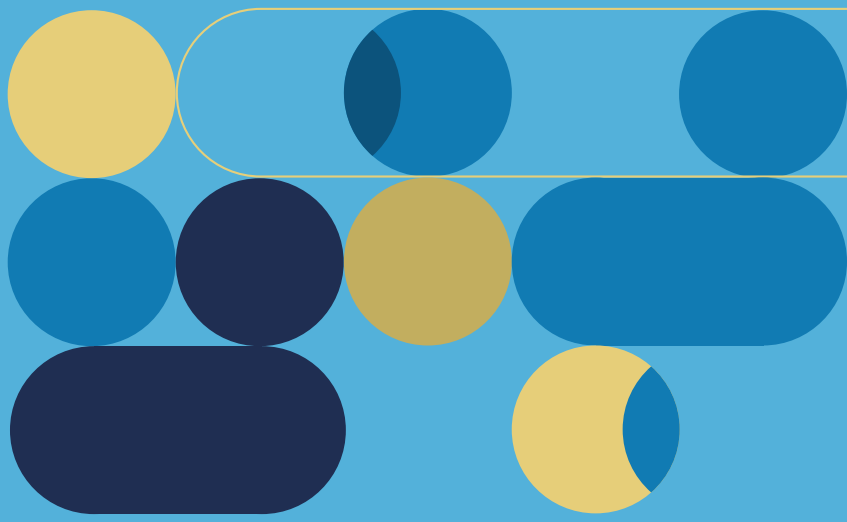
L'Équipe de soutien clinique et organisationnel en dépendance et itinérance

A Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT)

MARCH 2023



INSTITUT UNIVERSITAIRE SUR LES DÉPENDANCES

Québec

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A Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT) is a publication of the Équipe de soutien clinique et organisationnel en dépendance et itinérance at the Institut universitaire sur les dépendances (IUD) of the CIUSSS du Centre-Sud-de-l'Île-de-Montréal.

This publication is a translation of the *Guide d'utilisation de la morphine à libération lente uniquotidienne (Kadian^MC) dans le cadre d'un traitement par agonistes opioïdes (TAO) (Mars 2023)*.

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FUNDING

Project funding was provided by the Institut universitaire sur les dépendances (IUD) as part of Health Canada's Substance Use and Addictions Program (SUAP). SUAP funds are managed by the Ministère de la Santé et des Services sociaux du Québec.

DISCLAIMER

The content of this guide is based on scientific data and clinical guidelines. The content is the result of deliberations with a committee of Québec-based expert practitioners and organizations representing people who use opioids. This committee issued a recommendation on the use of slow-release oral morphine (SROM) in opioid agonist therapy (OAT) using the GRADE method. In addition, the document's content was verified with qualified experts to ensure that it would be as accurate as possible.

However, it should be noted that the guide is not prescriptive in nature, and its authors **cannot be held accountable** for the clinical practices of professionals. Clinicians are expected to assume responsibility for being appropriately qualified and trained. They must exercise clinical judgment when providing care and services, in compliance with the professional standards and codes of ethics to which they are subject.

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ISSN 2816-2927
Legal Deposit — Library and Archives Canada

To quote this document
Équipe de soutien clinique et organisationnel en dépendance et itinérance (ESCODI) du Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal (CCSMTL). A Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT). Montréal, Qc : CCSMTL ; 2023. 30 p.

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Québec recommendation developed using the GRADE method

In cases where opioid agonist therapies with methadone or buprenorphine-naloxone have been proven ineffective, are contraindicated or unacceptable, prescribers should consider using slow-release oral morphine (SROM).

Treatment with SROM should only be initiated by an experienced prescriber or after consulting with an expert.

Considering the lack of available data regarding misuse, overdose and diversion, and considering the risk of rapid loss of tolerance when doses have been missed, the expert committee recommends that:

- The prescription of unsupervised doses be allowed, based on the clinical judgment of the prescriber and the partner care team;[A]
- The prescription of unsupervised doses should be circumscribed by a decision support tool (see Appendix 2).

1. GENERAL PRINCIPLES

- SROM is a pure selective mu (μ)[1] opioid receptor agonist.
- Kadian®, the only SROM formulation so far available in Québec, is covered by the province's public drug plan, although its use as an OAT is currently off-label.
- SROM is approved and covered by Health Canada as an OAT under the Non-Insured Health Benefits (NIHB) program for First Nations and Inuit.[1]
- It is administered orally, once daily, and is released over a period of 24 hours.[2]
- Its peak plasma concentration is reached after 8.5 to 10 hours. Its elimination half-life is approximately 11 to 13 hours.[3]
- SROM has a lesser impact on the QTc than methadone.[4]
- SROM seems to lead to fewer heroin cravings than methadone.[5]
- Treatment retention with SROM is thought to be similar to that of methadone.[5,6]

2. ELIGIBILITY

To be eligible for the treatment, a patient must:

- Be 18 years of age or older (with some exceptions)
- Have a diagnosis of opioid use disorder (OUD) as described in the DSM-5

Exceptionally, subject to compliance with the rules regarding the consent of minors to treatment (in French only), a person under the age of 18 may be eligible for OAT with SROM based on the clinical judgment of an experienced prescriber.

A Partner care team: This refers to the interdisciplinary team that closely supports the person in treatment for an opioid use disorder, i.e. a physician, a nurse, a psychosocial worker, a peer helper and a community pharmacist. The team members are part of the same unit or collaborate through formal partnerships.

3. CONTRAINDICATIONS

Main contraindications

- Hypersensitivity to morphine sulfate or one of the non-medicinal ingredients
- Acute respiratory depression, asthma with severe bronchospasm, severe chronic obstructive pulmonary disease
- Gastrointestinal obstruction (including paralytic ileus)
- Concomitant use, or use within the last 14 days, of a monoamine oxidase inhibitor (MAOI)
- Significant acute intoxication with a central nervous system depressant (an opioid, alcohol, benzodiazepine, etc.)

For a full list of contraindications, see Appendix 1 and the Kadian® monograph.

4. TREATMENT PRINCIPLES

Pre-treatment assessment

- Since the use of SROM in OAT is an off-label practice, the prescriber is encouraged to document the individual's clinical history prior to initiation of treatment, including the following:
  - Why this treatment was selected for this individual;
  - The risks and benefits of this treatment compared to the risks and benefits of conventional therapies or no treatment;
  - The person's free and informed consent.[7] (consult Appendix 6).

For more information on the initial assessment required of an individual before prescribing an OAT, see the CMQ, OIIQ and OPQ guidelines (in French only).

Administration

- The capsules are taken once daily, every 24 hours. They can be swallowed whole with a glass of water.[2]
- To minimize the risk of diversion, the capsules should be opened. In this case, the granules in the capsules should be sprinkled into fruit puree, yoghurt or pudding and consumed within 30 minutes.[2,8]
  - In practice, the granules can also be diluted in water and consumed immediately.
- The contents of the capsules should never be chewed, crushed or dissolved, as this may alter the pharmacokinetics (morphine release and absorption rates, half-life, etc.) of SROM.

For pharmacists:

Snack-size fruit puree products (in a cup) are easy to use and store, and are readily available and inexpensive.

SROM doses can be prepared in advance in a pill dispenser, with the dates included on the prescription. This saves time and ensures that they are administered on the correct dates. If the patient is entitled to unsupervised doses, give them the pill dispenser compartments in a safe vial.

Unsupervised doses

- Supervision of the patient's SROM intake is strongly recommended at the start of treatment.
- Supervision of intake is also recommended if the person is clinically and psychosocially unstable, or if you suspect potential misuse or diversion.
- The clinical judgment of the prescriber and the partner care team plays a key role in the prescription of unsupervised doses. They will need to assess the associated risks and benefits.[8]
- The rationale for granting unsupervised doses should be clearly documented in the patient's medical file and communicated to the community pharmacist with the prescription.

For more information on unsupervised doses, see Appendix 2.

Prescription

- Kadian® is available in 10 mg, 20 mg, 50 mg and 100 mg sustained-release morphine sulfate capsules.
- When SROM is prescribed as part of OAT, it is important to state on the prescription: Substitution treatment for opioid use disorder (opioid agonist therapy) (in French only)
- For a model SROM prescription, see Appendix 3.

For pharmacists:

In order to obtain the fees associated with Service Code J of Rule 29, the pharmacist must contact RAMQ's pharmacist support centre for each new prescription prepared for the patient and fax a copy of the prescription to RAMQ.

Induction, dosage and stabilization of treatment

- If the person is not receiving OAT, SROM can be initiated on the same day, as long as there are no signs of acute intoxication.[9]
- In order to reduce the risk of overdose associated with the introduction of a new opioid, the general rule is to start with SROM doses that are lower than those reported by the person and increase them as needed. The maximum starting dose is usually 200 mg (see Table 1).
- If the person is already being treated with opioid agonists (methadone or buprenorphine-naloxone), induction with SROM can begin on the day following the last dose of the previous treatment.[7,10]
- Safer supply can be provided as a complement to the SROM prescription, during both the induction and stabilization periods. For more information on safer supply, see: Substance Replacement Therapy in the Context of the COVID-19 Pandemic in Québec.
- At the first assessment and at each subsequent follow-up appointment you should offer the naloxone kit and provide instructions on how to use it, as well as distribute essential harm reduction materials.

- There is no pre-established dosing protocol for the use of SROM in OAT. Due to variations in tolerance to opioids from one individual to the next and uncertainties around the composition of the substances sold on the illicit market, dosages administered in clinical practice may differ from those reported in the related literature.
- The person's treatment is maintained at a dose that relieves withdrawal symptoms for 24 hours and that suppresses cravings. This is called the stabilization dose.

Table 1 : Indications from the literature by type of opioid used and type of OAT

Induction and titration	Stabilization ratio	Stabilization dose
➜ Transfer from methadone (MTD)		The stabilization dose usually varies between 60 and 1200 mg/day.[1,9,12–17] Upward or downward variations may be considered, depending on the clinical presentation.
Start with an MTD:SROM ratio of **1:4** and gradually increase according to the severity of withdrawal symptoms and cravings.[7,11] Example: 60 mg of MTD = 240 mg of SROM	The stabilization dose is usually equal to an MTD:SROM ratio of **1:6 to 1:8**[11–15]. A recent study showed a higher ratio of **1:11,8**[10]. Example: 60 mg of MTD = 480 mg of SROM	
➜ Transfer from buprenorphine-naloxone (BUP)		
According to a recent study,[10] the initial ratio on the first day of BUP:SROM is **1:42.3**. Example: 6 mg of BUP = 254 mg of SROM	According to a recent study,[10] the average BUP:SROM ratio after 14 days of stabilization is **1:58**. Example: 6 mg of BUP = 348 mg of SROM	
N.B.: This proposal is based on a single study, so actual practice may differ.		
➜ Induction for persons without OAT and using illicit opioids		
The initial dose for the first day is 30-60 mg.[7] The dose is adjusted by 50 mg to 100 mg every 48 hours, depending on the severity of withdrawal symptoms and cravings.[16,17] According to the experts, the initial dose may be 200 mg.[17] Swiss protocols on Sevre-Long® (in French only, a SROM available in Switzerland as part of OAT) suggest an initial dose of up to 200 mg, with the possibility of an additional 120 mg if withdrawal symptoms persist 6 hours after the first dose, followed by daily increases of 120 mg.[18]	Given variations in the composition of substances sold on the illicit market, prescribers should exercise caution when converting any quantities reported by the person. As a result, no ratio can be presented.	

Missed doses

- Due to SROM's short half-life, a missed dose will lead to a faster loss of tolerance than what is observed with methadone or buprenorphine-naloxone.
- Once two consecutive doses have been missed, the pharmacist should refer to the prescriber for a readjustment.
  - Example of dose adjustment after several consecutive missed doses (according to guidelines published by the British Columbia Centre on Substance Use)[7] :

Number of consecutive missed doses	Dose Adjustment Schedule	
	Example of a prescribed dose: 200 mg	Example of a prescribed dose: 800 mg
1	200mg	800mg
2	120 mg (40% reduction)	480 mg (40% reduction)
3	80 mg (60% reduction)	320 mg (60% reduction)
4	40 mg or initial dose (e.g.: 60 mg) select the highest (80% reduction)	160 mg (80% reduction)
5	Redosing	Redosing

N.B.: The criteria to be considered when determining a dosage adjustment after a missed dose are: the usual daily dose, the number of missed doses, the potential for diversion, and other opioid use on the days of missed doses.[7]

5. PRECAUTIONS

Adverse effects

- The major (and relatively rare) adverse effects of SROM are the same as those associated with opioids: respiratory depression to respiratory arrest, severe bradycardia to cardiac arrest, altered consciousness to lethargy, and status epilepticus.[2]
- The most common adverse effects are constipation, nausea, vomiting, dyspepsia, abdominal pain, urinary retention, drowsiness, headache, dizziness, hypotension, diaphoresis, xerostomia, dental pain, dysphoria and insomnia.[2–4,7,12,19]
- SROM use, like the use of other opioids, can lead to opioid-induced hyperalgesia. If this occurs, the use of morphine should be tapered and an alternative opioid used.[16]
- Chronic use of SROM, much like chronic use of other opioids, may also be associated with endocrine disorders such as adrenal insufficiency and hypogonadism.[2]

Metabolism and elimination

- The main route for metabolizing SROM is by glucuronidation in the liver.
- The main route of elimination is renal.
- See Appendix 4 for the dosage adjustments required in the event of renal or hepatic impairment.
- Particular attention needs to be paid to geriatric population.

Drug interactions

- Prior to the introduction of SROM, it is important to consider certain drug interactions (see Appendix 5 and the Kadian® monograph for more information):
  - Central nervous system depressants
  - Serotonergic drugs
  - Naltrexone
  - Monoamine oxidase inhibitors
  - Diuretics
  - Antihypertensives
  - Efavirenz
  - Ritonavir
  - P-glycoprotein inhibitors
  - Rifampicin

Injection-related risks

- Injection of SROM can lead to a rapid increase in serum morphine levels, which is associated with an increased risk of lethal intoxication.
- Because SROM is less soluble than heroin and other fast-acting prescription opioids, its injection carries a greater risk of infection, embolism and vascular injury.[9,20]

Pregnancy and Breastfeeding

Pregnancy

- Considering the importance of ensuring the clinical stability of the pregnant person because of the risk of withdrawal symptoms associated with any changes in OAT,[22] **continuation of treatment with slow-release oral morphine (SROM) is recommended when the person was already stable on this medication prior to pregnancy**.
- Considering the lack of data on the use of SROM in OAT during pregnancy, compared to well-documented methadone and buprenorphine-naloxone treatments, **induction with SROM during pregnancy should be considered when methadone or buprenorphine-naloxone treatments[22] are ineffective, contraindicated or unacceptable**.
- Both in the context of induction and maintenance, an OAT with SROM during pregnancy should be initiated or maintained by experienced prescribers, and only after obtaining the informed consent of the pregnant person. Furthermore, decision-making should include a consultation with a perinatal and OAT expert to examine all the factors that should be taken into consideration in order to make a safe choice that is adapted to the pregnant person on OAT's circumstances. (see Appendix 7).
- Obstetric and neonatal monitoring should be the same as the monitoring of methadone and buprenorphine-naloxone users. In the absence of predictive data related to the impact of physiological changes on the pharmacokinetics of SROM during pregnancy, SROM doses should be adjusted according to need and clinical assessment.

Breastfeeding

- Breastfeeding is recommended for a person in OAT with SROM, as it is for a person in OAT with methadone or buprenorphine-naloxone, provided there are no other contraindications. However, due to the lack of data required to properly characterize the effects of exposure to SROM on breast milk and thus to establish infant safety, **individualization is essential when deciding whether or not to undertake breastfeeding**. In general, breastfeeding when in OAT with SROM carries risks, but there is no absolute contraindication. The inherent risk of using SROM during breastfeeding appears to be mainly associated with the potentially high dosage of the medication when used in OAT, and the extended treatment period.
  - The decision to breastfeed should be reached after consultation with professionals who have experience in postpartum and paediatric follow-up in the context of OAT during pregnancy. This decision should also take into account the prescribed dose of SROM, recent changes in dosage (increase or decrease), concomitant use of central nervous system depressants (alcohol, benzodiazepines, other opioids, certain psychiatric medications, etc.) or other illicit substances, the individual's overall biopsychosocial stability, and any other contraindications to breastfeeding (e.g. HIV).
  - The risks associated with the transfer of SROM into breast milk should then be weighed against the benefits of

breastfeeding (optimal nutrition, strengthening of the immune system, development of the attachment bond, reduced infant withdrawal symptoms in the first few days, etc.) and the risks mentioned above.

- Considering the potential risks of using SROM in OAT while breastfeeding (Appendix 7), paediatric monitoring and weaning protocols remain essential for all medications used in OAT.
  - The assessment should take into account that the infant has been exposed to SROM or opioids for a prolonged period during pregnancy and is therefore not opioid naïve.
  - Conversely, the introduction of SROM or another OAT in the postpartum period while breastfeeding places the infant at higher risk.

Available resources

- Canadian Paediatric Society
- Journal of Obstetrics and Gynaecology Canada

Quebec resources for support

- Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), CHU Sainte-Justine
  Centre d'information téléphonique réservé aux professionnels de la santé.
  Phone: 514 345-2333 (Monday to Friday)
  www.chusj.org/image
- Rond-Point, Centre d'expertise périnatal et familial en toxicomanie
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APPENDICES

Appendix 1: Contraindications

Appendix 2: Decision Support Tool for Granting Unsupervised Doses

Appendix 3: Model Prescription

Appendix 4: Adjusting Doses in Response to Renal or Hepatic Impairment

Appendix 5: Common Slow-Release Oral Morphine Drug Interactions

Appendix 6: Slow-Release Oral Morphine (Kadian®): Frequently Asked Questions

Appendix 7: Summary of the report: *Innocuité de la morphine à libération prolongée durant la grossesse et l'allaitement en traitement par agonistes opioïdes (TAO) dans le cadre du traitement des troubles liés à l'utilisation des opioïdes,* by Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), 2021

APPENDIX 1
Contraindications

Absolute contraindications to the use of SROM

- Hypersensitivity to morphine sulfate or any of the non-medicinal ingredients
- Acute respiratory depression
- Asthma with severe bronchospasm
- Severe chronic obstructive pulmonary disease (COPD)
- Gastrointestinal obstruction (including paralytic ileus)
- Concomitant use or use within the last 14 days of a monoamine oxidase inhibitor (MOAI)
- Significant acute intoxication with a central nervous system depressant (an opioid, alcohol, benzodiazepine, etc.)

Relative contraindications to the use of SROM

- Hypersensitivity to other opioid analgesics
- For pregnant or breastfeeding individuals or individuals in labour or delivery, refer to the pregnancy and breastfeeding section
- Asthma or mild to moderate chronic obstructive pulmonary disease (COPD)
- An acute abdomen (e.g. appendicitis or acute pancreatitis)
- Delirium tremens and seizure disorders
- Concomitant use of a central nervous system depressant
    - Before initiating SROM, it is essential to inform the patient of the risks associated with concomitant use of SROM and central nervous system depressants (alcohol, benzodiazepines, other opioids, certain psychiatric medications, etc.). Such combinations increase the risk of adverse effects as well as serious complications, including overdose and death from respiratory failure.
    - Regarding alcohol use disorders, although the Kadian® product monograph mentions an increased risk associated with acute alcohol intoxication, other data show that alcohol does not significantly alter the pharmacokinetics of SROM.[21]
- Renal or hepatic impairment (for more information, see Appendix 4: Dose Adjustment in the Event of Renal and Hepatic Impairment)
- Craniocerebral injury (mainly if associated with intracranial hypertension)
- Heart rhythm disorder

In this document a distinction is made between absolute and relative contraindications, based on clinical judgment and pharmacological references. However, the Kadian® monograph makes no distinction between absolute and relative contraindications.

APPENDIX 2
Decision Support Tool for Granting Unsupervised Doses

Unsupervised doses should only be offered after weighing the benefits against the anticipated risks. This means that even in the presence of a certain level of risk, it may be deemed appropriate to offer unsupervised dosing if this can improve autonomy, quality of life, adherence and retention, given the logistics required by OAT (regular visits to a pharmacy and clinic, transportation time, etc.). This tool is intended to assist prescribers and members of the partner care team, but it should never replace their clinical judgment.

The following questions can guide deliberations over the decision of whether to grant unsupervised doses. These questions allow for an objective and person-centered view of the recovery process. We have provided real-world clinical examples for each question, although the list is not exhaustive:

1. **What are the expected benefits of providing unsupervised doses?**
   - Less travel time and a reduction in the costs associated with travel to a pharmacy
   - Enabling a return to or a continuation of school, work, family obligations, etc.
   - Increased adherence to treatment
   - Facilitating a stay in therapy, in a rehabilitation centre, etc.
   - Facilitating a stay with relatives, holidays, travel outside Québec, etc.

2. **What are the expected risks?**
   - Intravenous injection
   - Severe intoxication or overdose
     - Uncontrolled active use of a central nervous system depressant, whether prescribed or not (e.g. alcohol, benzodiazepines, GHB, etc.)
   - Diversion or resale

3. **How is this person able to stay safe?**
   - By understanding the risks and their ability to provide consent
   - Through the stability of his or her doses and SROMintake in recent weeks
     - By not missing appointments (at the clinic and the pharmacy)
     - By not having missed doses at the pharmacy in recent weeks
   - Through a lack of suicidal ideation, a psychotic disorder or cognitive impairment

4. **How is this person able to ensure the safety of the community?**
   - By having a safe place to store unsupervised doses
     - By paying particular attention to high-risk living environments: e.g. where young children or people who use psychoactive substances are present, etc.
   - Through stable living arrangements
   - Through no history of stolen or lost unsupervised doses

For more information on unsupervised OAT dosing, see Le traitement du trouble lié à l'utilisation d'opioïdes – lignes directrices (CMQ, OIIQ, OPQ, 2020), Section 3.2.3 (in French only).

APPENDIX 3
Model Prescription

[Patient contact information]

PHARMACEUTICAL PRESCRIPTION – SLOW-RELEASE ORAL MORPHINE (KADIAN®)

Hospital ☐ **Recovery Housing** ☐ **Rehabilitation** ☐ **Frontline** ☐

Allergy/Allergies: _____ No known allergies: ☐ Adverse reactions to medications: _____

SLOW-RELEASE ORAL MORPHINE (KADIAN®)

INDICATION

QHR notice: **Substitution treatment for opioid use disorder (opioid agonist therapy)**

Period: _____ / _____ / _____ TO _____ /_____ /_____
DD MM YYYY DD MM YYYY

Daily Dosage: _____ mg DIE (Total quantity for the duration of the prescription: __mg)

- Number of daily doses in the presence of the pharmacist _____ days/week.
- The patient can never bring more than _____ doses home between supervised doses taken in the presence of the pharmacist.
- The pharmacist may increase the dose up to _____ mg q.a.d PRN if the patient remains in withdrawal and/or keeps using illicit opioids. Do not increase if highly intoxicated.
- The dose may be increased up to _____ mg total to a maximum permitted of _____ mg q.d.
- **Once two consecutive doses have been missed, the pharmacist should adjust the prescription downward according to the recommended schedule, or refer to the prescriber for a readjustment.**

Number of consecutive missed doses	Example of a prescribed dose: 200mg	Example of a prescribed dose: 800mg
1	200mg	800mg
2	120mg (40% reduction)	480mg (40% reduction)
3	80mg (60% reduction)	320mg (60% reduction)
4	40mg or initial dose (e.g.: 60mg) select the highest (80% reduction)	160mg (80% reduction)
5	Redosing	Redosing

- Do not dispense if the patient is visibly under the influence of alcohol or intoxicated by medication or drugs.
- Check, as needed:
  - ☐ The capsule should be opened during a supervised intake. Sprinkle the pellets into fruit puree, yoghurt, pudding or water and serve immediately. CAUTION: Do not chew, crush or dissolve the granules.
  - ☐ Please provide a naloxone kit and instructions on how to use it.

OTHER MEDICATIONS

CONFIDENTIAL TRANSMISSION BY FAX

Pharmacy: _____

Fax number: _____ Date/Time: _____

[Identification of the prescriber's location of practice]

Prescriber's name (block letters): _____ **Permit n°:** _____

Prescriber's signature: _____ **Date and time:** _____

PHARMACEUTICAL PRESCRIPTION – SLOW-RELEASE ORAL MORPHINE (KADIAN®)

APPENDIX 4
Dose Adjustment in the Event of Renal or Hepatic Impairment

Mild to moderate hepatic impairment

Caution is suggested, but no specific recommendation is made for cases of mild to moderate hepatic impairment. This is because only a small amount of glucuronide metabolites are excreted in the bile, and the enterohepatic cycle of SROM is considered minor.

Severe hepatic impairment

Downward dose adjustments are recommended. This includes considering dosing intervals that are 1.5 to 2 times longer. Hepatic cirrhosis may alter the morphine's pharmacokinetics, i.e. by extending the half-life and increasing the area under the curve, resulting in higher plasma concentrations.

Renal impairment

The use of SROM and its impacts on renal impairment have not been formally studied. However, since it is known that active morphine metabolites are excreted in the urine and that there is a significant risk of accumulation in renal impairment, caution is recommended when using SROM in such a context. Precautionary strategies include slower titration, reduced dosing, and even a change of drug, if necessary. For information purposes only, here are some recommendations from experts based on current literature:

Creatine Clearance	Dose Adjustment
ClCr ≥ 60 ml/minute	No adjustment required.
ClCr from 30 ml to 60 ml/minute	Consider using an alternative treatment if possible. If necessary, administer 50% to 75% of the initial dose.
ClCr from 15 ml to 30 ml/minute	Avoid use if possible. If necessary, give 25% to 50% of the initial dose.
ClCr < 15 ml/minute	To be avoided.

Geriatric population

Caution and lower doses are suggested, as aging may alter the pharmacokinetics of morphine. Geriatric population is therefore more likely to present with higher plasma morphine concentrations and develop adverse effects.

APPENDIX 5
Common Drug Interactions with SROM

Central nervous system depressants (benzodiazepines, barbiturates, sedative H1 antihistamines, pregabalin, gababentin, etc.), including alcohol and other opioids

Increased cardiorespiratory risk, ranging from hypotension to life-threatening respiratory distress.

Serotonergic drugs (antidepressants including SSRIs, SNRIs, tricyclics and mirtazapine; some psychiatric drugs including buspirone, lithium and trazodone; antimigraine drugs including triptans; antiemetics including ondansetron; other serotonergic drugs including linezolid, dextromethorphan, cyclobenzaprine, St. John's wort and tryptophan; etc.)

Increased risk of serotonin syndrome (clinical triad of altered mental status, autonomic hyperactivity and neuromuscular abnormalities such as myoclonus and hyperreflexia).

Naltrexone

Risk of sudden opioid withdrawal. Naltrexone is an opioid antagonist and can therefore precipitate opioid withdrawal syndrome or reverse virtually all the therapeutic effects of opioids.

Monoamine oxidase inhibitors (MAOIs: moclobemide, selegiline, phenelzine, tranylcypromine)

Increased risk of serious drug interactions affecting the central nervous system and cardiorespiratory function (e.g. serotonin syndrome). The risk is present with concomitant use of MAOIs and for 14 days after discontinuation.

Diuretics

Morphine reduces the effectiveness of diuretics by inducing the release of antidiuretic hormone (ADH). Morphine can also lead to acute urinary retention by causing spasms in the bladder sphincter.

Antihypertensives

Morphine may exacerbate the hypotensive effect of antihypertensive drugs. Caution should therefore be exercised when combining these two types of agents.

Efavirenz

Efavirenz can potentially increase plasma morphine concentrations through competition for the UGT2B7 enzyme binding site and therefore cause morphine toxicity. Close monitoring is recommended.

Ritonavir (including atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir and fosamprenavir/ritonavir)

Ritonavir can increase hepatic metabolism (UGT) and decrease plasma morphine concentration. In addition, ritonavir can inhibit P-glycoprotein and increase plasma morphine concentration. Close monitoring is essential when antiretrovirals containing ritonavir are prescribed for a patient stabilized on SROM.

P-glycoprotein inhibiting agents (amiodarone, macrolide antibiotics, some antifungals, some antiretrovirals, etc.)

Greater risk of increased plasma SROM concentrations. Since morphine is a substrate of P-glycoprotein, a PGP inhibiting agent could have a major impact on morphine plasma concentrations, mainly in patients stabilized on high doses of SROM. Although there is a paucity of data on the pharmacokinetics of this type of combination, extreme caution and close monitoring would appear essential.

Rifampicin

Greater risk of decreased plasma morphine concentrations, which may lead to withdrawal symptoms. Combining SROM with rifampicin should therefore be avoided whenever possible. If rifampicin must be used, consider monitoring the patient closely and escalating the doses as needed.

APPENDIX 6

SLOW-RELEASE ORAL MORPHINE (KADIAN®) Frequently Asked Questions

What is this drug?

Once-daily slow-release oral morphine is a drug in the opioid class, just like methadone, hydromorphone (Dilaudid®), heroin, fentanyl, etc.

It was developed to treat chronic pain, but it is also used to treat opioid dependence.

It comes in the form of a capsule containing granules, and it is to be administered once a day. The morphine is then released into the body over a period of 24 hours.

Why is this drug prescribed?

When someone develops an opioid dependency – now called opioid use disorder (OUD) – the scientific evidence shows that long-term opioid agonist treatment (OAT) is the safest and most effective way to treat their dependency.

The best-known opioid agonists are methadone and buprenorphine-naloxone (Suboxone®).

OAT is a long-term treatment, also known as a "maintenance" treatment. It consists of taking a drug that reduces withdrawal symptoms, diminishes the desire to use drugs, and causes little drowsiness or euphoria.

How is this drug taken?

This drug is to be taken through the mouth only. Either the capsule is swallowed whole, with a glass of water, or it is opened and the granules are sprinkled into a fruit puree, some yoghurt or a pudding. The granules can also be mixed with water. The granules in the capsules must never be chewed, crushed or dissolved, as this could lead to the quick release of a large dose of morphine, resulting in an overdose.

As a general rule, this drug must be taken every day at a pharmacy. Unsupervised doses may be granted on a case-by-case basis.

At the start of treatment, when the comfort dose has not yet been reached, the dose will be gradually increased (generally every two days).

It is important not to inject this drug. Since once-daily slow-release oral morphine does not dissolve as easily as heroin and other opioids such as hydromorphone (Dilaudid®), injecting it carries a greater risk of infection, embolism and vein damage.

How should this drug be stored?

It is important to store once-daily slow-release oral morphine safely, out of the reach of children. It is a drug that must never be shared, as this can be very dangerous and may even lead to a fatal overdose.

How long does the treatment last?

Stopping treatment for opioid dependence is generally not recommended because of the risks associated with withdrawal, in particular the risk of relapse and overdose if another opioid is taken. If the decision is nevertheless made to stop treatment, it is important to turn to the partner care team for support. Treatment can be resumed at any time.

What should I do if I miss a dose?

It is important to stick to the schedule, because your tolerance to once-daily slow-release morphine will be quickly lost if you miss a dose. Do not take two doses at the same time.

After two consecutive missed doses, your dose will need to be reduced, for your personal safety. The dose will then be gradually increased, back up to your comfort level.

What are the side effects?

The most common side effects are similar to those of other opioids, including constipation, nausea and vomiting, drowsiness and headaches. If these side effects cause discomfort, speak to your partner care team about how to reduce their impact.

Can alcohol or other psychoactive substances be consumed during treatment?

The use of opioids, even an OAT, in combination with alcohol or other depressants, such as benzodiazepines (Ativan®, Xanax®, Rivotril®, etc.) or GHB, causes drowsiness. Such use may carry a particularly dangerous risk of overdose that could, in some cases, lead to death.

If you are thinking of continuing to take opioids during treatment, it is important to discuss this with the partner care team. The prescriber may prescribe drugs to replace your opioid use. This is known as safer supply.

Will I be able to drive and do manual work?

Like any opioid, this drug may cause drowsiness, dizziness and weakness, especially at the start of treatment. For these reasons, it is not recommended to drive or operate machinery until your treatment has stabilized and any symptoms of drowsiness are gone. In the eyes of the law, individuals are always responsible for their actions.

Can this drug be taken during pregnancy or while breastfeeding?

If you are planning to become pregnant or if you become pregnant during treatment, do not stop treatment. It is recommended that you continue as usual and talk to the partner care team about it, to determine whether any adjustments are needed to the dosage and/or drug.

If you want to breastfeed, you will need to continue treatment as usual and talk to the partner care team about it, so that, together, you can assess the benefits and risks associated with taking this drug while you breastfeed.

What should I do if I'm taking other drugs or natural health products?

If this is the case, it is important to inform the prescriber and other health professionals involved in assessing your state of health, as well as the pharmacist, who will assess the risks of any interactions between the drugs or with the natural products. Some drug mixtures can cause serious side effects.

Who can I turn to for help or to ask questions?

If you have any questions about the treatment, if you are having side effects and it is hard to know if they are normal, or if you continue to have symptoms or cravings, it is important to contact a member of the partner care team.

You can also quickly get some advice from the community pharmacist on the care team.

Naloxone and safer injecting, safer smoking and safer sex supplies: everywhere, all the time, for everyone!

Each time you meet with the team, you should be offered naloxone and instructed on its use. You can also expect to be offered drug use equipment and personal protection equipment.

Naloxone, which is sometimes called the "opioid overdose antidote," saves lives by reversing the effects of an opioid overdose. This is why it is so important for family and friends to be included

when naloxone is distributed, and why they must also taught how to use it. In addition, the distribution of drug use equipment and personal protection equipment helps reduce the risk of infection.

Health and social service facilities can distribute naloxone as well as provide drug use equipment and personal protection equipment as part of their services. People receiving treatment and their family and friends can also obtain these things from pharmacies and certain community organizations.

Safer injecting, safer smoking and safer sex supplies

- [ ] **Naloxone kits:**
  Find a resource providing naloxone

- [ ] **Safer injecting, safer smoking and safer sex supplies:**
  - ✓ Syringes and injection equipment
  - ✓ Pyrex tubes
  - ✓ Recovery bin
  - ✓ Condoms

Document inspired by the CHUM's Addiction Medicine Department

APPENDIX 7

Summary of the report: *Innocuité de la morphine à libération prolongée durant la grossesse et l'allaitement en traitement par agonistes opioïdes (TAO) dans le cadre du traitement des troubles liés à l'utilisation des opioïdes*, by Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), 2021

Full report available upon request

PREGNANCY

1st trimester

- Although specific data on the use of morphine during the first trimester is limited, there is already considerable clinical evidence, and no reports of teratogenicity to date.
- Some studies have suggested associations between opioids in general and certain abnormalities, but no clear causal link has been established to date. A number of methodological difficulties limit the overall value of many of these studies.[1]

2nd and 3rd trimesters

- Despite significant clinical experience, there is little published data on the impact on maternal and fetal outcomes of prolonged exposure to morphine during the second and third trimesters.

Neonatal considerations

- As with other opioids, use of morphine during pregnancy warrants perinatal monitoring as it may cause:
  - Respiratory depression in the neonate if high doses are taken shortly before delivery.
  - Neonatal opioid abstinence syndrome if exposure is prolonged during pregnancy.
- Limited available data indicate that neonatal abstinence syndrome following parental treatment with slow-release oral morphine preparations is similar to that reported for methadone (in terms of duration of treatment and infant hospitalization) and possibly more severe than with buprenorphine.[2,3]
- The interval between birth and onset of withdrawal symptoms may be shorter with morphine than with methadone due to morphine's shorter half-life, but available data has not yet addressed this issue.

Pharmacokinetics considerations

- Morphine clearance may be accelerated during pregnancy.
- The impact of physiological changes during pregnancy on the pharmacokinetics of slow-release oral morphine formulations has not yet been studied but should be expected.

Other considerations

- There is still a limited understanding of the impact of opioids on the neurobehavioural development of children exposed *in utero*, and there are many confounding factors in published studies. Specific potential effects of slow-release oral morphine formulations have yet to be evaluated.

Specific data on the use of slow-release oral morphine formulations in OAT during pregnancy

- Three studies were documented in the scientific literature:
  - A randomized open study (48 women)[3]
  - A comparative observational study (390 women)[2]
  - A comparative observational study (160 women)[4]
- While one of these studies reports less use of benzodiazepines and other opioids during pregnancy in people treated with slow-release oral morphine than in those treated with methadone3, another study suggests the opposite (although the results were not statistically significant).[2]
- Quality of life appears to be similar regardless of treatment used, according to one study.[2]
- Neonatal abstinence syndrome appears to be similar (duration of treatment, length of hospital stay and treatment doses required) in neonates whose parents had been treated with slow-release oral morphine as in those whose parents had been treated with methadone,[2,3] although the average and peak Finnegan scores were shown to be higher with morphine in one of the studies.[2]
- In one study buprenorphine was found to have an advantage over slow-release oral morphine and methadone in terms of gestational age, birth weight, duration of neonatal treatment and length of hospital stay.[2] However, this study was not randomized, which limits the interpretation of its results.

Expert group and learned society opinion

- The Society of Obstetricians and Gynaecologists of Canada (Clinical Practice Guideline No. 349 – Substance Use in Pregnancy)[5] recognizes the use of slow-release oral morphine preparations during pregnancy when methadone or buprenorphine are not available.
- The British Columbia Centre on Substance Use (Treatment of Opioid Use Disorder During Pregnancy – Guideline Supplement)[6] recognizes the potential use of slow-release oral morphine preparations and provides guidelines for their administration during pregnancy.

BREASTFEEDING

Transfer into breast milk

- Data on the transfer of morphine into breast milk are limited, and available studies have not accurately characterized the transfer of active morphine metabolites into breast milk.

Clinical trials

- Published clinical trial on the use of morphine during breastfeeding are limited to short-term use immediately postpartum.
- Data on chronic high-dose morphine use are almost non-existent, unlike for methadone and buprenorphine, for which there is significant clinical experience and stronger data on the transfer into breast milk.

Specific data on the use of slow-release oral morphine formulations in OAT during breastfeeding

- Only one published study has documented the use of slow-release oral morphine in OAT during breastfeeding:
  - Breastfeeding appears to attenuate neonatal abstinence syndrome (lower average and peak withdrawal scores, as well as shorter duration of treatment and hospital stay among the 21 children who were breastfed, compared to the non-breastfed children).
  - Many key elements for assessing these results are not specified (e.g. morphine doses of breastfeeding parents, extent of breastfeeding [mixed or exclusive], duration of breastfeeding, clinical follow-up, and the child's progress beyond the immediate neonatal period).

Infant risk

- As with other opioids, a child exposed to morphine through breastfeeding is at risk of respiratory and central nervous system depression, particularly if the child was not exposed to opioids *in utero*, if treatment is initiated postpartum, if doses are high or increased rapidly, or if other central nervous system depressants are used. The younger the infant, the greater the risk.
- There is also a risk of withdrawal for the infant if breastfeeding is abruptly terminated.

Expert group and learned society opinion

- The Society of Obstetricians and Gynaecologists of Canada (Clinical Practice Guideline 349 – Substance Use in Pregnancy)[5] acknowledges the overall reassuring data on opioid use while breastfeeding.
- The Academy of Breastfeeding Medicine (Guidelines for Breastfeeding and Substance Use or Substance Use Disorder)[8] acknowledges the data supporting the use of methadone and buprenorphine during breastfeeding, while pointing out the lack of clinical experience and data on the use of moderate to high doses of opioids over long periods of time and insisting on the importance of individualizing clinical decisions when it comes to the administration of high doses of opioids during breastfeeding.
- The Drugs and Lactation Database (LactMed)[9] stresses the increased neonatal vulnerability in children and the importance of limiting the duration of opioid exposure for the parent (excluding OAT).

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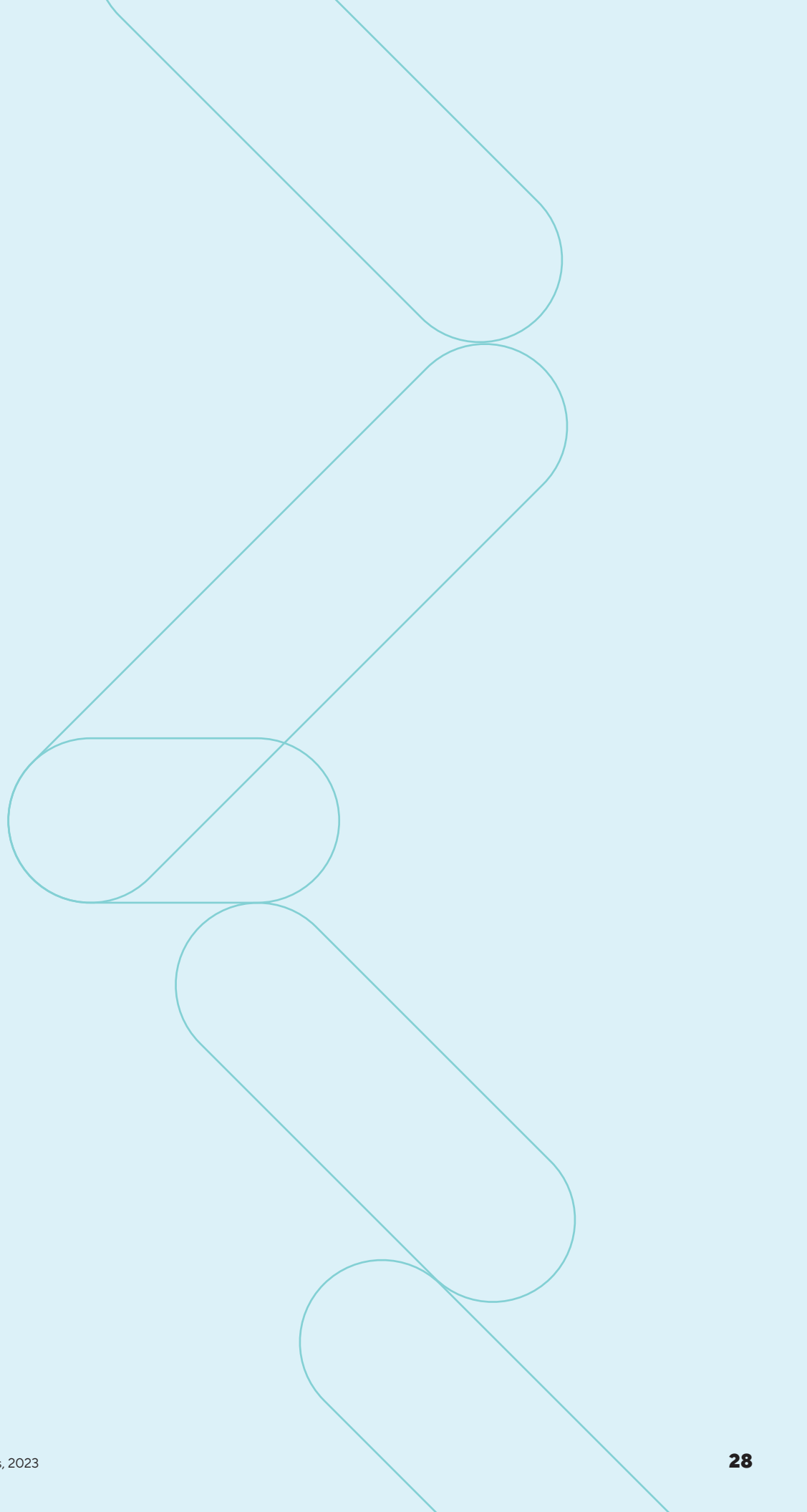

A publication of the Équipe de soutien clinique et organisationnel en dépendance et itinérance at the Institut universitaire sur les dépendances (IUD) of the CIUSSS Centre-Sud-de-l'Île-de-Montréal

In collaboration with:
Health Canada
Ministère de la Santé et des Services sociaux

With support from:
Directorate of University Education and Research

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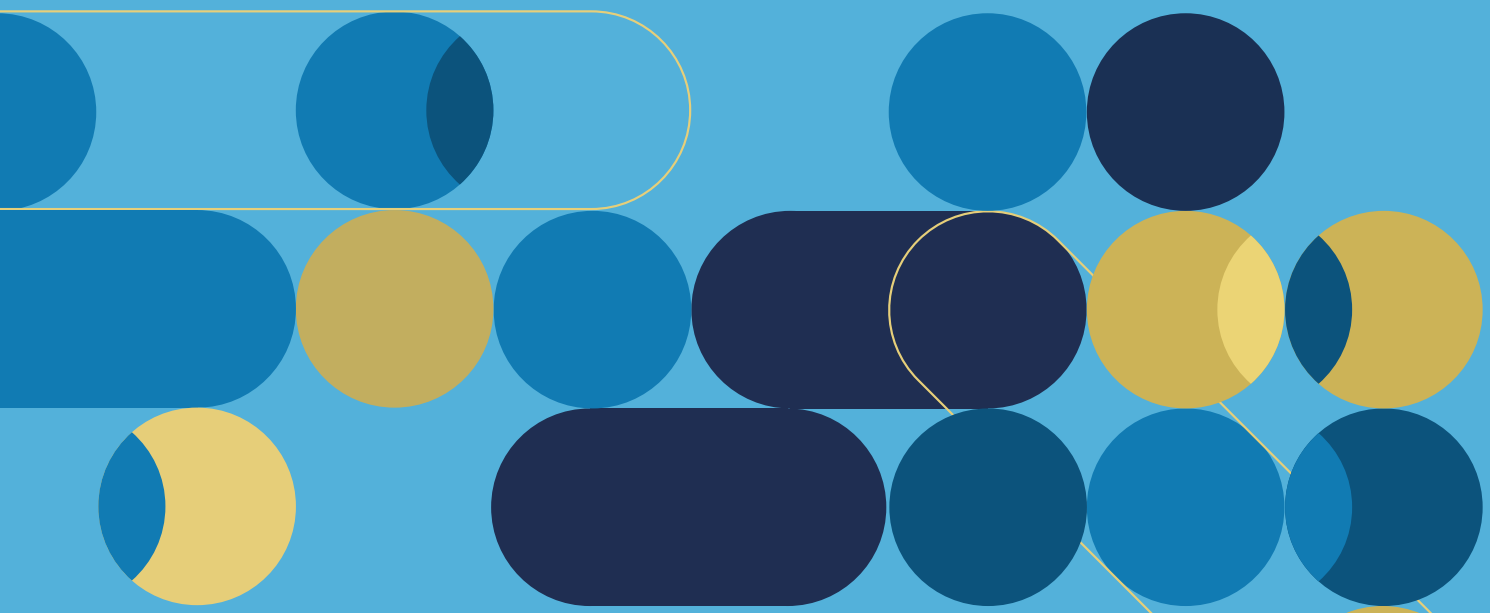

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