a new or additional drug to a patient's regimen and with the overall proposed treatment regimen* • Prescribing in the elderly *Discuss any issues with prescribing in the elderly were appropriate* • Concomitant disease *Including hepatic and renal impairment*	

Endorsement and Confirmation

We, the patient's physician and the above described specialist, agree upon the prescribed regimen outlined within Table III, and confirm that all the information given is true and correct.

Signed (patients physician): *Date:*	*Signed (specialist):* *Date:*

APPENDIX

INDICATIONS AND DOSING
(evidence of specialist endorsement is required)

Sativex® indications include:

- nausea, anorexia and wasting (cachexia) associated to cancer and AIDS;
- chronic pain (including cancer pain) for which other pain relief treatments are ineffective, or have significant/severe adverse side-effects;
- neuropathic pain (associated with conditions including multiple-sclerosis, stroke, cancer, spinal cord injury, severe physical trauma and peripheral neuropathy resulting from diabetes);
- muscle spasm and spasticity associated with MS or spinal cord injury.

Individualisation of Dose

The pharmacologic effects of Sativex® are dose-related and subject to considerable inter-patient variability. Systemic absorption from a buccal spray is similar to that of inhalation from smoking cannabis and the intensity of the effect due to this route of administration is greater than an equal dose taken orally.

The Sativex® data-sheet states that dosing for MS should be started at a maximum rate of one spray every four hours on the first day and up to a maximum of four sprays on the first day. On subsequent days, the patient may gradually increase the total number of sprays as needed and tolerated. As such dosing is self-limiting, individual response and side effects will establish an upper-limit for the dosing of this medicine. It is suggested that during initial titration, doses are evenly spread out over the day. If unacceptable adverse reactions such as dizziness or other intoxication type reactions occur then dosage should be reduced and potentially tapered off or dosing ceased.

Dose selection for an elderly patient should be conducted with caution, starting at the low end of the dosing range. This low dose reflects the greater frequency of decreased hepatic, renal and cardiac function and the incidence of concomitant disease, an increased body fat content, and the probability of poly-pharmacy in this population.

Some of the psychological effects of the psychoactive cannabinoid Δ^9-THC experienced by patients include dysphoria and anxiety and dependence potential. These can be minimised through preparation, explanation and reassurance given before the start of the treatment and should especially be considered when administered in the palliative setting.

PRECAUTIONS

Cannabis based therapeutics are useful in a wide range of disease states. Such therapeutics provide a 'broad spectrum' effect due to the interaction of cannabinoids with many tissue and organ systems (and its modulating effect on excitatory and inhibitory neurons).

The safety profile of cannabis based therapeutics is considered good due to cannabis's wide therapeutic index. However, there is a narrow dosing window between the desired and undesired effects. Drug interactions and con-commitment disease may influence this safety profile significantly; inter-individual physiological and psychological response may also vary.

The frequency/incidence of reported adverse reactions to cannabis therapeutics are influenced by factors such as drug dose and concomitant drug use and disease, the administration setting, the physician's judgements and detection techniques, the patient's subjective opinion, and the ongoing use or overall tolerance to the drug.

The risk-benefit ratio of using Sativex® should be carefully evaluated in patients because of individual variation in response and tolerance to the effects of this drug.

Contra-indications

A cautious approach should be taken when treating patients with complex diseases such as AIDS and cancer who may be taking several drugs in their daily regimen.

Sativex® is contraindicated in patients with current or previous psychiatric disorders (including manic depressive illness, depression, and schizophrenia), as the symptoms of these disease states may be unmasked or exacerbated by the use of cannabinoids.

Risk-benefit Analysis

A risk-benefit analysis should be conducted to assess the patient's suitability to the prescription of this drug.

In AIDS or immuno-compromised patients, long-term administration should be carefully monitored as cannabinoids interact with aspects of the immune system. Such patients are therefore at risk of aggravating certain aspects of this disease, which includes ulceration of the mucosa at the site of administration.

Elderly patients are more sensitive to the neurological, psychoactive and postural-hypotensive effects of cannabinoids. This is especially applicable to elderly patients who are prone to falls and those with dementia. Patients with glaucoma are susceptible to the effects of an acute fluctuation in blood pressure and heart rate following the administration of Sativex®, additionally there exists a potential for interaction with drugs prescribed for this condition.

Adverse Effects

The most common reported side-effects are dizziness, disturbance in attention, dry mouth, tachycardia, and gastro-intestinal symptoms. Short-term memory and attention, motor skills, reaction time and skilled activities may be altered under the influence of this substance, and impaired while a patient is "intoxicated". Users may experience feelings of anxiety, dysphoria, paranoia

and distortion of time and space. In the elderly, hypothermic reactions or chills and postural-hypotensive effects are of significance.

Administration site irritation or oro-mucosal ulceration is very common during both the short-term and long-term use of Sativex®. Regular inspection of the oral mucosa, by the prescribing physician, is advised. Patients should be advised not to continue spraying on to sore or inflamed mucosa. For this reason caution should be applied in patients presenting with AIDS.

Intoxication may be as a result of interaction or additive effects with other drugs in the patient's regimen.

The risk of adverse effects from acute and chronic administration is dose dependant. Adverse effects include sedation (this is exacerbated by the use of sedatives and depressants such as alcohol, benzodiazepines and opiates) and impairment of psychomotor and cognitive performance, especially in complex tasks (that are not already impaired by other drug substances and disease states).

Because of the rate of elimination of cannabinoids adverse effects may persist for more than 24 hours after a single dose; use within a therapeutic dosing regimen can lead to compounding of these adverse effects.

For most patients the primary adverse effect of acute cannabis use is impaired psychomotor performance. This makes it inadvisable for anyone under the influence of cannabis to operate machinery, drive or engage in hazardous activity.

Reporting Adverse Drug Reactions

An awareness of potential adverse drug reactions, the diagnosis of such events, and their reporting, is essential during the course of a patient's treatment with Sativex®. If an adverse reaction to this medicine is diagnosed it should be referred to the Centre for Adverse Reactions Monitoring in Dunedin (CARM).
CARM's web address is http://carm.otago.ac.nz/index.asp?link=reporting

Tolerance

Tolerance to Sativex® has been shown to develop for many of its therapeutic and non-therapeutic effects. Similar to cannabis tolerance in normal subjects; tolerance to the effects of Sativex® can occur including effects on mood, heart rate, blood pressure, salivary flow, intraocular pressure, cardiovascular effects, and psychomotor performance. Tolerance is advantageous in decreasing the unwanted effects, but a disadvantage if a desired effect is involved.

Dependence and Withdrawal

Dependence is unlikely to present a problem with clinically prescribed doses for ill patients in therapeutic settings. The effects of withdrawal, such as rebound rise in intraocular pressure, nausea, diarrhoea and other significant physiological symptoms, may be undesirable and pose risk to the patient's

medical condition. Additionally, there may be rebound actions from other drugs included in that patient's regimen. The rebound effects associated to withdrawal should be considered in patients suffering from glaucoma. Patient's should be warned to look out for withdrawal effects and provided with advice on how to best manage any effects that may occur.

Interaction with Other Drugs and Concomitant Disease

Other medicines in the patient's drug regimen may enhance or attenuate certain actions of cannabis/THC/CBD and *vice versa*. Interaction with other drugs may depend on the activity of similar effector systems, metabolic interactions, or competition for protein binding.

The co-administration of pharmaceutics to combat these effects is not considered warranted. Such an approach is outside the scope or purpose of cannabis based therapeutics.

Plasma Proteins

Cannabinoids are highly bound to plasma proteins and therefore might displace other protein-bound drugs. These properties have the potential to lead to drug-drug interactions and affect the pharmacokinetics of similar behaving co-administered drugs.

Metabolism and Effector Systems

Caution should be applied in the dosing of patients with hepatic and renal impairment, and/or concomitant use of drugs that induce/enhance or attenuate hepatic enzymes or alter renal clearance. Corresponding high blood levels of THC can increase the patient's risk of experiencing adverse effects.

Sativex® should be used with caution in individuals receiving concomitant therapy with sedatives, hypnotics, or other psychoactive drugs because of the potential for additive or synergistic central nervous system (CNS) effects.

In elderly patients, the total body water decreases with a corresponding increase in total body fat. Consequently, the distribution and concentration of fat soluble cannabinoids are increased in these subjects.

Because of the extensive volume of distribution, including into adipose tissue, the active ingredients and metabolites of Sativex® may be excreted at low levels for prolonged periods of time.

CYP450 Interactions with Cannabinoids

Cannabidiol (CBD) affects the metabolism of several drugs, including Δ^9-THC, by selectively inhibiting or inactivating isozymes belonging to the cytochrome P_{450} enzyme families CYP2C and CYP3A. Inhibitory effects also appear with CYP2D. The CYP3 isozyme A inhibition or inactivation will likely result in the reduction in metabolism and clearance of several drugs including diazepam, warfarin, digoxin, quinadine, oral contraceptives, fentanyl (and related opioids) and cyclosporine and therefore increase the effective dose within the same regimen. Caution is advised for patients taking concomitant medications metabolised via these enzymes.

Table IV: Potential Therapeutic Drug Interactions

(this a guide and not meant to be exhaustive)

CONCOMITANT DRUG	CLINICAL EFFECT
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Atropine, hyoscine (scopolamine), antihistamines, other anti-muscarinics	Additive or super-additive tachycardia, hypertension, enhancement of sedation and pain reduction
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia and hypertension. Sedating effects may be enhanced
Anti-depressants (SSRIs): fluoxetine etc	THC may increase the effect of SSRIs. Hypomanic reaction reported with smoking cannabis
Alcohol	Increase in the positive subjective mood effects of smoked cannabis. Additive drowsiness and CNS depression
Barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism. Additive drowsiness and CNS depression
Benzodiazepines	Respiratory depression and depression of the brain function may be increased. The antiepileptic action may be enhanced.
Disulfiram	Reversible hypomanic reaction reported with smoking cannabis
Naltrexone	THC effects are enhanced by opioid receptor blockade
Neuroleptics	THC may antagonize the antipsychotic actions of neuroleptics. It may improve their therapeutic effects in motor disorders
Non steroidal anti-inflammatory drugs (NSAID)	Indomethacin, acetylsalicylic acid (aspirin), and other NSAIDs antagonise THC effects. Indomethacin significantly reduced subjective "high" and acceleration of heart frequency
Opioids	Enhancement of sedation and pain reduction. Cross-tolerance and mutual potentiation. CNS depression & drowsiness
Phenothiazines (anti-psychotics/ anti-emetics)	Attenuates the psychotropic effects of THC and increases anti-emetic effects
Theophylline	Increased theophylline metabolism reported with smoking cannabis, effect similar to that following smoking tobacco
Metabolic interaction with warfarin, OC's, fentanyl, cyclosporine, digoxin, quinadine, diazepam, etc	Induction or inhibition of metabolic processes that may increase or decrease the effective dose of such drugs
Miscellaneous: lithium, buspirone, muscle relaxants	Additive drowsiness and CNS depression

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