Herbal cannabis and pharmaceutical cannabinoid treatment following motor vehicle accidents:  
A state of the science review

Final Report

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Glossary of terms, abbreviations and language use

ACMPR – Access to Cannabis for Medical Purposes Regulations
AE – Adverse events - Unwanted effects (possible side effects) that occur after taking a drug
Cannabis – the plant
Cannabinoids – pharmacologically active constituents of cannabis
CB1 receptor – Cannabinoid receptor type 1 which binds with THC
CBD – cannabidiol, a pharmacologically active but not psychoactive major cannabinoid
CI – a confidence Interval indicates the percent probability statistically that the number being estimated will fall within the interval
CUD – cannabis use disorder
CPSBC – College of Physicians Surgeons of BC
DSM-5 – The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
Herbal cannabis – plant based products with variable composition of cannabinoids and no regulatory assessment
MS – Multiple sclerosis
NHP – natural health products
NNH – number needed to harm
NNT – number needed to treat
Pharmaceutical cannabinoids – medications that have strict composition and Drug Identification Numbers (DINs) from Health Canada
Post-traumatic stress disorder (PTSD) – the diagnosis of PTSD requires exposure to a traumatic or stressful event, re-experiencing phenomena, persistent negative thoughts and feelings and avoidance of trauma-related stimuli as specified by the DSM-5.
RCT – randomized controlled trial
RR – risk ratio being the probability of an event in an exposed group compared to the non exposed group
THC – delta 9-tetrahydrocannabinol, the most psychoactive cannabinoid and the one responsible for the intoxication effects of herbal cannabis
WHO – World Health Organization
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1.0 Developing a funding policy framework for ICBC insurance claims

The Insurance Corporation of British Columbia (ICBC) has recognized the need to develop funding policy for insurance claims involving use of herbal cannabis and pharmaceutical cannabinoids for post injury medical management.

Cannabinoids are chemical constituents of the cannabis plant that may have been extracted from a plant, synthesised in a laboratory or remain in plant form. Pharmaceutical cannabinoids are chemical constituents approved by Health Canada.

The research on herbal cannabis intoxication as a cause of motor vehicle accidents, while relevant to and important for ICBC, is out of scope for this review.

ICBC asked for assistance with developing funding policy for herbal cannabis and pharmaceutical cannabinoid therapy from the Therapeutics Initiative (TI). The TI is an independent prescription drug therapy assessment group, consisting of doctors, pharmacists, epidemiologists and drug policy experts, based at the University of British Columbia. The TI conducts systematic reviews of the clinical efficacy of prescription drug therapy for provincial, federal and international funding agencies. In addition, the TI has assisted governments and organizations, such as ICBC, to develop drug funding policies that utilize the best available scientific evidence.

Section 1 of the report provides an overall framework for funding policy for ICBC and a summary of clinical trial evidence, harm, and pharmacology. Sections 2 to 4, compiled in larger technical reports include details of clinical trial evidence (Section 2); harm (Section 3) and pharmacology (Section 4).

1.1 Scientific medical knowledge of prescription drug therapy

Scientific medical knowledge of prescription drug therapy involves applying the highest level of research methods, usually randomized controlled trials to study a specific drug for a specific medical condition.

It follows that, to utilize scientific medical knowledge in funding policy, the policy must focus on and make decision regarding, specific therapeutic products for specific medical conditions.

In Canada, diagnosing conditions and treating them with prescription drugs almost always falls to a medical practitioner prescribing a pharmaceutical product licensed by Health Canada. Pharmaceutical licensing by Health Canada requires consistency of the therapeutic product,
evaluation of harm in pre-clinical studies and efficacy in randomized clinical trials versus
placebo.

In most established clinical medical care in Canada, of necessity, therapeutic uses of herbal
cannabis and pharmaceutical cannabinoids must fall within this overall Health Canada
evaluative and clinical medical utilization framework.

1.2 ICBC prescription medication funding policy

ICBC insurance claims often involve doctors diagnosing medical conditions and prescribing
drugs licensed by Health Canada.

ICBC has a well-established framework for how, when and how much it will pay for drugs
prescribed by doctors as part of an injury claim. Typically, ICBC requires both a medical
diagnosis and a doctor’s prescription which, to some extent, it adjudicates as to the
appropriateness of diagnosis and the type and volume of drugs prescribed.

Decisions regarding funding of herbal cannabis and pharmaceutical cannabinoids fit within this
well established ICBC funding policy framework.

1.3 Herbal cannabis and pharmaceutical cannabinoids in clinical medical
practice in Canada

The application of scientific medical knowledge of herbal cannabis and pharmaceutical
cannabinoid therapy to clinical medical practice in Canada remains limited to date. This is
primarily because few cannabinoid products have been evaluated by Health Canada and of
these, approval has been granted for marketing for only a few specific medical conditions (see
details below).

Clinical medical practice guidelines remain similarly restrained by the limited number of Health
Canada approved cannabinoid products and the small range of medical conditions studied.

The key issue limiting medical prescribing of herbal cannabis and the key issue in this TI review
for ICBC is that herbal cannabis products are not purified products of standardized composition
suitable for pharmacological assessment by Health Canada or for use in scientifically valid
(replicable) clinical trials.

There are two major species of herbal cannabis (Cannabis sativa and Cannabis indica) and
thousands of different strains or cultivars. The chemistry and pharmacology of these products
is exceedingly complex and varies by plant source, including the anatomical parts of the plant
from which product may be derived and growing conditions from season to season.

The discovery in the 1970s of an internal (endo) cannabinoid system primarily located in the
human brain garnered increasing research interest and gave cannabis use for medical purposes
the possibility of a scientific basis. There are at least 400 chemical compounds, including over 100 cannabinoids (Atakan, 2012), some of which interact in complex ways with endocannabinoid receptors (Russo & Marcu, 2017). The body produces internal (endogenous) cannabinoids and interacts with ones that are produced external to the body (exogenous cannabinoids). The endocannabinoid system modulates appetite, pain and mood. Research is advancing on how exogenous cannabinoids act on the endocannabinoid system.

Since 2001 in Canada, a medical doctor’s role has been limited to legalizing a patient’s largely unsupervised access to herbal cannabis -- not to prescribe a pharmaceutical cannabinoid. The current Access to Cannabis for Medical Purposes Regulations (ACMPR) granted physicians the ability to authorize herbal cannabis use where provincial regulators (i.e. British Columbia) included such endorsement within a physician’s scope of practice (Department of Justice Canada, 2016). See Appendix 1. The Health Canada Form for Authorizing use of Cannabis.

This legalization role for patient use of herbal cannabis is a departure from a physician’s usual role in applying scientific medical knowledge to prescribing a Health Canada approved product for treatment of a diagnosed condition.

Herbal cannabis producers have a strong interest in medicalizing the use of herbal cannabis by persuading medical practitioners to recommend certain products for treatment of certain medical conditions. However, the foundation of clinical research that physicians use to support their clinical decision-making remains sparse on herbal cannabis as a therapeutic intervention.

Clinical trials are available to assess the efficacy of the therapeutic use of pharmaceutical and herbal cannabinoids for some medical conditions, including pain and spasticity in multiple sclerosis, chemotherapy induced nausea, and palliation in terminal cancer patients as well as more recently, treatment of rare forms of pediatric epilepsy. Most of these conditions are irrelevant to ICBC and therefore out of scope for this review. Instead, as requested by ICBC, this review will focus on use of pharmaceutical cannabinoids and herbal cannabis for chronic pain and related anxiety, depression and post-traumatic stress disorders associated with motor vehicle accident injury.

### 2.0 An overview of a graduated evidence-informed, ICBC funding model

An evidence-informed ICBC funding model would extend funding to pharmaceutical cannabinoids and herbal cannabis if and when sufficient clinical study evidence supports their use for specific medical conditions. Figure 1 illustrates this funding model where the strongest clinical trial evidence is for pharmaceutical cannabinoids and involves relatively few clinical conditions. This becomes Level 1 at the top of the pyramid.

Level 2 would extend funding to a pharmaceutical cannabinoid for an indication that does not have regulatory approval when appropriate randomized controlled trials have been conducted and the findings demonstrate the efficacy of that pharmaceutical cannabinoid for that specific
indication. Level 2 evidence would reflect the highest state of science on pharmaceutical cannabinoids without or perhaps before the product is licensed for marketing for that indication by Health Canada.

Level 3 would extend funding to more medical conditions by accepting weaker clinical trial evidence on non-standardized herbal cannabis. However, a requirement would be sufficient clinical trial evidence to develop clinical practice guidelines.

Level 4 would extend funding to most medical conditions even when there is insufficient clinical trial evidence to develop clinical practice guidelines, a policy in clear departure from standard clinical medical practice.

**Figure 1. Gradual expansion of funding from most to least evidence-based**

Funding of Level 1 and 2 would be consistent with existing ICBC policy to fund Health Canada approved medications prescribed by a doctor. Expansion of funding to Level 3 to herbal products would occur if evidence-based conditions are met. All levels would require prescription by licensed medical physicians and products supplied by licensed producers for medical purposes. Level 4 is the least restrictive category because clinical trial evidence of efficacy would not be required for coverage.
2.1 Funding policy decisions within a graduated, evidence informed ICBC funding model

A graduated evidence-informed funding model allows for incorporation of new pharmaceutical cannabinoids or clinical indications as evidence emerges:

Level 1. Pharmaceutical cannabinoids for regulator approved clinical indications

- Receiving a Drug Identification Numbers (DIN) provides physicians and pharmacists with assurance that the product is of pharmaceutical grade and that a threshold of efficacy evidence has been met before formal approval for a specific indications is granted by Health Canada. Health Canada Approved indications for pharmaceutical cannabinoids include multiple sclerosis pain and spasticity, post chemotherapy nausea and vomiting and as an adjunct to other analgesics in advanced cancer pain management.

Level 2. Pharmaceutical cannabinoids for clinical indications without regulatory approval

- Indications for pharmaceutical cannabinoids that have not received Health Canada approval include chronic pain, post traumatic stress disorder, anxiety and depression. These conditions are of greater relevance to ICBC claims following motor vehicle accidents than the Health Canada approved indications. As new clinical trial evidence is published in the academic literature it becomes available for systematic review and meta-analyses by review organizations (see Section 3.1, 3.2). Reviewers may use different standards than those used by federal regulators for these non-Health Canada approved indications. ICBC would specify the strength and quality of evidence needed for funding approval.

Level 3. Herbal cannabis coverage for indications with sufficient clinical trial evidence

- Funding of a herbal cannabis product requires a systematic review and critical appraisal of clinical trial evidence and a determination of efficacy for that indication. Clinical practice guidelines are required that specifying product composition, dosage, frequency and duration. Physicians must verify a clinical diagnosis matching the indication for which there is clinical trial evidence. In addition, the cannabis product must be obtained from a Health Canada Licensed Producer of cannabis for medical purposes.

Level 4. Herbal cannabis coverage for indications without supportive clinical trial evidence

- In specific instances, ICBC may consider funding herbal cannabis for clinical conditions without or with minimal clinical trial evidence of efficacy and not included in or rejected by practice guidelines. Level 4 funding decisions are outside the scope of this report because they are based on factors other than clinical trial evidence.
2.2 Pharmaceutical cannabinoid medications for regulatory approved indications (LEVEL 1)

The most evidence-informed ICBC funding policy would fund cannabinoid medications with a Drug Identifier Number (DIN) for the specific clinical conditions for which they have been approved by Health Canada.

Two pharmaceutical cannabinoid medications have been approved by Health Canada and therefore have DINs: Nabiximols (Brand name - Sativex®) and Nabilone (Brand name - Cesamet®). Health Canada maintains a database (Government of Canada, 2018) of Health Canada-authorized product monographs described as ‘a factual, scientific document on a drug product that, devoid of promotional material, describes the properties, claims, indications and conditions of use of the drug and contains any other information that may be required for optimal, safe and effective use of the drug (Government of Canada, 2014).’

Nabilone is an oral medication that is based on the tetrahydrocannabinol (THC) molecule but is significantly different in its pharmacological effects. It is delivered in a capsule and has Health Canada marketing authorization for ‘nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments’(Apotex Inc., 2015). It gained FDA approval in 1985, however, over the last 30 years it has not been widely used in Canada.

Nabiximols is a mouth spray (buccal) containing two cannabinoids (delta-9 THC) and cannabidiol (CBD) that have been extracted from herbal cannabis and are present in a 1 to 1 ratio. Nabiximols has market authorization:

- as adjunctive¹ treatment for the symptomatic relieve of spasticity (useful) and neuropathic pain (may be useful) in adult patients with multiple sclerosis or
- as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (may be useful).

In summary, there are two pharmaceutical cannabinoid medications (nabilone and nabixomols) with Health Canada approved medical indications: multiple sclerosis, cancer pain palliation and post chemotherapy nausea and vomiting.

2.3 Pharmaceutical cannabinoids for indications without regulatory approval (LEVEL 2)

The two pharmaceutical cannabinoid medications (nabilone and nabixomols) have been studied in clinical trials for non-Health Canada approved indications. Chronic pain and PTSD, for example, are clinical conditions that are included in clinical practice guidelines on the basis of additional clinical trial evidence not submitted to regulators.

¹ An adjunct treatment is one that is used in combination with a primary treatment.
An ongoing process for assessing emerging evidence would keep the evidence informed ICBC funding model up-to-date by revising policy decisions as new scientific evidence becomes available.

Reviewers of clinical research evidence acknowledge that clinical trial evidence is of variable quality for proving causation. Nevertheless, there is a standard hierarchy of evidence (see Appendix 2. Standard Hierarchy of Evidence) as well as standard ways of grading the quality of evidence (see Appendix 3. Quality of Evidence Grades from the GRADE approach).

Different approaches to assessing and interpreting clinical trial evidence can result in different recommendations. Two approaches are provided as examples. See Appendix 4. ‘Weight-of-Evidence categories’ for the US National Academies review approach and Appendix 5. ‘GRADE Representations of quality of evidence and strength of recommendations’. Appendix 6. ‘CFP summary of findings and GRADE Recommendations on pain’ provides an example of how the evidence for herbal cannabis for pain can be evaluated and summarized using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (The Grade Working Group, 2018).

Both nabiximols and nabilone have been investigated for chronic pain, nabilone has been studied for PTSD although none of these are approved Health Canada indications. Therefore this research has not been reviewed by regulators, nor is it in product monographs.

It is anticipated that, as the science on therapeutic uses of pharmaceutical cannabinoids advances, additional products and indications will be added to level 2.

2.4 Herbal cannabis coverage (LEVEL 3 and 4)

Herbal cannabis does not meet basic pharmaceutical product purity and composition standards and does not have Health Canada DIN numbers or product monographs. Therefore, the pharmacological and clinical evidence available to physicians and pharmacists is limited.

Similarly to Level 2, an evidence informed system requires that clinical evidence of benefit and harm be examined (Allan, Finley, et al., 2018).

The position of the Board of the College of Physicians Surgeons of BC (CPSBC) is very clear and strict regarding its guidance to physicians prescribing herbal cannabis (College of Physicians and Surgeons of British Columbia, 2018).

Few reliable published studies are available on the medical benefits of cannabis. The amount of active ingredients in cannabis varies significantly, depending on the origin and method of production of the substance.
Physicians are advised that they should not prescribe any substance for their patients without knowing the risks, benefits, potential complications and drug interactions associated with the use of that agent. Physicians may be the subject of accusations or suggestions of negligence, including liability if the use of cannabis produces unforeseen or unidentified negative effects.

Cannabis is generally not appropriate for patients who; (The College of Family Physicians of Canada, 2014)

- are under the age of 25
- have a personal history or strong family history of psychosis
- have a current or past cannabis use disorder
- have an active substance use disorder
- have cardiovascular (angina, peripheral vascular disease, cerebrovascular disease, arrhythmia) or respiratory disease
- are pregnant, planning to become pregnant or are breastfeeding

The College recognizes that there are sometimes circumstances in medical practice where exceptions to strong relative contraindications may be appropriate. When physicians utilize a therapeutic agent despite strong relative contraindications, the standard of care mandates detailed documentation of their rationale... The College considers the medical document authorizing patient access to cannabis to be equivalent to a prescription (College of Physicians and Surgeons of British Columbia, 2018).

The CPSBC standard goes on to specify the documentation required to meet the College standard and protect physicians legally. This includes describing previous unsuccessful attempts to manage a medical condition, assessment with a validated addiction risk assessment tool, discussion of risks, review of PharmaNet information and processes to identify misuse/abuse/diversion by the patient in reassessment. This amounts to considerably more work for physicians than usual prescribing practices with the exception of opioids.

2.5 Federal regulatory frameworks

Herbal cannabis for medical purposes has been made exempt from the general prohibitions’ of the Controlled Drugs and Substances Act that regulates prescription medications. It has also been made exempt from the Canadian Food and Drugs Act that regulates natural health products (NHP) providing them with a NHP (comparable to a Health Canada DIN). Health Canada reviews safety and effectiveness evidence before issuing a NHP number. Such reviews include a much wider range of permissible evidence, such as traditional texts, compared to the standardized clinical trials required of pharmaceutical drugs.

As herbal cannabis is legalized for recreational use, concerns with criminal consequence for possession and use largely disappears. However, the strict College standards for doctors to prescribe herbal cannabis will almost certainly remain. At the time of writing of this report the Cannabis Act has passed into law (Parliament of Canada, 2018).
Cannabis has its own legislative framework and may continue to have separate regulatory pathways after a 5 year trial period following which a re-evaluation is expected (in 2023).

In the meantime licensed producers will need to produce products to quality standards with clear labeling of THC and CBD content to aid dosing (see product image right).

In arriving at a dual system with pharmaceutical cannabinoids regulated under the Controlled Drugs and Substances Act and herbal cannabis under the ACMPR, the Task Force on Cannabis Legalization and Regulation was set up to consider patient, physician and industry perspectives (Task Force on Cannabis Legalization and Regulation, 2016). The Task Force acknowledged that products used for medical purposes may be the same as for recreational use recognizing that medical use may be ‘a necessity, not a choice.’ The concerns of the medical community about a ‘lack of information to guide clinical decision making’ were also acknowledged. In summary the Task Force Reports:

- The ‘long-standing concerns [of the medical community] about being responsible for authorizing the use of a substance that is not an approved medicine and who see no need to play the role of “gatekeeper” moving forward’;
- Patients with a ‘variety of serious medical conditions that derive therapeutic benefit from both THC and CBD’. Patient concerns about accessing ‘recreational’ cannabis were
  - ‘the loss of recognition that their use of cannabis is for medical purposes and occurs under the supervision of a physician;
  - shortages of supply;
  - barriers for young people; and
  - the stigma associated with having to purchase cannabis for medical purposes from a non-medical retail outlet (Task Force on Cannabis Legalization and Regulation, 2016).’

In striking a balance, the Task Force recommended that the existing ‘dual systems’ for pharmaceutical cannabinoids and herbal cannabis be sustained and evaluated in 5 years (Task Force on Cannabis Legalization and Regulation, 2016).

Regardless of the legal standing of herbal cannabis, the medical community faces the same challenge of requiring adequate clinical evidence of benefit over harm before therapeutic application.
2.6 Third party payer management tools

A set of insurance policies that restrict reimbursement of selected drugs or drug classes may go by the name of special authorization, special authority, special consideration, prior authorization, prior approval, pre-authorisation, restricted access, exemptions and ‘for limited use’ (Green et al., 2010). The common feature is that, before paying for a prescription medications, a program requires patient specific information and completion of special forms. The material is then considered in a predefined decision process to see if a patient’s use meets criteria.

Some practical applications of this type of tool are provided. The first is a BC Pharmacare form for use when there is no condition or drug specific form available (see Appendix 7) (Government of British Columbia, 2018). BC Pharmacare provides numerous examples of condition and drug specific forms however none for a cannabinoid based drug. Nabilone is on the formulary of both BC and Ontario.

A shortage of Nabilone 0.5 and 1 mg required an exceptional access form to obtain a 0.25 formulation in Ontario (see Appendix 8). This illustrates exceptions made for a dosage different from that funded in the province.

Nabiximols is covered in Ontario by Exceptional Access Program (EAP) however with a specified dose, reimbursement criteria and standard approval duration (See Appendix 9).

Canada’s Veterans Affairs (VA) policy is to cover herbal cannabis with no limitation on condition but has deferred authorization to physicians subject to a number of other qualifying conditions. Reimbursement of a maximum daily dosage up to 3 grams, for example, is a restriction except by Exceptional Approval (see Appendix 10).

2.7 Checklist for ICBC cannabis claims adjudication decisions

The emerging evidence on cannabis can be incorporated into a management tool in a similar format to the ones presented in Section 2.6 and Appendices 8-10. We illustrate this with a sample checklist in Table 1 below. This checklist can be modified to dovetail and comply with other organizational processes outside the mandate of this report. As the evidence is updated or reviewed for other indications the checklist can and should be updated. Sections 3 and 4 provide a summary of the evidence review.
### Table 1. Sample checklist for using evidence in cannabis claims adjudication decisions

<table>
<thead>
<tr>
<th>1. PRESCRIBED OR AUTHORIZED BY A MEDICAL PRACTITIONER</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes – continue</td>
</tr>
<tr>
<td>□ No – reject</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. PHARMACEUTICAL CANNABINIODS with Drug Identification Numbers for approved indications (See Product Monograph)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabiximols (Sativex)</td>
</tr>
<tr>
<td>• symptomatic relief of spasticity in adults with multiple sclerosis (MS) as an adjunctive treatment</td>
</tr>
<tr>
<td>• neuropathic pain in adult patients with MS as an adjunctive treatment</td>
</tr>
<tr>
<td>□ Yes – consider funding in the context of the overall claim</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. PHARMACEUTICAL CANNABINIODS for an unapproved indication with evidence review and current clinical practice guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabiximols (Sativex) or Nabilone (Cesamet) for chronic pain, neuropathic pain</td>
</tr>
<tr>
<td>□ Yes – consider funding with additional criteria</td>
</tr>
<tr>
<td>ADDITIONAL CRITERIA Other drugs tried?</td>
</tr>
<tr>
<td>□ Yes – consider as per guideline as a 3&quot; line treatment</td>
</tr>
<tr>
<td>□ No – reject pending a trial of at least 2 other analgesics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL CANNABINIODS for unapproved indications that have not had an ICBC evidence review or require an update</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Pending</td>
</tr>
<tr>
<td>An adjudication committee including ICBC staff and/or the UBC Therapeutics Initiative (TI) to conduct review</td>
</tr>
</tbody>
</table>
5. HERBAL CANNABIS for indications with an ICBC evidence review and current clinical practice guideline
   - chronic pain,
   - neuropathic pain

[ ] Yes – see additional criteria

ADDITIONAL CRITERIA
Other drugs tried

[ ] Yes – consider as a 3rd line treatment
[ ] No – reject or require a trial of at least 2 other analgesics

Maximum daily quantity of dried cannabis 1 gram

[ ] Yes – consider funding
[ ] No – consider limiting coverage to 1 gram per day or requesting further justification for higher dose

Herbal cannabis obtained from a licensed producer

[ ] Yes – consider funding in the context of the claim overall
[ ] No – reject

4. HERBAL CANNABIS for indications that have not had an ICBC evidence review or require an update

[ ] Pending – An adjudication committee including ICBC staff and/or the UBC Therapeutics Initiative (TI) to conduct review
3.0 Clinical guidance for prescribing herbal cannabis

Clinical trial evidence and clinical guidelines provide limited support for use of herbal cannabis for two conditions relevant to ICBC claims: chronic pain (particularly neuropathic) and PTSD. Table 2 provides an overview of the evidence reviewed in this section and adapted to an ICBC Cannabis Funding Model.

Table 2. An Evidence Informed ICBC Cannabis Funding Model

<table>
<thead>
<tr>
<th>Level of Restriction from Most To Least Restrictive Funding Policy Options</th>
<th>Evidence Statements by Review Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL 1. MOST RESTRICTIVE: PHARMACEUTICAL CANNABINIODS WITH REGULATORY APPROVED INDICATIONS</strong></td>
<td>HEALTH CANADA APPROVED STATEMENTS</td>
</tr>
<tr>
<td>Limited to pharmaceutical cannabinoids i.e., nabiximols, nabilone, which have met the purity standards and evidence requirements of Health Canada and therefore have a drug identified number (DIN) and product monograph (PM) for specific indications (clinical conditions for which benefit over placebo has been demonstrated)</td>
<td>Clinical indications in product monographs</td>
</tr>
<tr>
<td>Nabiximols: ‘adjunctive treatment of neuropathic pain and spasticity in multiple sclerosis / adjunctive analgesic treatment in adults with advanced cancer’</td>
<td>Nabilone: ‘nausea and vomiting associated with cancer chemotherapy’</td>
</tr>
<tr>
<td>The above indications are expected to be rare among ICBC cannabis claims</td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL 2. LESS RESTRICTIVE: PHARMACEUTICAL CANNABINIODS FOR INDICATIONS WITHOUT REGULATORY APPROVED INDICATIONS</strong></td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Specific clinical indications with randomized controlled trials of pharmaceutical cannabinoids. Therefore the evidence reflects the highest state of science on pharmaceutical cannabinoids but not licensed for marketing by Health Canada.</td>
<td>Canadian Family Physician (CFP): ‘We recommend against medical cannabinoids as first- or second-line therapy in neuropathic pain owing to limited benefits and high risk of harms (strong recommendation)’</td>
</tr>
<tr>
<td>US Nat Academies: ‘There is substantial evidence that cannabis is an effective treatment for chronic pain in adults’ (‘the majority of studies on pain ... evaluated nabiximols’)</td>
<td>US Nat Academies: ‘There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of PTSD’</td>
</tr>
<tr>
<td>Post-Traumatic Stress Disorder (PTSD)</td>
<td></td>
</tr>
</tbody>
</table>
### LEVEL 3. LESS RESTRICTIVE: HERBAL CANNABIS COVERAGE FOR INDICATIONS WITH CLINICAL TRIAL EVIDENCE

**Funding criteria:**

- Limited to physician prescription for diagnosed conditions for which there is clinical trial evidence from scientifically valid trials
- Limited by product characteristics including:
  - THC and CBD content
  - dose,
  - frequency
  - duration

**Chronic Pain**

CFP: ‘If considering medical cannabinoids, we recommend against medical marijuana (particularly smoked) as the initial product (strong recommendation)

- Evidence for smoked cannabis has a very high risk of bias, and long-term consequences are unknown
- Products available can have far higher concentrations of THC and CBD than those researched’

US Nat Academies: ‘ the committee found that only a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States.’

**PTSD**

US Veterans Affairs sponsored review:

Evidence is insufficient to draw conclusions

Walsh et al, 2017: Preliminary results are promising

### LEVEL 4. LEAST RESTRICTIVE: HERBAL CANNABIS COVERAGE

- Limited to physician prescribed use
- No restriction by medical condition or product characteristics

As per basic ICBC protocols that apply to all pharmaceutical products, funding of cannabis products at this level would require a physician’s prescription / endorsement and provision of cannabis by a licensed producer for medical use
3.1 Chronic Pain

Three reviews summarise the clinical trial evidence for pharmaceutical cannabinoids and herbal cannabis treatment of chronic pain:

- **Canadian Family Physicians (CFP) 2018** (Allan, Finley, et al., 2018; Allan, Ramji, et al., 2018)
  - Umbrella review for Clinical Practice Guideline development (Allan, Ramji, et al., 2018)
- **Cochrane Collaboration 2018** (Mucke, Phillips, Radbruch, Petzke, & Hauser, 2018)
  - Systematic review on cannabis for chronic neuropathic pain
- **US National Academy of Sciences, Engineering and Medicine, 2017** (National Academies of Sciences Engineering Medicine, 2017)
  - State of the science review and research recommendation development

All three reviews combine findings of pharmaceutical cannabinoids and herbal cannabis. Studies used to satisfy the regulatory approval process for pharmaceutical cannabinoids are the most scientifically rigorous, which explains why pharmaceutical cannabinoids dominate the systematic review findings. The US National Academies review reports:

For chronic pain, most studies examined oral cannabis extract [i.e. pharmaceutical cannabinoids], although some examined smoked or vaporized cannabis. It is unknown whether and to what degree the results of these studies can be generalized to other products and routes of administration (p. 127).

### 3.1.1 Canadian Family Physicians (CFP) 2018

The CFP review pooled data from 23 systematic reviews reporting randomized controlled trial (RCT) findings of pharmaceutical cannabinoids and herbal cannabis for pain in adults compared to placebo or another drugs. They found:

Meta-analysis of 15 RCTs found more patients taking cannabinoids attained at least a 30% pain reduction: risk ratio (RR) of 1.37 (95% CI 1.14 to 1.64), number needed to treat (NNT) of 11. Sensitivity analysis found study size and duration affected findings (subgroup differences, P \leq .03), with larger and longer RCTs finding no benefit.

Comparing types of medical cannabinoids, inhaled cannabinoids had an RR of 1.52 (95% CI 1.17 to 1.99) and an NNT of 6, while buccal-spray cannabinoids had an RR of 1.28 (95% CI 1.02 to 1.61) and an NNT of 16, but with no clear difference in subgroups (P = .34) (p. e82)

The authors concluded:

There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain and the benefit is likely small. Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy (p. e78).
The findings and interpretation are similar to that of the Cochrane Collaboration review. The CFP however went on to use these findings in the development of clinical practice guidelines for family physicians (Allan, Ramji, et al., 2018). The full recommendations are presented below.

**Canadian Family Physician 2018 clinical practice guidelines recommendations summary**

**Management of pain**
- Acute pain: We **strongly recommend against** use of medical cannabinoids for acute pain management owing to evidence of no benefit and known harms (strong recommendation)
- Headache: We **recommend against** use of medical cannabinoids for headache owing to lack of evidence and known harms (strong recommendation)
- Rheumatologic pain: We **recommend against** use of medical cannabinoids for pain associated with rheumatologic conditions (including osteoarthritis and back pain) owing to lack of evidence and known harms (strong recommendation)
- Neuropathic pain: We **recommend against** medical cannabinoids as first- or second-line therapy in neuropathic pain owing to limited benefits and high risk of harms (strong recommendation)
  - Clinicians **could consider** medical cannabinoids for refractory neuropathic pain, with the following considerations (weak recommendation):
    — a discussion has taken place with patients regarding the benefits and risks of medical cannabinoids for pain
    — patients have had a reasonable therapeutic trial* of ≥ 3 prescribed analgesics† and have persistent problematic pain despite optimized analgesic therapy
    — medical cannabinoids are adjuncts to other prescribed analgesics....

- Types of medical cannabinoids for pain:
  - If considering medical cannabinoids, we **recommend** a pharmaceutically developed product (nabilone or nabiximols) as the initial agent (strong recommendation)
    — Nabilone is off-label for pain and has limited evidence of benefit. However, it is less expensive than nabiximols and dosing is more consistent than for smoked cannabis
    — Nabiximols is expensive and, in some provinces, only available through specialist prescribing or special authorization.
  - However, nabiximols has better evidence than nabilone does
  - If considering medical cannabinoids, we **recommend against** medical marijuana (particularly smoked) as the initial product (strong recommendation)
    — Evidence for smoked cannabis has a very high risk of bias, and long-term consequences are unknown
    — Products available can have far higher concentrations of THC and CBD than those researched (p. 112).
3.1.2 Cochrane Collaboration 2018: Systematic Review on Chronic Neuropathic Pain

The Cochrane systematic review included 16 randomized control trials of ‘cannabis-based medications’, two of which were trials of herbal cannabis (Mucke et al., 2018). The authors conclude:

The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms. The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes (p. 2).

Of the 2 studies of herbal cannabis included in the Cochrane review, one was from Canada using herbal cannabis from Saskatchewan (Ware et al., 2010). The Ware 2010 study enrolled 23 participants, who were randomly assigned to receive 0.0%, 2.5%, 6.0% or 9.4% THC over four 14-day periods in a cross-over design. The study authors concluded:

A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated. Further long-term safety and efficacy studies are indicated (p. E694).

The study was assessed by Cochrane reviewers as having a number of risks of bias including small sample size, incomplete outcome reporting and uncertain randomization protocol.

The other study used herbal cannabis from the University of Mississippi, a site that, until recently, had a monopoly on producing cannabis for research in the USA. The quality of the US ‘research cannabis’ has been criticized as having low and variable THC levels which has restricted dose response research. The US study was in an HIV population, not relevant to ICBC.

3.1.3 US National Academy of Sciences, Engineering and Medicine, 2017

The National Academies review focussed on all chronic pain, not just post injury or trauma conditions of most interest to ICBC. This review primarily aimed to map the state of the science with a view to making recommendations for research (National Academies of Sciences Engineering Medicine, 2017). A summary of findings on herbal cannabis (inhaled cannabis) follows:

Only 1 trial (n = 50) that examined inhaled cannabis was included in the effect size estimates from Whiting et al. (2015). This study (Abrams et al., 2007) also indicated that cannabis reduced pain versus a placebo (OR, 3.43, 95% CI = 1.03–11.48). It is worth noting that the effect size for inhaled cannabis is consistent with a separate recent review of 5 trials of the effect of inhaled cannabis on neuropathic pain (Andreae et al., 2015). The pooled ORs from these trials contributed to the Bayesian pooled effect
estimate of 3.22 for pain relief versus placebo (95% CI = 1.59–7.24) tested across 9 THC concentrations. There was also some evidence of a dose-dependent effect in these studies (p. 89).

With regard to the evidence on cannabis for chronic pain the report explains that:

The majority of studies on pain cited in Whiting et al. (2015) evaluated nabiximols outside the United States. In their review, the committee found that only a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States (p. 90).

Conclusion of the US National Academies Review

There is substantial evidence that cannabis is an effective treatment for chronic pain in adults (p. 90).

This conclusion differs from the other two reviews on cannabinoids for chronic pain in that it notes the volume (substantial) as opposed to the quality of the evidence and the size of treatment effect. In keeping with its mandate, this review included the largest and widest range of evidence from observational and quasi-controlled studies, not the stricter quantitative analysis requirement of the CFP review or the RCTs required by the Cochrane review. However, this National Academies review is important to note because it has been influential in shaping public perception of benefit from herbal cannabis in large part due to the power and influence of the national research institutions represented.

3.1.4 TI Summary of herbal cannabinoids for chronic, including neuropathic, pain

The three reviews documented their review methodology showing the variations in literature search, study appraisal and synthesis of efficacy data. These similarities and differences are presented in detail in Technical Report 2 Efficacy.

The Cochrane Review was the most focused on evidence of causality and found the evidence fell far short of the high standard they set. The CFP similarly required scientifically valid clinical evidence to be able to guide clinical practice. Both reviews pooled data from a large number of pharmaceutical and herbal cannabinoids products with different doses and compositions. This combination of pharmaceutical and herbal products is unusual but understandable given the minimal amount of clinical trial data available.

The US National Academies review had a broad mandate to make recommendations for research for the widest range of clinical conditions and health effects. As a result, this review included all levels of evidence, such as observational and quasi-controlled studies unlike the
CFP and Cochrane reviews that limited their inclusion criteria to clinical trials. Lower levels of evidence have less protection against bias.

Nine trials were reviewed by all three review groups. The CFP and Cochrane reviews judged that the study designs were not sufficiently rigorous to protect them against bias. (See Technical Report 2 Efficacy). Overall, the clinical trials are relatively short in duration with small study populations. For example, the RCTs included in the Cochrane review had durations of 2 to 26 weeks with study populations from 20 to 339 individuals.

A search of the database that registers clinical trial protocols (U.S. National Library of Medicine, 2018) revealed only one trial recruiting patients to investigate cannabinoid use for chronic neuropathic pain — a protocol investigating low back pain treated with vaporized cannabis (3.7% THC/5.6% CBD), dronabinol or placebo. This trial was of 8 weeks duration and does not appear to require a 50% pain reduction as its clinical outcome, the current recommended standard for pain trials. Therefore, little new clinical trial evidence is likely to be added in the next few years to the already limited number of studies using herbal cannabinoids for chronic pain generally and for neuropathic pain in particular.

One indication of the relative weakness of trials of ‘smoked cannabis’ was presented as the median number of patient-days (a number combining the number of patients and the duration of the trial) (Whiting et al., 2015). While the trials of oral or oral spray formulations (pharmaceutical cannabinoid medications) had a median (mid-point number) of 1470 patient-days, smoked cannabis trials had a median of 115 patient-days. (Allan, Finley, et al., 2018) (p. e91) This statistical analysis demonstrates how much more data was available to evaluate the pharmaceutical cannabinoid medications.

**Benefit and Harm**
Both Cochrane and CFP reviews assessed a balance of evidence of benefit and harm from the clinical studies included in their reviews. They did not include broader population-based harm data from observational studies or harm registries. Their conclusions were similar (see Technical Report 2 Efficacy).

None of these reviews explicitly weighed harm versus benefit using a hierarchy of outcomes, starting with the most consequential outcomes of death, overdose, hospitalization and development of physical tolerance and dependence.

**Comparison studies**
Notably absent are trials comparing pharmaceutical cannabinoids or herbal cannabis to opioids or alternative pharmacotherapies commonly used for chronic pain. Therefore, while manufacturers, patients and government policy are all seeking alternative medications for chronic pain, there is an absence of even moderate level studies establishing a role for cannabinoids. There could be a substantial reduction in harm if herbal cannabis could at least partially replace opioids as cannabis has less risk of overdose and less addiction potential (Reiman, Welty, & Solomon, 2017)
3.2 Post traumatic stress disorder, anxiety, and depression

Patients may develop post-traumatic stress disorder (PTSD), depression or anxiety disorders or other psychological issues following a motor vehicle accident. In this section we summarize the findings from one of the three evidence reviews cited above for treatment of chronic pain. We also cite findings from other recent independent reviews that met selection criteria.

3.2.1 Post traumatic stress disorder

Only one of the reviews cited above for chronic pain reviewed PTSD. The CFP review group did not consider PTSD because it only looked at conditions that had sufficient evidence to inform clinical practice guidelines. PTSD evidence was insufficient. The Cochrane Collaboration has reviewed pharmaceutical therapies for PTSD. However, no pharmaceutical cannabinoid or herbal cannabis medication has been subjected to RCT research for PTSD (Stein, Ipser, & Seedat, 2006). The National Academies review includes PTSD, but reports the limited available evidence (National Academies of Sciences Engineering Medicine, 2017).

There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of post-traumatic stress disorder.

A single, small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. (Jetly, Heber, Fraser, & Boisvert, 2015) This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (plant derived forms) and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder. (p. 124).

Note, the National Academies review provides evidence for nabilone not herbal cannabis. For the purposes of the ICBC funding model this evidence would only apply to Level 2 – Pharmaceutical cannabinoids for indications without regulatory approval.

US Veterans Affairs (VA) sponsored review, 2017

A VA sponsored review (O’Neil et al., 2017) provides the following summary statements on herbal cannabis use in PTSD:

Data Synthesis: Two systematic reviews, 3 observational studies, and no randomized trials were found. The systematic reviews reported insufficient evidence to draw conclusions about benefits and harms. The observational studies found that compared with nonuse, cannabis did not reduce PTSD symptoms. Studies had medium and high risk of bias, and overall evidence was judged insufficient. Two randomized trials and 6 other studies examining outcomes of cannabis use in patients with PTSD are ongoing and are expected to be completed within 3 years. Limitation: Very scant evidence with medium to high risk of bias.
Conclusion: Evidence is insufficient to draw conclusions about the benefits and harms of plant-based cannabis preparations in patients with PTSD, but several ongoing studies may soon provide important results (p. 332).

Walsh et al., 2017

A ‘guided systematic review’ by Walsh et al., 2017 has some prominence in British Columbia and Canada and therefore its findings are presented and critiqued here (Walsh et al., 2017). The review concludes:

Research on the efficacy of cannabis for the treatment of PTSD is still in its infancy; however preliminary results are promising (p. 22).

For the purposes of the ICBC funding model this evidence also would only apply to Level 2: pharmaceutical cannabinoids for clinical indications without Health Canada approval. However, the evaluation by Walsh was based on studies that are too weak to meet the inclusion criteria of our core set of reviews (see standard hierarchy of evidence scale between II- and III Appendix 2). As a result the studies have few safeguard against bias and are better suited to hypothesis generation than establishing causal relationships.

Dr. Walsh, with the Department of Psychology at UBC Kelowna is the lead author and also the lead researcher on a randomized clinical trial in progress (Tilray, 2016) of herbal cannabis for PTSD, sponsored by Tilray - a Canadian licensed cannabis producer. When these trials and other trials are complete they will represent a more suitable evidence base upon which to base prescribing and policy decisions.

Not all the observational data cited by Walsh et al., 2017 was positive. They also cite a longitudinal observational study using a US Veterans Affairs PTSD treatment dataset that showed an association between worse PTSD symptoms after treatment discharge and reported cannabis use (Wilkinson, Stefanovics, & Rosenheck, 2015).

The evidence of harm for individuals with PTSD who develop cannabis use disorder (CUD) was cited as follows:

Importantly, evidence also cautions that individuals with PTSD who develop CUDs may later experience diminished benefit from traditional PTSD treatments (Bonn-Miller, Boden, Vujanovic, & Drescher, 2013), heightened withdrawal during a quit attempt (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013) (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013), and poor short-term cessation outcomes (Bonn-Miller et al., 2015). Given these potential consequences, individuals with PTSD who are interested in or already using cannabis should be monitored for development of CUDs (p. 22).
Communities of Canadian veterans have embraced herbal cannabis for PTSD (Leeder, 2018). Veterans Affairs Canada was the first government program to institute a policy of reimbursing herbal cannabis for veterans with physicians’ authorization within the limits of the policy. Expenditures increased to over $60 million in 2016 (see Appendix 11). However, there is a clear and undisputed lack of clinical trial evidence in support of the therapeutic use of cannabis for PTSD or of the Canadian VA policy (The Canadian Press, 2016).

### 3.2.2 Anxiety disorders

Only one of the three reviews cited for chronic pain treatment (US National Academies) included evidence on anxiety disorders. The CFP review excluded anxiety treatment due to a lack of clinical trial evidence to inform prescribing. The Cochrane Collaboration does not have a review of pharmaceutical cannabinoids or herbal cannabis for anxiety disorders.

The National Academies review reported that one RCT on cannabidiol was identified from a 2015 review (Whiting et al., 2015):

No additional good quality and more recent primary literature was identified.... Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms (p. 119).

The report concluded:

There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (p. 120).

On the harm side, this review reported:

In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety symptoms and heavy cannabis use is associated with social phobia disorder (p. 119).

### 3.2.3 Depression disorders

Depression appears prominently as an adverse event in CFP and Cochrane reviews.

The US National Academies review (National Academies of Sciences Engineering Medicine, 2017) presents the following knowledge statements on cannabis and depression:

The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015, p. 9); therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms (p. 121).

In addressing the question “Are Cannabis or Cannabinoids an Effective Treatment to Reduce Depressive Symptoms?” the review concluded:
There is limited evidence that nabiximols, dronabinol, and nabilone are ineffective treatments for the reduction of depressive symptoms in individuals with chronic pain or multiple sclerosis (p. 121).

The limited evidence referred to is a trial comparing these three prescription medications. The review by Whiting et al. (2015) was the most recent good-quality review. No RCTs were identified that specifically evaluated cannabis in patients with a depressive disorder. Five RCTs (634 participants) enrolled patients for other conditions (chronic pain or multiple sclerosis with spasticity) and reported on depressive symptoms... (p. 120).

Although patients report using cannabinoids for depression, our search for a good-quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There are no trial data addressing the effects of cannabinoids for major depressive disorder (p. 121).

3.2.4 TI Summary of herbal cannabinoids for PTSD, anxiety and depression

The available clinic trial evidence is insufficient to support use of pharmaceutical cannabinoids for PTSD, anxiety, depression or other psychological or psychiatric conditions. The US National Academies review provides the most complete summary of clinical trial and observational study data. It concludes that rather than resulting in improvement of psychological or psychiatric conditions, use of pharmaceutical cannabinoids could result in depression. This US National Academies evidence is relative to Level 2 in the proposed ICBC funding policy model: pharmaceutical cannabinoid medications for clinical indications not approved by Health Canada.

For herbal cannabis (Level 3 of the ICBC funding model) there is insufficient clinical trial evidence of efficacy to support their use in clinical practice. There are studies with weak designs revealing a range of harms from risk of developing cannabis use disorder, to increases in anxiety and social phobias. In the next section, both anxiety and depression appear as adverse events.
4.0 Harm

The three reviews highlighted in this report summarise the harm evidence for pharmaceutical cannabinoids and herbal cannabis:

- Canadian Family Physicians 2018 (Allan et al., 2018)
  - Reviews of adverse events (AE) from use of medical cannabinoids
- US National Academy of Science, Engineering and Medicine, 2017
  - Associations between health outcomes and cannabis use in the general public
- Veteran’s Affairs Funded Project 2017 (Nugent et al., 2017)
  - Herbal cannabis use for therapeutic purposes as well as general public use

4.1 Overall safety: Herbal cannabis intoxication

Herbal cannabis intoxication has characteristic clinical effects. The US National Academies 2017 review (National Academies of Sciences Engineering Medicine, 2017) describes these features as follows:

During acute cannabis intoxication, the user’s sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened. Some users report feeling relaxed or experiencing a pleasurable “rush” or “buzz” after smoking cannabis (Agrawal et al., 2014). These subjective effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills. When very high blood levels of delta 9-THC are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations (Li et al., 2014). Furthermore, as legalized medical and recreational cannabis availability increase nationwide, the impairment of driving abilities during acute intoxication has become a public safety issue.

In addition to delta 9-THC dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of delta 9-THC, and the loss of sensitivity to its pharmacological actions. Prolonged CB1 receptor occupation as a consequence of the sustained use of cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of delta 9-THC and other cannabinoid agonists (Gonzalez et al., 2005). Animals exposed repeatedly to delta 9-THC display decreased CB1 receptor levels as well as impaired coupling between CB1 and its transducing G-proteins (Gonzalez et al., 2005). Similarly, in humans, imaging studies have shown that chronic cannabis use leads to a down-regulation of CB1 receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (Hirvonen et al., 2012) (p. 53).

The acute intoxication effect of herbal cannabis may or may not be an unwanted side effect for patients using it for medical purposes. These psycho-social issues related to delta-9 THC may not
be completely captured in the benefit or harm sections of this report as dose used for medical purposes may not reach the level of intoxication. CBD, which is an important cannabinoid, does not contribute to the intoxication effects and may attenuate them.

4.2 Estimating the harm profile of cannabis

4.2.1 CFP review of adverse events in the context of medical uses

The Canadian Family Physician review extracted and pooled adverse event data from 23 reviews that summarized studies of pharmaceutical cannabinoids and herbal cannabis for a variety of medical conditions (Allan, Finley, et al., 2018). They presented their finding in a statistical format of Number Needed to Harm (NNH) as well as Numbers Needed to Treat (NNT) – a common way physicians use these estimates.

For ‘inhaled cannabinoids’ (herbal cannabis) CFP estimated that 6 patients need to be treated for 1 to have 30% or greater pain reduction. They estimated that one in every 8 to 22 patients treated will stop treatment with an adverse event; of every 5 treated one will experience dizziness; one in 5 will experience sedation; one in 15 will experience confusion; and one in 20 will experience dissociation. They concluded that the harm outweighs the benefit for adults using herbal cannabis or pharmaceutical cannabinoids for chronic pain reduction.

4.2.3 US Veterans Affairs funded review on therapeutic use and general harms

The US VA funded overview of harms of herbal cannabis included systematic reviews of therapeutic use as well as studies of use in the general public (11 systematic reviews and 32 primary studies) (Nugent et al., 2017). This review found that:

Harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment...

Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is insufficient.

Conclusion: ...

Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects (p. 319).

4.2.4 US National Academies review of general harms

This review of reviews states it ‘was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report’s chapters’ (National Academies of Sciences Engineering Medicine, 2017)(p. 6).
In other words, the statistical associations that were examined between cannabis use (not limited to medical uses) and the development of health effects (positive or adverse events) were separate analyses. This is understandable in such a broad state of the science review. Here are select examples of the health effects (adverse) where the evidence was assessed as substantial.

There is substantial evidence of a statistical association between cannabis use and:
- Increased risk of motor vehicle crashes (9-3)

Here are further associations for topics of interest to the ICBC:

There is limited evidence of a statistical association between cannabis use and:
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

4.2.4 TI Summary of harm

The science on the intoxication effects of cannabis presented in the US National Academies report is relevant. Cannabis intoxication is dose related. Also the response to cannabis is known to vary by individual with some individuals withdrawing quickly from clinical trials due to adverse effects. It is unknown whether dosing at low or below intoxication effects by varying THC amounts or THC to CBD ratios can preserve therapeutic benefits.

Herbal cannabis products include THC from < 1% to over 20%, CBD <1% to over 10% in a variety of delivery systems (dried to be smoked or vaped, oil based, dried contained in capsules, topical creams). However, there is almost no valid research data on the AE profile of CBD without or with low levels of THC - the key psychoactive constituent.

Cannabis use disorder (CUD) is a well-documented risk of cannabis use with a DSM-5 designation and diagnostic criteria. The pharmaceutical cannabinoid medication nabilone which mimics THC has been formulated to decrease the potential for dependency. CBD on its own has been documented to have no risk of dependency. The risk of developing CUD with herbal cannabis products containing significant amounts of THC used for medical purposes rather than recreational use is unknown.
5.0 Cannabinoid pharmacology

Pharmacology is the study of the properties and behaviour of drugs at the basic science level of chemistry, including modes of action and effects in the body. The product monographs available for nabiximols (GW Pharma Ltd., 2012) and nabilone (Apotex Inc., 2015), the two available pharmaceutical cannabinoids, contain pharmacological information that has been supplied by the manufacturer and approved by the regulator Health Canada. In addition to information on clinical uses (known as ‘indications’), the product monograph contains information on mechanism of action, warnings and precautions, adverse reactions, dosage and administration as well as a summary of clinical trial data (see Section 4 Technical report). This is the information that physicians and pharmacists rely on in their clinical decision making.

Unlike pharmacologic cannabinoids, herbal cannabis products do not have product monographs. Health Canada has made information available for professionals and consumers (Health Canada, 2016a, 2016b). This information comes with a caveat that ‘despite the similarity of format, it is not a Drug Product Monograph which would be required if the product were to receive a Notice of Compliance authorizing its sale in Canada (see Appendix 12).

The Health Canada information primarily relates to the state of the science on delta-9 THC. This document was used to access data on tolerability and dose, how long impairment lasts, effects of smoked preparations, delivery system (appropriateness), standardized THC levels (THC strains vs non THC strains) and which prescription drugs are contraindicated. See Section 4 Technical report for a summary. This data pertains primarily to the THC psychoactive component that dominates herbal strains that were hybridized to maximize the intoxicating effects of THC.

The chemical composition of herbal cannabis however varies from batch to batch, supplier to supplier and type of plant strain. Furthermore each supplier has numerous products formulated specifically to have a different composition in terms of THC to CBD volume and ratio. All these products also have unknown but presumed variable compositions of chemical constituents many of which may have a health impact and some of which when smoked may cause harm similar to tobacco. Herbal cannabis products do not have comparable assurance of quality in meeting the rigorous production standards of pharmaceutical products. The industry may claim that herbal cannabis products are ‘pharmaceutical grade’, however, at this time, they can provide little scientific data on the specific pharmacology of their products.

The pharmacology of each cannabinoid constituent can be studied separately in their pure forms. CBD, for example, is a non-psychoactive constituent of cannabis, that does not cause intoxication and is often used in oral delivery system rather than dried forms that are smoked or vaped. Recently the WHO conducted a pre-review of CBD that appears to be part of a global movement to remove it from the most highly restricted and controlled drug schedules reserved for substances with a high potential for abuse, no medical benefit and lack of accepted safety. The WHO pre-review reports: ‘CBD is generally well tolerated with a good safety profile. Reported adverse effects may be as a result of drug-drug interactions between CBD and
patients’ existing medications’ (World Health Organization, 2017)(p. 5). One pharmaceutical cannabinoid product that is a pure CBD herbal extract in an oral solution has been approved by the US Food and Drug Agency (FDA) for use in children with two rare forms of epilepsy (U.S. Food & Drug Administration, 2018).

Some third party insurers have opted to include CBD funding in their policy under some conditions due to the favorable safety profile and risk mitigation with a non-smoking delivery system. For example, the New Brunswick Workers Compensation policy on medical cannabis states that ‘The authorization must be for CBD rich medicinal cannabis, the maximum THC content being less than one (1)%, (as THC is the component that causes impairment). Medicinal cannabis will not be approved unless the authorization explicitly indicates a non-smoking related route of administration, such as vaporization’ (WorkSafe NB, 2018). While this policy satisfies concerns about intoxication by requiring a low percentage THC herbal and eliminates harm from smoking, it neglects the critical need for any product to undergo rigorous testing for composition or clinical study to evaluate the effects of all of its components, not just CBD and THC.
Appendix 1. The Health Canada Form for Authorizing use of Cannabis (Health Canada, 2017)

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 6 of the ACMPR).

Your health care practitioner may use this form to provide you authorization to use cannabis for medical purposes. Your health care practitioner may use a different form, but the required information as per section 8 of the ACMPR (outlined below) must be included.

Access via Health Canada licensed producers: Should you choose to access cannabis from a licensed producer, this form must be sent directly to the licensed producer of your choice. You may choose any licensed producer who is authorized to sell to registered clients. Please see the Health Canada website for a list of licensed producers. Should you wish to switch from one Health Canada licensed producer to another a new medical document will be required as licensed producers are required to keep the original medical document on file.

Access via production for own medical purposes: Should you choose to produce your own cannabis, or designate someone to produce it for you, the original of this document must be sent to Health Canada with your Registration Application Form.

Patient's Given Name and Surname:

Patient's Date of Birth (DD/MM/YYYY):

Daily quantity of dried marijuana to be used by the patient: grams / day

The period of use is [ ] day(s) or [ ] week(s) or [ ] month(s).

Note: The period of use cannot exceed one year

Health care practitioner's given name and surname:

Profession:

Health care practitioner's business address:
Full business address of the location at which the patient consulted the health care practitioner (if different than above):

Phone Number: 

Fax Number (if applicable): 

Email Address (if applicable): 

Province(s) Authorized to Practice in: 

Health Care Practitioner's Licence number: 

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: 

Date Signed (DD/MM/YYYY): 

Important Note for Authorizing Health Care Practitioner

If the patient chooses to produce cannabis for their own medical purposes or you are not submitting this document via secure fax do not initial the box below.

If your patient chooses to access cannabis for medical purposes via a licensed producer, this medical document can be submitted from the health care practitioner's office to the licensed producer by secure fax. If you choose to submit the medical document by secure fax, initial the statement below to acknowledge agreement.

I, the health care practitioner, acknowledge that the faxed medical document is now the original medical document and that I have retained a copy of this document for my records only.

Initial here: 


Appendix 2. Standard hierarchy of evidence Levels (Scottish Intercollegiate Guidelines Network, 2011)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I++</td>
<td>High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>I+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>I-</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>II++</td>
<td>High-quality systematic reviews of case-control or cohort studies</td>
</tr>
<tr>
<td></td>
<td>High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>II+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>II-</td>
<td>Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>III</td>
<td>Nonanalytic studies (e.g., case reports, case series)</td>
</tr>
</tbody>
</table>

BOX S-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

continued
MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.
### Appendix 4. Quality of Evidence Grades from the GRADE approach used by CFP (Schünemann, 2013) (Table 5.1)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very Low</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</td>
</tr>
</tbody>
</table>

### Appendix 5. GRADE Representations of quality of evidence and strength of recommendations (Schünemann, 2013) (Table 6.4)

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Symbol</th>
<th>Letter (varies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>★★★★★</td>
<td>A</td>
</tr>
<tr>
<td>Moderate</td>
<td>★★★★</td>
<td>B</td>
</tr>
<tr>
<td>Low</td>
<td>★★★</td>
<td>C</td>
</tr>
<tr>
<td>Very low</td>
<td>★★</td>
<td>D</td>
</tr>
<tr>
<td>Strength of Recommendation</td>
<td>Symbol</td>
<td>Number</td>
</tr>
<tr>
<td>Strong for an intervention</td>
<td>★★★★</td>
<td>1</td>
</tr>
<tr>
<td>Weak for an intervention</td>
<td>★★</td>
<td>2</td>
</tr>
<tr>
<td>Weak against an intervention</td>
<td>★★</td>
<td>2</td>
</tr>
<tr>
<td>Strong against an intervention</td>
<td>★★★★</td>
<td>1</td>
</tr>
</tbody>
</table>
## Appendix 6. CFP summary of findings and GRADE Recommendations on pain (Allan, Finley, et al., 2018) (p. e92)

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>COMPARATOR</th>
<th>RELATIVE EFFECT (95% CI)</th>
<th>CERTAINTY OF EVIDENCE (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30% reduction of pain</td>
<td>Placebo</td>
<td>RR = 1.37 (1.14 to 1.64)</td>
<td>Overall: Very low owing to serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoked medical marijuana: Very low owing to serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Buccal cannabinoids: Very low owing to serious risk of bias, serious inconsistency, and serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>First or second line for pain: Very low owing to serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Third line for pain: Very low owing to serious risk of bias, serious inconsistency, and serious indirectness</td>
</tr>
<tr>
<td>Change in pain scale</td>
<td>Placebo</td>
<td>WMD = 0.5 (0.11 to 0.80)*</td>
<td>Overall: Very low owing to serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision</td>
</tr>
</tbody>
</table>
Appendix 7. A BC Pharmacare Special Authority Request Form (British Columbia Ministry of Health, 2016)

**SECTION 1 - PRESCRIBER INFORMATION**
- PRESCRIBER'S NAME AND MAILING ADDRESS
- PHONE NUMBER
-關鍵字: 紅色

**SECTION 2 - PATIENT INFORMATION**
- PATIENT'S FAMILY NAME
- DATE OF BIRTH (YYYY, MM, DD)
- PERSONAL HEALTH NUMBER (PHN)

**SECTION 3 - MEDICATION DETAIL INFORMATION**
- NEWLY REQUESTED
- RENEWAL
- INDICATIONS FOR SPECIAL AUTHORITY (PLEASE CHECK ALL THAT APPLY, AND SPECIFY WITH SUPPORTING DETAILS)
- Diagnosis requiring use
- Previously tried therapies, and response
- Patient specific contraindications to alternatives (if applicable)

I have discussed with the patient that the purpose of releasing their information to PharmaCare is to obtain Special Authority for prescription coverage and for the purposes set out here.

Prescriber's Signature (Mandatory)

PharmaCare may request additional documentation to support the Special Authority request. Actual reimbursement is subject to the rules of a patient's PharmaCare plan, including any annual deductible requirement, and to any other applicable PharmaCare pricing policy.

**PHARMACARE USE ONLY**
- STATE
- EFFECTIVE DATE (YYYY, MM, DD)
- DATE OF APPROVAL

REQUEST FOR REIMBURSEMENT of NABILONE 0.25 MG CAPSULES THROUGH THE EXCEPTIONAL ACCESS PROGRAM (EAP)
Request for Interim funding of Nabilone 0.25mg Capsules during Drug Shortage of brands and strengths of Nabilone 0.5 mg and 1 mg funded on the Ontario Drug Benefit Formulary.
FAX requests to EAP toll-free at 1-844-829-6807 or Toronto(GTA) local: 416-314-3857

<table>
<thead>
<tr>
<th>SECTION 1 – Prescriber Information</th>
<th>SECTION 2 – Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>First name</td>
<td>Initial</td>
</tr>
<tr>
<td>Street no.</td>
<td>Street name</td>
</tr>
<tr>
<td>City</td>
<td>Province</td>
</tr>
<tr>
<td>Fax no.</td>
<td>Telephone no.</td>
</tr>
</tbody>
</table>

SECTION 3 – Drug Requested
Nabilone 0.25 mg Capsules

Dosage Regimen:

SECTION 4 – Diagnosis and Reason for Use

Diagnosis for which drug is requested: ___________________________________________

Reason for use over formulary alternatives:

☐ Drug shortage of formulary funded 0.5mg and 1mg nabilone capsules. Requesting pharmacy has supply or is able to obtain a supply of 0.25mg nabilone capsules to be utilized in the interim.
☐ Yes ☐ No If No, specify reason(s) for request and/or submit request on the usual EAP standard request form.
**Prescriber signature will be required for a No response.

**Specify reason(s) for request if not being used as a substitute for nabilone 0.5 mg or 1 mg drug shortage:

REQUEST FOR INTERIM FUNDING OF NABILONE 0.25 MG CAPSULES THROUGH EAP:

Note to Pharmacists who are completing this request on behalf of the physician who has authorized the appropriate use of nabilone 0.5 mg and 1 mg capsules in this patient. Please clearly indicate ALL the following:

NAME OF PHARMACY:

TELEPHONE NUMBER OF PHARMACY:

CONTACT NAME AT THE PHARMACY:

While a physician or nurse practitioner are not required to sign this EAP request for reimbursement of nabilone 0.25 mg capsules being used as an alternative to manage the confirmed drug shortage of all strengths of nabilone funded on the ODB formulary, the name of the prescriber must be completed clearly in Section 1 and the pharmacist/pharmacy technician is expected to follow all required legislation, regulations, policies, and patient care expectations for switching a patient to the new nabilone product to ensure appropriate use of the new strength of product by the patient.

Pharmacies are expected to switch back to the ODB formulary funded strengths and most cost-effective options once the 0.5 mg and 1 mg nabilone capsules become available.

<table>
<thead>
<tr>
<th>Pharmacist Name</th>
<th>Registration/License Number</th>
<th>Date</th>
</tr>
</thead>
</table>

Authorized Prescriber Name ** | Registration/License Number | Date |
Appendix 9. Criteria for reimbursement of nabiximols for MS pain management
(Ontario Ministry of Health and Long-term Care, 2018)

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>BRANDS REIMBURSED</th>
<th>DOSAGE FORM/STRENGTH</th>
<th>REIMBURSEMENT CRITERIA</th>
<th>STANDARD APPROVAL DURATION</th>
</tr>
</thead>
</table>
| Cannabidiol and delta-9-tetrahydrocannabinol | Sativex | 25 mg/27 mg per mL buccal spray | For the treatment of neuropathic pain related to multiple sclerosis in patients who have:  
- Ineffective response or intolerable side effects / contraindications to adequate trials* of a tricyclic antidepressant and gabapentin and pregabalin; and  
- Ineffective response or intolerable side effects / contraindications to adequate trials* of Cytosan (nabifone) and Marinol (delta-9-tetrahydrocannabinol); and  
- No contraindications to Sativex therapy.  
* Adequate trial is defined as 2 months unless intolerable side effect(s) occur.  
Note: Side effects and contraindications must be described in detail. Side effects should be deemed serious by the physician such that no further therapy with the agent would be warranted.  
Renewal will be considered for patients responding to Sativex therapy as demonstrated by decreased pain and other pain-related symptoms; no initiation of new analgesics; and no increase in doses of any analgesics.  
Sativex is also reimbursed for the treatment of refractory pain in palliative cancer patients according to specified criteria. | Initial: 1 year  
Renewal: Lifetime | 6 months |


Appendix 10. Policy of Veterans Affairs Canada for Exception to 3g daily cannabis limit (Veterans Affairs Canada, 2018)

Annex A

Exceptional Approval of More than 3 Grams

1. Reimbursement may be authorized for more than 3 grams of dried marihuana or equivalent when confirmation is received from the treating physician that the Veteran is palliative. In end of life situations, documentation is not required from a medical specialist.
2. Palliative care is defined in the Palliative Care policy. The policy also includes additional considerations for Veterans requiring end of life care.
3. When authorization of cannabis for medical purposes is for Amyotrophic Lateral Sclerosis (ALS), validation of the diagnosis from the attending physician will be required.

Other Exceptional Requests

4. In all cases, other than the circumstances as noted above, requests for reimbursement of more than 3 grams of dried marihuana or equivalent must be accompanied by additional documentation from a medical specialist. The required documentation from the medical specialist must indicate:
   a. the rationale for the use of more than 3 grams per day;
   b. there are no contraindications to the use of marihuana; and
   c. alternative treatments were found to be ineffective or contraindicated.
5. When authorization of cannabis for medical purposes is for chronic pain, additional documentation will be required from a medical specialist in the area of the treatment of chronic pain.
6. When authorization of cannabis for medical purposes is for a psychiatric condition(s), additional documentation will be required from a psychiatrist.
7. When both chronic pain and a psychiatric condition are present, additional documentation will be required from either a medical specialist in the treatment of chronic pain or a psychiatrist.
8. For any other health conditions, additional documentation will be required from a medical specialist with expertise in the diagnosed condition, including but not limited to chemotherapy-induced nausea and vomiting, wasting syndrome, or loss of appetite in AIDS and cancer patients.
Appendix 11. Increases in Costs of Reimbursing Cannabis for Veterans (Veterans Affairs Canada, 2016)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Veterans</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008-2009</td>
<td>5</td>
<td>$19,088</td>
</tr>
<tr>
<td>2009-2010</td>
<td>15</td>
<td>$43,385</td>
</tr>
<tr>
<td>2010-2011</td>
<td>23</td>
<td>$63,057</td>
</tr>
<tr>
<td>2011-2012</td>
<td>37</td>
<td>$103,424</td>
</tr>
<tr>
<td>2012-2013</td>
<td>68</td>
<td>$284,632</td>
</tr>
<tr>
<td>2013-2014</td>
<td>112</td>
<td>$406,809</td>
</tr>
<tr>
<td>2014-2015</td>
<td>628</td>
<td>$5,160,747</td>
</tr>
<tr>
<td>2015-2016</td>
<td>1762</td>
<td>$20,538,153</td>
</tr>
<tr>
<td>2016 – April to September</td>
<td>3071</td>
<td>$31,000,000</td>
</tr>
</tbody>
</table>
Appendix 12. Health Canada disclaimer on information provided for health care professionals (Health Canada, 2016b)

Information for Health Care Professionals

**Cannabis (marihuana, marijuana)** and the cannabinoids
Dried plant for administration by ingestion or other means
Psychoactive agent

This document has been prepared by the Controlled Substances and Tobacco Directorate at Health Canada to provide information on the use of cannabis and cannabinoids for medical purposes. **Cannabis is not an approved therapeutic product and the provision of this information should not be interpreted as an endorsement of the use of this product, or cannabis generally, by Health Canada.**

Despite the similarity of format, it is not a Drug Product Monograph, which is a document which would be required if the product were to receive a Notice of Compliance authorizing its sale in Canada. This document is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis (marihuana) and cannabinoids. It is not meant to be comprehensive and should be used as a complement to other reliable sources of information.

**This document should not be construed as expressing conclusions from Health Canada about the appropriate use of cannabis (marihuana) or cannabinoids for medical purposes.**
References


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