

## Slow-release oral morphine (SROM) for opioid use disorder treatment in Alberta

Methadone and buprenorphine/naloxone (Suboxone®) are the most frequently used agonist therapies for opioid use disorder (OUD) treatment. Both of these medications have unique side-effects that can impact treatment retention and response in individual patients.<sup>1, 2</sup> Slow-release oral morphine (SROM; marketed as Kadian®) acts as a pure agonist at opioid receptors and may be an option in these cases. The formulation, consisting of extended release pellets in a capsule, allows for a once daily administration.<sup>3</sup>

Emerging evidence suggests that slow-release oral morphine may help to reduce opioid cravings and be particularly useful in patients with inadequate withdrawal suppression or intolerance to traditional options.<sup>4-8</sup> However, the available studies are few in numbers and have limitations in study design, duration and/or population. Of note, only the 24-hour slow release formulation, Kadian®, has been studied for its use as an opioid use disorder (OUD) treatment. Other long-acting formulations of morphine, such as MS Contin®, Morphine SR and M-Eslon®, or another synthetic opioid, have not been studied for OUD treatment and should not be used in this context. There is also no evidence to support OUD treatment with SROM during pregnancy and lactation.

Health Canada's Non-Insured Health Benefits (NIHB) program includes SROM on its formulary as a treatment option for OUD where methadone and Suboxone® are not appropriate or are unavailable.<sup>9</sup> CPSA also acknowledges slow release oral morphine as a third line treatment option for patients with an opioid use disorder. While the College does not have any guidelines specific to the use of SROM in opioid use disorder, the College recognizes related clinical advice provided in the [BC Opioid Use Disorder guidelines](#) (excerpts appended).<sup>10</sup> The College expects physicians wishing to prescribe slow-release oral morphine for an opioid use disorder to have an OAT Initiation Approval. This expectation is consistent with clinical guidelines<sup>10,11</sup> and the place of SROM as a third-line option for OUD. At minimum, prescribing physicians should seek expert advice through a specialist consultation. Primary care physicians may call RAAPID to consult with an OUD specialist.

As with other OUD treatments, SROM has associated safety risks. For instance, an immediate exposure to the high dose contained in the formulation can lead to a potentially fatal overdose. The slow-release design of SROM can be circumvented by chewing or crushing the pellets to release the entire morphine content as a bolus dose. Co-ingestion with alcohol can also cause dose-dumping. Another consideration is that once absorption is complete, the morphine in the bloodstream follows its usual kinetics and has a short half-life (2 to 4 hours compared with 8 to 59 hours for methadone).<sup>12</sup>

<sup>13</sup> As such, missed doses can lead to loss of tolerance relatively quickly. In addition to the risk of opioid toxicity, slow release oral morphine also carries a diversion risk.<sup>11, 12</sup> Potential for harms to the patient and public should be considered and be appropriately managed.

Strategies must be in place to reduce the risk of harms when prescribing SROM for opioid use disorder. Ideally, treatment should be preceded by assessment of addiction history including concurrent alcohol use, a review of Netcare's Pharmaceutical Information Network (PIN), a baseline urine drug screen and a treatment agreement. OUD treatment with SROM should almost always be in the form of daily witnessed ingestion. Carries may be considered in very exceptional circumstances, but are discouraged. Clear policies around scheduled and random urine drug screen (UDS) and the regular monitoring of patient dispenses through PIN are important. Clinicians should note that immunoassay-based point of care urine tests may be insufficient to rule out illicit heroin or prescription opioid use in patients on slow release oral morphine. Local and hospital testing laboratories can assist with details on available options and interpretation. Physicians should work collaboratively with other healthcare professionals involved in the patients' care, such as pharmacists, to ensure close monitoring and patient safety during treatment.

Please refer to the [Opioid Agonist Treatment Program](#) webpage for updates. To contact the program, email [Oat.Info@cpsa.ab.ca/cpsa.ca](mailto:Oat.Info@cpsa.ab.ca/cpsa.ca) or call 1-800-561-3899.

#### References:

1. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014;2: CD002207
2. Dyer KR, White JM. Patterns of symptom complaints in methadone maintenance patients. *1997;92:1445-55.*
3. Smith HS. Enteral Controlled-Release Opioid Delivery Systems. *2009;10:30-8.*
4. Ferri M, Minozzi S, Bo A, et al. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev* 2013;6: CD009879.
5. Kastelic A, Dubajic G., Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction* 2008; 103: 1837-46.
6. Bond A. J., Reed K. D., Beavan P., Strang J. After the randomized injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug Alcohol Rev* 2012;31: 492-8.
7. Beck T, Haasen C, Verthein U, Walcher S, Schuler C, Backmund M, et al. Maintenance treatment for opioid dependence with slow-release oral morphine : a randomized cross-over , non-inferiority study versus methadone. *2013;617-26.*
8. Hämmig R, D M, Köhler W, D M, Bonorden-kleij K, D M, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat.* 2014;47(4):275-81.
9. Health Canada First Nations and Inuit Health Branch. Non-insured health benefits Drug Benefit List 2017. Available from: <https://www.canada.ca/en/health-canada/services/publications/health-system-services/non-insured-health-benefits-drug-benefit-list.html>. Accessed 22 Aug 2017.
10. BC Ministry of Health, British Columbia Centre on Substance Use. A Guideline for the Clinical Management of Opioid Use Disorder. Jun 2017. Available from: <http://www.bccsu.ca/care-guidance-publications/>
11. Bruneau et al. Management of opioid use disorders: a national clinical practice guideline. *CMAJ* 2018 March 5;190:E247-57. doi: 10.1503/cmaj.170958
12. BGP Pharma. Kadian Capsules Product monograph. 2014;(171610):1-37. Available from: [http://www.mylan.ca/-/media/mylanca/documents/english/product\\_pdf/kadian-pm-e.pdf](http://www.mylan.ca/-/media/mylanca/documents/english/product_pdf/kadian-pm-e.pdf)
13. Methadone Drug information Lexicomp. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com> (Accessed on Aug 22 2017.)

## Appendix 3: Dosing recommendations for slow-release oral morphine

Slow-release oral morphine—which refers to the **24-hour formulation** of the extended-release capsules (brand name Kadian®)—is a potential option for individuals who respond poorly to buprenorphine/naloxone and methadone and may require an alternative treatment approach (see Table 1). These guidelines are based on the protocols used in randomized controlled trials that demonstrated efficacy of slow-release oral morphine for opioid dependence. It is important to note that there is currently no “best” clinical treatment protocol established for agonist treatment with slow-release oral morphine. Thus, treatment with slow-release oral morphine requires diligent measures to avoid overdose (i.e., close monitoring of initiation and stabilization, appropriate titration and, where appropriate, specialist referral) and diversion (see [Appendix 4](#)). As such, patients require close monitoring until stability is achieved. It is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of opioid use disorder. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations (brand name M-Eslon®), have not been empirically studied in this context and are not recommended by this committee for treatment of opioid use disorder.

The CPSBC has set safe prescribing standards for the use of opioids for treatment of chronic non-cancer pain. Since the use of slow-release oral morphine for opioid agonist therapy is currently off-label and the dose needed to stabilize a highly tolerant patient with an OUD can exceed 90 mg morphine milligram equivalents (MME), clear and careful assessment, patient consent, and documentation is needed.

It is strongly recommended that physicians who wish to prescribe slow-release oral morphine as an opioid agonist treatment should hold a valid federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone, or only after formal consultation with an addiction medicine specialist (e.g., [RACE](#)).

Clinicians are also encouraged to call the Rapid Access to Consultative Expertise ([RACE](#)) line to speak with an addiction medicine specialist if any questions or concerns:

### 1 ELIGIBILITY

**These recommendations are most applicable to patients who are:**

- Adults (≥ 19 years in BC) with opioid use disorder
- Switching to slow-release oral morphine from methadone or while actively using another opioid
- Not pregnant or breastfeeding

**Common contraindications to initiation:**

- Hypersensitivity to morphine sulfate or any component of the formulation
- Significant respiratory depression
- Acute or severe bronchial asthma
- Known or suspected paralytic ileus
- Currently taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days
- Severe respiratory compromise or obstructive disease
- Severe respiratory distress
- Delirium tremens
- Acute alcohol intoxication

### 2 PHARMACOLOGY

- Slow-release oral morphine is administered via once-daily oral doses.
- Slow-release oral morphine is released over 24 hours.
- Peak plasma levels are achieved within 8½ to 10 hours.
- Elimination half-life: The terminal elimination half-life of morphine following a single dose of slow-release oral morphine administration is approximately 11 to 13 hours. However, this is primarily due to the delayed

absorption of the pellets. Once absorption is complete, the plasma elimination half-life is the same as immediate-release morphine (2 to 4 hours).

### 3 ADMINISTRATION

- Slow-release oral morphine should be swallowed whole. Crushing, chewing, or dissolving slow-release oral morphine capsules can cause rapid release and absorption of a potentially fatal dose of morphine sulphate.
- To reduce risk of diversion, daily witnessed ingestion via opening capsules and sprinkling the enclosed pellets for immediate ingestion is strongly recommended.
- Pellets may be sprinkled onto a small amount of applesauce and ingested immediately. Alternatively, in settings where applesauce may not be available or patient allergies are a concern, pellets may be sprinkled into a 30 mL medicine cup and ingested followed by a cup of water to ensure all pellets have been swallowed.
- Pellets must not be chewed or crushed.
- Those prescribing slow-release oral morphine should call and discuss these requirements with a dispensing pharmacy to ensure compliance with witnessed ingestion instructions.

### 4 ASSESSMENT AND MONITORING

#### Baseline assessment

- Addiction history including assessment for tobacco and other substance use disorders, in particular, concurrent use of alcohol, benzodiazepines, and sedatives (i.e., CNS depressants)
- Review of PharmaNet and other requirements outlined in CPSBC Professional Standards and Guidelines for Safe Prescribing of Drugs with the Potential for Misuse/Diversion. Please refer to [www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf](http://www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf) for more information.

#### Monitoring treatment efficacy:

- Urinalysis, other opioids and other drug use, cravings, withdrawal
  - ◆ Note: Non-quantitative point-of-care (POC) urine drug tests cannot be used to rule out use of illicit heroin or some prescription opioids (i.e., morphine) among patients treated with slow-release oral morphine.
  - ◆ Lifelabs® and other local or hospital laboratories are able to perform mass spectrometry urine drug testing that can distinguish between illicit heroin and prescribed slow-release oral morphine. With the support of a laboratory, distinguishing between heroin, acetaminophen with codeine, and slow-release oral morphine can be made using laboratory urine drug tests that employ mass spectrometry, as follows:
    - Heroin: variably high morphine, 5–10% codeine, heroin metabolite 6-acetylmorphine (6-AM) may be present
    - Acetaminophen with codeine (Tylenol® #3): high codeine, relatively low morphine
    - Slow-release oral morphine: very high morphine, trace levels of codeine (i.e., < 50 mg/mL)
    - These data may not be reported unless specifically requisitioned for individuals on slow-release oral morphine, point-of care urine drug tests will be positive for the morphine metabolite and it may be difficult to distinguish on UDT between illicit heroin and prescribed slow-release oral morphine.
  - ◆ Clinical interpretation, availability, cost, and general process for requesting UDT can be discussed with local laboratory services when needed. Clinicians should also be aware that fentanyl may be present in urine drug tests for many active heroin users in BC.
  - ◆ Urine drug testing should be performed monthly, or more frequently as required to confirm self-reported abstinence from illicit opioid use and/or when patients wish to pursue take-home

dosing. During stabilization, both supervised and random UDT should be employed as appropriate. It is recommended that patients receiving take-home doses (see Appendix 4) should have at least eight random UDTs per year, or more frequent as required if there are safety concerns (e.g., relapse, diversion). Patients who fail to comply with random or scheduled UDT should be reassessed as this may indicate risk of relapse, misuse or diversion.

- **Adverse effects:** most common are stomach cramps, abdominal pain, headache, dizziness, hyperhidrosis, toothache, dry mouth, constipation, frequent urination, nausea, vomiting, and insomnia.
- **As with other types of chronic opioid therapy, there is potential for opioid-induced hyperalgesia,** which may require weaning the slow-release oral morphine dosage downward, introducing an opioid-sparing adjuvant for analgesia, or rotating to an alternative treatment. For this reason, only one or two dose escalations should be permitted in the years after initial stabilization. If the patient continues to build tolerance or develops hyperalgesia, then transition to buprenorphine/naloxone or methadone is strongly recommended.

## 5 INDUCTION AND DOSING

- Prior to treatment start, review risks and benefits of slow-release oral morphine. Obtain informed consent and complete Slow-release Oral Morphine Treatment Agreement and Consent Form (see [Appendix 8](#)).
- Begin with a 1-week adjustment/titration phase aiming to achieve a stable daily dosage.
- Because of the sustained-release properties of slow-release oral morphine (see Pharmacology section above), dosage increases should generally be separated by 48 hours.
- For individuals using street opioids other than methadone, refer to induction example below.

*Switching from methadone oral solution to slow-release oral morphine:*

- No wash-out of previous treatment is required (to minimize potential for withdrawal symptoms). Withdrawal symptoms may recur temporarily during the switch-over period.
- Generally a switch will require an ultimate dose of 1:6 to 1:8, but the committee suggests beginning with a 1:4 induction with titration upwards based on withdrawal scores and craving. Titrate upward in incremental doses according to withdrawal scores.

*Sample dosing schedules:*

There are a variety of dosing schedules described in the literature. Examples include:

Example 1: MMT to slow-release oral morphine	Example 2: Daily or lower frequency heroin use
<ul style="list-style-type: none"> <li>• Begin with estimated methadone-to-slow-release oral morphine dose equivalence of 1:4 on Day 1 (e.g., 60 mg methadone = 240 mg slow release oral morphine), and then increase incrementally according to withdrawal scores.</li> <li>• Several studies have found an average methadone-to-slow-release oral morphine stabilization dose of approximately 1:7.75 to be appropriate.</li> </ul>	<ul style="list-style-type: none"> <li>• Day 1: 30 to 60 mg slow-release oral morphine</li> <li>• Titrate dose upward according to individual patient's withdrawal.</li> <li>• Because of the sustained-release properties of slow-release oral morphine (see Pharmacology section above), dosage increases should generally be separated by 48 hours.</li> </ul>

According to existing literature, the average (mean) slow-release oral morphine dose ranges from 235–791 mg/day. The full range of slow-release oral morphine doses described in the literature is 60–1200 mg/day.

## 6 MISSED DOSES

- Despite delayed absorption, the underlying short morphine half-life results in the potential for rapid loss of tolerance following missed doses, and the possibility of harmful over-sedation or overdose.
- To mitigate this, prescribers should work very closely with pharmacists regarding missed doses and daily patient assessments.

- In determining dose adjustments after missed doses, clinical judgment must take into account: (i) total daily dose, (ii) number of missed doses, (iii) possibility of diversion, and (iv) other opioid use during periods of missed dosing.

*Sample missed dosing schedules:*

There are a number of possible approaches to dealing with missed doses of slow-release oral morphine—all based upon expert opinion and limited clinical experience or research data:

Number of missed days	Missed dosing schedule	
	<i>Example prescribed dose = 200 mg</i>	<i>Example prescribed dose = 800 mg</i>
1	200 mg	800 mg
2	120 mg (40% reduction)	480 mg (40% reduction)
3	80 mg (60% reduction)	320 mg (60% reduction)
4	40 mg or starting dose (e.g., 60 mg), whichever is higher (80% reduction)	160 mg (80% reduction)
5	Resume at initiation dose (e.g., 60 mg)	Resume at initiation dose (e.g., 60 mg)

Due to lack of clinical experience or clinical trials for slow-release oral morphine re-induction protocols, patients should be seen daily to assess for intoxication or withdrawal, with dose increases or decreases titrated accordingly.

## 7 STABILIZATION

The goal is to stabilize the once-daily dose at the lowest dose that relieves withdrawal symptoms and suppresses illicit opioid use. Currently, there is no published literature to guide treatment decisions beyond the 36-week duration of clinical trials. The committee recommends following similar stabilization and tapering practices as methadone and buprenorphine/naloxone.

**References:**

1. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction* 2014;109:617-26.
2. Eder H, Jagsch R, Kraigher D, et al. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction* 2005;100:1101-9.
3. Ferri M, Minozzi S, Bo A, et al. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev* 2013;6:CD009879.
4. Hammig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat* 2014;47:275-81.
5. Jegu J, Gallini A, Soler P, et al. Slow-release oral morphine for opioid maintenance treatment: a systematic review. *Br J Clin Pharmacol* 2011;71:832-43.
6. Giacomuzzi S, Kemmler G, Ertl M, et al. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants. *Subst Use Misuse* 2006;41:223-44.
7. BGP Pharma ULC. Kadian® Capsules (Morphine Sulphate Sustained Release Capsules, Mfr. Std.). [amended 2015 Aug 11; cited 2016 Aug 24]. In: Mylan Pharmaceuticals ULC, [Internet]. Etobicoke, ON: BGP Pharma ULC. 2015. Available from: <http://www.mylan.ca/-/media/mylanca/documents/english/kadian-pm-2015.08.11.pdf>.
8. Actavis Pharma, Inc. Kadian® (morphine sulfate) Extended-Release Capsules, for oral use. [amended 2014 Apr; cited 2016 Aug 24]. In: Kadian® Morphine Sulfate Extended-Release Capsules, [Internet]. Parsippany, NJ: Actavis Pharma, Inc. 2014. Available from: <http://www.kadian.com/>.
9. Verthein U, Beck T, Haasen C, et al. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. *Eur Addict Res* 2015;21:97-104.
10. Verthein U, personal communication, August 19, 2016.
11. Yi P, Pryzbylowski P. Opioid Induced Hyperalgesia. *Pain Med* 2015;16 Suppl 1:S32-6.
12. Palaty J, personal communication, November 9, 2016

## SLOW-RELEASE ORAL MORPHINE TREATMENT AGREEMENT AND CONSENT FORM

Patient Information	
Surname: _____	Given name(s): _____
Date of birth: _____	PHN: _____

Patient Agreement
<p>I UNDERSTAND AND AGREE THAT:</p> <ul style="list-style-type: none"><li><input type="checkbox"/> I am being started/continued on:<ul style="list-style-type: none"><li><input type="checkbox"/> Slow-release oral morphine for the treatment of opioid addiction. While I may choose to taper off this treatment at any time, I understand that most patients benefit from at least one year of treatment or longer.</li></ul></li><li><input type="checkbox"/> Slow-release oral morphine was originally developed to treat pain, but, based on new research findings, is now also used outside of its currently approved indications (“off label”) to treat opioid addiction. I will be receiving medication “off label”.</li><li><input type="checkbox"/> While I am receiving slow-release oral morphine treatment, I will only get opioid prescriptions from my slow-release oral morphine prescriber and will not get any from other doctors or clinics.</li><li><input type="checkbox"/> For my safety, I give consent to my slow-release oral morphine prescriber to communicate with my pharmacist and any other physicians involved in my care, and to check my PharmaNet profile.</li><li><input type="checkbox"/> I will work with my slow-release oral morphine prescriber to develop a treatment plan and set goals. We will review them regularly and change as needed.</li><li><input type="checkbox"/> In addition to slow-release oral morphine, I can participate in counselling or peer-support groups and other programs as part of my treatment plan. My slow-release oral morphine prescriber will give me information about the different options and programs available in my community.</li><li><input type="checkbox"/> I can expect confidentiality about my treatment from my doctor and other healthcare providers. My personal information will not be shared except with other healthcare providers as I agreed to above.</li><li><input type="checkbox"/> I can choose my clinic and pharmacy and can decide to change either if necessary.</li><li><input type="checkbox"/> I can decide if I want to continue or stop treatment at any time. I agree to make this decision with my prescriber.</li><li><input type="checkbox"/> Beginning slow-release oral morphine treatment will require daily trips to the pharmacy and regular visits to my prescriber, which may impact my work, school or other responsibilities.</li><li><input type="checkbox"/> My prescriber may make changes to my treatment to provide the safest and best possible care. These changes might include dosage, how often I pick up my medication, how often I visit the clinic, and how often my urine is tested. Until I am stable, I will receive slow-release oral morphine through daily witnessed ingestion at a pharmacy or another healthcare provider.</li><li><input type="checkbox"/> Once I am stable, my prescriber will work with me to determine if take-home doses are appropriate. Generally, for individuals who want take-home dosing, alternative medications are more appropriate.</li><li><input type="checkbox"/> I will not give my prescriptions or medications to anyone else.</li><li><input type="checkbox"/> I will not take my medication more often or at higher doses than my prescription states.</li></ul>