



PRINCE EDWARD ISLAND  
**COLLEGE OF PHARMACISTS**

*Member organization of National Association of Pharmacy Regulatory Authorities (NAPRA)*

## **Treatment of Opioid Dependence Practice Directives for Community Pharmacies**

Approved: September 2014

Revised: November 2015

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## Introduction

### Purpose

The primary goal of the *Treatment of Opioid Dependence: Practice Directives for Community Pharmacies* document is to enhance the safety, consistency, and effectiveness of the opioid dependence treatment services provided by community pharmacies in Prince Edward Island, contributing to improved patient and societal outcomes.

These practice directives are intended to provide Island pharmacists with the processes for providing methadone and buprenorphine/naloxone in the treatment of opioid dependence in a safe and effective manner that is compliant with the relevant legislation and consistent with best practices. While methadone and buprenorphine are also used in the treatment of chronic pain, these standards will not address best-practices in its provision for this indication.

It is recognized that there may be rare, exceptional situations, or extenuating circumstances, in which some of the provisions of these practice directives may not be appropriate. In such situations, where these practice directives are not followed, it is required that the pharmacist will communicate with the prescriber and document the rationale for the deviation. Such deviations will occur only in the interest of providing optimal patient care.

### Acknowledgment

These Practice Directives were developed from best practice documents from other provincial pharmacy regulatory authorities including British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Newfoundland and Labrador; and from best practice documents of the College of Physicians and Surgeons of Ontario, British Columbia and Nova Scotia; as well as from the Centre for Addiction and Mental Health's publication, —Methadone Maintenance Therapy: A Pharmacist's Guide – 2nd edition. The PEICP acknowledges these documents throughout the Practice Directives.

The Prince Edward Island College of Pharmacists gratefully acknowledges the work of the Methadone Committee as well as the physician reviewers.

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**Support**

While this document is specific to pharmacy practice, the Prince Edward Island College of Pharmacists (PEICP) recognizes that a pharmacist's adherence to these practice directives will have implications for the manner in which other health care professionals provide treatment for opioid dependence to their patients. As such, support of these practice directives by the other health care professionals involved in providing treatment for opioid dependence is essential for effective collaboration towards optimal patient and societal outcomes. The PEICP appreciates the PEI College of Physicians and Surgeons review of the *Opioid Dependence Treatment- Practice Directives for Community Pharmacies in Prince Edward Island*.

## Opioid Dependence Treatment: Introduction

Substance dependence is a medical illness. It is a chronic and relapsing disorder and not an acute condition that can be rapidly cured by detoxification. The cost of this illness to the dependent individual and to society is significant, including severe decline of the individual's physical and psychological health, unemployment, family disruption, and criminal activities, such as prostitution, vandalism, drug dealing, and theft. Relapses are a common part of recovery. The fact that these patients are also at a high risk for concomitant health conditions and comorbidities only serves to complicate the matter and demonstrate the need for a holistic approach to the patient.

The goal of a treatment program for opioid dependence should be to provide broad access to effective treatments that are assessed, administered, monitored, and supported by experts trained in addiction to ensure optimal safety and efficacy from the therapy. These experts not only use their skills and knowledge to make appropriate decisions about the use of available treatments, but must also understand the complex challenges of addiction and be able to provide guidance and support for the psychosocial aspects that can complicate the lives of individuals with opioid dependence.

Treatment success is not contingent on an individual being able to eventually stop medication-assisted treatment and to continue to remain abstinent from opioids, although this is an ideal outcome. Since opioid dependence treatment itself can result in physiological dependence, for some, methadone or buprenorphine/naloxone therapy may be required chronically in order to prevent relapse. Medication-assisted treatment for opioid dependence is based on harm reduction and serves to bring normal functioning back to an individual. The benefits can be physiological, psychological, and social. When used as part of a maintenance program, methadone and buprenorphine/naloxone cause little to no euphoric effect but enable suppression of the withdrawal symptoms and cravings experienced in opioid addiction that often contribute to relapse.

Also critical to the success of medication-assisted treatment for opioid dependence is collaboration between health care professionals involved in the care of the patient. Many problems in patient care have been found to be a direct result of lack of communication between the prescriber and the pharmacist. Effective collaboration and communication between prescribers and pharmacists is essential and can have a positive impact on patient care and safety. (NLPB 2015)

These practice directives are intended to provide information and guidance to **community pharmacists** involved in medication assisted treatment of opioid dependence and to promote consistency in the provision of such medications to patients in Prince Edward Island.

## Treatment Choices

The main treatment options for opioid dependence are abstinence based treatments and opioid agonist therapy (also known as opioid substitution therapy) with methadone or buprenorphine/naloxone (see [Appendix A- Comparison of Methadone and Buprenorphine](#)). The choice between methadone and buprenorphine/naloxone will depend on a number of factors including (but not limited to):

- The degree of opioid dependence and tolerance experienced by the patient;
- An evaluation of the patient's risk of harm from the chosen therapy including the risk of non-compliance;
- The patient's allergies, concomitant health conditions and comorbidities;
- The potential for significant drug interactions with other concomitant therapies;
- The patient's ability to access the specialized services and expertise of an opioid dependence program;
- The patient's response to therapy;
- The patient's ability to afford the chosen therapy; and
- The patient's lifestyle and social history.

### Abstinence Treatment

Abstinence based treatment may consist of medically supervised withdrawal from opioids, followed by an inpatient or outpatient psychosocial treatment program, and/or 12 Step group participation (Alcoholics Anonymous, Cocaine Anonymous, Narcotics Anonymous). While abstinence based treatment is less effective than opioid dependence treatment, patients may prefer a trial of abstinence before committing to long-term opioid agonist therapy. (CPSO, 2011)

### Opioid Agonist Therapy

Long-acting opioids used in the treatment of opioid dependence include methadone and buprenorphine/naloxone.

#### Buprenorphine/Naloxone

Buprenorphine/naloxone is a partial  $\mu$  agonist that, at the appropriate dose, relieves withdrawal symptoms and cravings for 24 hours or more. Because it has a ceiling effect, buprenorphine appears to be safer in overdose compared to methadone. However, buprenorphine may also be somewhat less effective than methadone at retaining patients in treatment. (CPSO, 2011)

## **Methadone**

Methadone is a long acting orally effective opioid. In the treatment of opioid dependence. Methadone is used as a substitute for opioids, eliminating withdrawal and reducing cravings for opioids. Methadone does not necessarily produce a "high" and it blocks the euphoric effects of other opioids so patients can focus on their rehabilitation without the distraction of opioid withdrawal symptoms or the hindrance of the reinforcing effects of opioid euphoria. When used in the treatment of opioid dependence, a single oral dose is most often effective for at least twenty-four hours. Therefore, once daily dosing is generally the optimal dosing regimen for the treatment of opioid withdrawal. (CPSO, 2011)

More information on the pharmacokinetics and actions of methadone can be found in [Appendix C Pharmacokinetics and Actions of Methadone](#).

Methadone or buprenorphine/naloxone alone do not constitute effective treatment of opioid dependency. Effective opioid dependence programs should comprise the following components:

- an appropriate methadone/buprenorphine-naloxone dose;
  - routine medical care;
  - treatment for other substance dependence;
  - counselling and support mental health services;
  - health promotion, disease prevention and education;
  - linkages to other community-based services; and
  - outreach and advocacy.
- (CPSO, 2011)



## Pharmacist Requirements

### Extended Practice Certification

All pharmacists who are involved in the provision of methadone or buprenorphine/naloxone for the treatment of opioid dependence, must apply for an Extended Practice Certification (EPC) from the PEI College of Pharmacists in order to dispense methadone or buprenorphine (effective April 1, 2016). Dispense in the context of the legislation includes the following activities:

- a) assessing the pharmaceutical and therapeutic suitability of the drug for its intended use;
- b) assessing the patient, the patient's health history and the patient's medication record;
- c) preparing, packaging and labelling a drug;
- d) providing the drug to the patient or a representative of the patient;
- e) counselling the patient or a representative of the patient on the use of a drug.

It is the expectation of the PEI College of Pharmacists that any pharmacists who participates in the above activities with respect to the provision of methadone or buprenorphine/naloxone will obtain an Extended Practice Certification in Dispensing Methadone and Suboxone.

In order to apply for an EPC in Dispensing Methadone and Suboxone, pharmacists must complete the following:

- a) Complete the EPC application and submit to the PEI College of Pharmacists.
- b) Provide proof of successful completion of either the Centre for Addiction and Mental Health (CAMH) Opioid Dependence Treatment Core Course or the Optimizing Opioid Dependence Treatment in PEI online course.

### Expected Role of the Pharmacist

Before engaging in the provision of opioid dependence treatment services, pharmacists need to consider the activities they are expected to undertake and establish a plan of how to address the associated time and physical space requirements.

The expected activities of pharmacists providing methadone or buprenorphine/naloxone include but are not limited to:

- Medication dispensing (including witnessed administration 7 days a week\*);
- Providing assistance with dosing;
- Educating and counselling patients on the use of their treatment;
- Patient monitoring and support;
- Thorough record keeping;

- Communicating progress of treatment to the physician (i.e., missed/lost doses, patient behavior, treatment plan changes etc.); and
- Providing input to the physician or treatment team on authorization of take home doses, etc.

**(\*For stores that are not open 7 days a week, see “Pharmacy Hours” for recommended options.)**

Just as it is required for the safe and effective care of patients with other clinical conditions, it is essential that pharmacists providing methadone or buprenorphine/naloxone are competent in this clinical area, including an understanding of:

- i. Substance dependence;
- ii. Opioid abuse and opioid dependence;
- iii. Opioid withdrawal and its management;
- iv. Harm reduction treatment strategy;
- v. Methadone and buprenorphine/naloxone (i.e., chemistry, pharmacokinetics, pharmacology, therapeutics, etc.);
- vi. Expected activities of the pharmacist providing opioid dependence treatment;
- vii. Dosing issues (including management of overdose, dosing in special and emergency circumstances, etc.);
- viii. Inter-professional collaboration (i.e., working with the treatment team);
- ix. Pharmacy legislation, guidelines and practice directives pertaining to opioid dependence treatment service; and
- x. Community support and referral resources.

## Operational Requirements

### Pharmacy Layout and Design

The pharmacy should be designed to allow for all pharmacist-patient discussions, witnessed doses and the provision of take home doses to take place in a patient care environment that ensures privacy and confidentiality and that is clean, safe and comfortably furnished for the patient.

### Pharmacy Registration

Pharmacy managers will ensure that the PEI College of Pharmacists is aware that their pharmacy is participating in the provision of medication for the treatment of opioid dependence. Pharmacy managers will log into their manager account in the member area of the PEI College of Pharmacists website and indicate their participation.

## Pharmacy Hours

When a patient is prescribed daily witnessed ingestion of methadone or buprenorphine/naloxone, they should ideally attend a pharmacy that is open every day of the week. Pharmacies which are open only five or six days each week will have to adjust their practices for patients for whom take-home doses are not appropriate. (CPBC, 2007)

Options include:

- opening for a few hours so patients can have their daily dose observed, or
- coordinate weekend witnessed ingestion with another pharmacy and the prescribing physician. In this situation, communication between the weekday dispensing pharmacy and the weekend pharmacy shall occur, when appropriate, to ensure continuity of dosing.

## Security

The security of the pharmacy should address the potential risks associated with the provision of medication for the treatment of opioid dependence and the risks to the community that can result from theft of methadone or buprenorphine/naloxone. As with other controlled drugs and substances, preparations containing methadone and buprenorphine/naloxone should be stored in a locked and secure location at all times including when the pharmacy is open and when the pharmacy is closed for business.

## Staff Education

The pharmacy manager is responsible for ensuring that all pharmacists have an Extended Practice Certificate in Dispensing Methadone and Suboxone prior to dispensing either medication. The pharmacy manager is also responsible for ensuring that all staff in the pharmacy understand the scope of their role in the provision of medications for the treatment of opioid dependence.

## Establishing Relationships

The interactions a patient has with their health care providers have a significant impact on the patient's success in a medication-assisted opioid dependence treatment program. Pharmacists are in the unique position of seeing and interacting with the patient daily. This daily interaction affords a pharmacist the opportunity to monitor a patient's progress, identify actual and potential drug-related problems and make recommendations for changes to their care. Pharmacists who have a clear understanding of the goals of the program, of their role on the patient's collaborative care team and who are committed to providing optimal care can substantially contribute to their patients' success.

## Pharmacist/Prescriber Collaboration

Effective communication and collaboration between the pharmacist and the patient's prescriber enables clinical decisions to be based on current, comprehensive patient information. Therefore, pharmacists are encouraged to develop a solid working relationship with the prescribers for their patients. (CPBC, 2007)

Physicians are encouraged to send a written Physician-Pharmacist Treatment agreement (see [Appendix F Prescriber-Pharmacist Agreement](#)) to the patient's pharmacy that puts in writing his or her expectations regarding missed doses and intoxication of the patient. Physicians are also encouraged to include their contact information for use by the pharmacist in situations of an emergency.

## Pharmacist/Patient Relationship

A patient enrolling in the medication assisted opioid treatment program the pharmacists should offer the patient the option to receive counselling in a **private area** in the pharmacy where conversation cannot be overheard by others, respecting the patient's right to privacy and confidentiality

The patient should receive an orientation to the pharmacy and be provided with the following information about their medication:

- Methadone and buprenorphine/naloxone are opioids the patient will become physically dependent upon and if the patient abruptly discontinues the medication, withdrawal symptoms will develop.
- During the stabilization period, sedation and/or withdrawal symptoms may be present. Driving an automobile or operating machinery during the stabilization period of opioid dependence treatment may be dangerous. Such dangers can also arise again during dose adjustment or periods of instability.
- Illicit drug or alcohol use with methadone and buprenorphine/naloxone can be dangerous. The use of other substances including prescribed or non-prescribed medications while taking methadone should be discussed with the patient's physician and pharmacist as drug interactions may occur.
- For reasons of safety the methadone and buprenorphine/dose may be withheld if the patient appears to be sedated or intoxicated.
- Signs of toxicity and of the need to seek medical attention should they occur
- Because a single dose of methadone and buprenorphine/naloxone is effective for 24 hours, patients should attend the pharmacy at the same time every day, preferably in the morning to receive their dose. This will result in more consistent blood levels, fewer adverse effects and allow patients to be monitored for signs of toxicity. (CPSO 2011)
- Missed doses will be discussed with the patient including the consequences of missing those doses. It must be stressed by the pharmacist that the average daily dose of methadone and buprenorphine/naloxone may result in death if taken by a person not dependent on an opioid.

- Potential side effects from their treatment.
- Fertility improves with stabilization on medication assisted opioid treatment, so patients should consider this factor during family planning.
- Patients have a legal obligation to inform any physician if they have received a narcotic from another physician within the preceding thirty-day period; otherwise the patient will have committed the offence of double doctoring (CDSA).
- It is preferable that the patient receives treatment from only one pharmacy. There is a risk to the patient if methadone is split between pharmacies.  
(NFLD, 2007)

The patient will be given an opportunity to ask questions about their treatment or any other currently prescribed drugs. Relevant written information will be made available about the pharmacy, including hours of operation. (NLPB, 2007)

A treatment agreement can help the pharmacist explain to their patients the goals of the program, the responsibilities of the pharmacist and the responsibilities of the patient (See [Pharmacist-Patient Agreement Appendix E](#)). The pharmacist must review the treatment agreement with the patient and keep a copy signed by both the pharmacist and patient in the patient's record.

A pharmacist may decide, during initial consultation with the patient and in compliance with the Code of Ethics, they do not wish to provide opioid dependence treatment to the patient.

## Opioid Dependence Treatment- Methadone

### Assessing the Prescription

#### Prescriber Eligibility

Physicians must have special authorization issued by the Office of Controlled Substances, Health Canada, to prescribe methadone for maintenance therapy, detoxification or analgesia.

**Methadone Line:** (613) 946-5139\*\* or toll free at (866) 358-0453\*\*  
 (Mon-Fri 7.30am-3.30pm Eastern Time)  
 Fax: (613) 952-2196  
 Email: exemption@hc-sc.gc.ca  
 (\*\*accurate at date of printing)

Physicians who are authorized to prescribe methadone for opioid dependence are **not** automatically authorized to prescribe methadone for pain. Pharmacists may call the federal Methadone Line for verification of a physician's authorization for either indication.

Physicians in PEI must also comply with the College of Physicians and Surgeons of PEI (CPSPEI) Methadone Maintenance Treatment for Opioid Dependence Policy. The policy can be found on the CPSPEI website [www.cpspei.ca](http://www.cpspei.ca).

### **Prescription Requirements**

Methadone is a straight narcotic. All federal and provincial laws and regulations that apply to straight narcotics apply to methadone. Verbal prescriptions or refills are not permitted. In accordance with the *PEI Pharmacy Act-General Regulations* **all methadone prescriptions for opioid dependence must be written on the Methadone Maintenance Prescription Fax Form and faxed to the pharmacy ([See Appendix D](#))**. If the prescriber wishes to make any changes to an existing prescription, a new prescription must be signed and faxed to the pharmacy.

**Physicians are not required to write buprenorphine/naloxone prescriptions on the Methadone Maintenance Prescription Fax Form.**

If for some reason the treatment period of a prescription overlaps with that of a previously issued prescription, instructions should be included on the new prescription to cancel the previous prescription. Methadone prescriptions must include:

- The number of doses to be provided
- The start date and end date of the prescription
- The daily dose in mg written in both numbers and words
- The dispensing schedule including:
  1. The dosing frequency;
  2. Which doses must be administered as supervised ingestion; and
  3. Whether take home doses are permitted, and if so, the schedule.

If this information is not included on the prescription, clarification from the prescriber is required.

Consistent with current best practices, the number of consecutive take home doses should be limited to a maximum of six for methadone. An exception to this maximum can be made for reasons including the following:

1. The patient is going on vacation to an area where methadone is not readily available.
2. The patient has employment opportunities in an area where methadone is not readily available.
3. Other exceptional circumstances as agreed upon by the pharmacist and physician in collaboration.

**If the number of take home doses prescribed exceeds the recommended maximum, the pharmacist will contact the physician and document the reason(s). [See Take-Home Doses](#).**

## Methadone Dosing

Methadone's long half-life allows it to be dosed once daily and is generally the optimal dosing regimen for opioid dependence treatment.

Dosing of methadone must be undertaken carefully, individually titrating the optimal dose for each patient. An effective dose for one patient can be a lethal dose for another. Methadone overdose cases resulting in death have been reported with single methadone doses as low as 40 mg in non-tolerant patients. Many factors impact an individual's optimal vs. toxic dose including their opioid tolerance, physiologic and metabolic response, concurrent drug therapy, and methadone's pharmacokinetic activity. (CPSO, 2011)

Methadone reaches steady state in 5 to 7 days. Therefore, blood levels of methadone continue to rise for 5 to 7 days after starting therapy or increasing a dose. Toxicity or death may result from increasing a dose before the full effect of the current dose is known. A dose that is barely adequate on day one can be toxic by day 3 to 5. (CPSO, 2011)

There is wide variability in plasma methadone levels among people prescribed the same dose. There is no consensus regarding interpretation of blood levels in clinical practice.

Methadone dosing for the treatment of opioid dependence is generally divided into distinct phases:

**Table 1. Phases of Methadone Dosing**

Phase	Description
Initiation	When the first dose of methadone is given
Early Stabilization	The initial period when the dose is increased safely but rapidly enough to minimize significant withdrawal symptoms (0 – 2 weeks)
Late Stabilization	The period during which the stable dose is being approached (2 – 6 weeks)
Maintenance	When a stable dose has been reached (6 + weeks)

The prescriber should base the initial dose on the patient's underlying risk for methadone toxicity. A number of factors increase this risk, including but not limited to:

- Recent benzodiazepine use;
- Use of other sedating drugs;
- Alcohol-dependent patients;
- Over 60 years old;
- Respiratory illnesses;
- Taking drugs that inhibit methadone metabolism;

- Lower opioid tolerance;
- Decompensated hepatic disease;
- Recent discharge from inpatient rehabilitation facility; and
- Recent incarceration (development of reduced tolerance to opioids during incarceration)

Since opioid tolerance is difficult to establish by history, if in doubt, it is safer to initiate on a lower dose.

Once initiated, dose increases should take place only after an in-person assessment. During the early and late stabilization phases, doses should only be increased for those patients who are experiencing significant opioid withdrawal symptoms. Prescribers should generally be assessing patients at least once weekly during these phases.

During the maintenance phase (generally when the methadone dose is 80 mg or more), the physician should increase the dose by no more than 5-10 mg every 5-7 days. Physicians should be assessing patients once weekly when ongoing dose adjustments are occurring and less frequently thereafter as required.

The optimal dose range for most patients is 60-120 mg.

**Table 2. Methadone Dosing During Phases**

Patient Factors	Initial Dose	Dosing During Early and Late Stabilization Phases		Dosing During Maintenance Phases	
		Dose Increases	Frequency	Dose Increases	Frequency
Recent abstinence from opioids	10 mg or less	5 mg or less	Every 5 days or more	5- 10 mg	Every 5-7 days
Higher risk for methadone toxicity	20 mg or less	5-10 mg	Every 3-5 days		
No risk factors or recent abstinence	30 mg or less	10-15 mg	Every 3-5 days		

Reference: CPSNL, Methadone Maintenance Treatment Standards and Guidelines, 2013.

Pharmacists should assess each methadone prescription to determine whether or not the dose falls within these recommended guidelines. Generally speaking, the above criteria should be adhered to unless special circumstances such as concomitant acute pain treatment or



pregnancy exist, or if the patient's dose is being tapered due to voluntary or involuntary withdrawal from the program:

- i) For voluntary tapers, the dose should be reduced by 10% or less every one to four weeks
- ii) For involuntary tapers, the dose should be decreased by 5-10 mg every three to seven days until 50 mg is reached, then by no more than 5 mg every three to seven days.

If pharmacists see doses being prescribed outside of these practice directives, they shall consult with the prescribing physician and document the rationale for the deviation in the patient record.

### **Take-Home Doses**

Take-home doses are key to the success of treatment of opioid dependence. It has been demonstrated that not only do patients markedly reduce their use of opiates when given take-home doses, but it also helps to prevent the decline in treatment outcomes over time. Patients strongly value take-home doses, and treatment retention rates are lower in clinics with restrictive take-home policies.

The dispensing and administration of witnessed ingestion of methadone to patients must be done on a daily basis until such time as the prescriber authorizes take home privileges. The overarching considerations for granting take-home doses are patient safety, public safety and risk of diversion. (Isaac, 2004)

Based on certain criteria, take home privileges may be granted by prescribers to stable patients in order to improve the quality of the patient's daily life. Once a patient is assessed to be functionally stable on methadone, not all doses may have to be witnessed by a pharmacist, and the prescriber may grant take-home doses. In keeping with best practice, a patient should have a dose witnessed prior to be provided take-home doses. Pharmacists are required to contact the prescriber for directions that deviate from this practice.

The practice of dispensing continuous take-home doses without a witnessed ingestion is strongly discouraged because:

- It is inconsistent with current best practices.
- It places the patient at risk of overdose or toxicity.
- It places the public at risk of diversion.
- Take-home doses are not recommended during the first two to three months of treatment.
- Take-home doses are a progression of treatment. A decision to grant take-home doses by the physician should ideally be made in consultation with other

professionals involved, including counselors and pharmacists. Therefore, it is important that pharmacists understand the general criteria for take-home doses.

### Criteria for Take-Home Doses

1. Program participation including:
  - a) Attendance at the pharmacy on schedule for their methadone dose;
  - b) Attendance at scheduled appointments with the physician, nurse or counselor; and
  - c) Compliance with the treatment agreement.
2. Demonstration of cognitive stability to assume responsibility for the care and use of the medication.
3. Use of drugs improves (as evidenced by acceptable urines for 3 months), either from abstinence or non-harmful use of drugs (harm can be seen as a continuum and can result from a single use or from long term use of drugs).
4. Social integration via employment, school attendance, child-care responsibilities, or volunteer work.
5. Patients with take-home doses must be able to accept responsibility for the doses, which includes proper security and use of the methadone.
  - a) Patients with unstable living arrangements such as those living on the street or in hostels without storage facilities may not be appropriate candidates to receive take-home doses. If the pharmacist is aware of such circumstances, they will notify the prescriber.
  - b) Patients **must bring an impenetrable locked box** with them in which to place their take-home doses. Patients should be counselled to store the locked box in a safe and secure location.

**Table 3. Best Practice; Take-Home Dose Schedule**

<b>Typical Take-Home Dose Schedule</b>	
Schedule A	Schedule B
<ul style="list-style-type: none"> <li>• Start with one take-home dose per week.</li> <li>• Increase by one take-home dose per week every four weeks, as appropriate, to a maximum of six take-home doses per week.</li> <li>• Each additional take-home dose should be prescribed only after the patient has had at least four additional weeks without substance use.</li> </ul>	<ul style="list-style-type: none"> <li>• Start with two take-home doses on consecutive weekend days.</li> <li>• After a further eight weeks free of substance use, take-home doses may be increased to one set of three consecutive days and one set of two consecutive days with an intervening witnessed dose.</li> <li>• After an additional 12 weeks free of substance use, take-home doses may be increased to six take-home doses per week.</li> </ul>

Reference: NLPB, Standards for the Safe and Effective Provision of Medication for the Treatment of Opioid Dependence. Sept 2015

**Exceptional Circumstances- Take-Home Doses**

In situations where a patient is clinically stable, and receiving three to six take-home doses per week, the prescriber may allow for exceptional take-home doses to be given in the case of travel for work, vacation or family crisis, but only if a local pharmacy cannot be found. **The maximum** recommended number of take-home doses should not exceed 13 doses at a time with an observed dose, in such special situations. However, circumstances may dictate that the prescriber authorizes more than this. Pharmacists shall contact the prescriber to discuss any take-home doses that exceed the usual 6/week schedule. The previous take-home dose schedule should be resumed after the period of exceptional take-home dose is completed. Generally the following criteria are advised:

**Table 4. Exceptional Circumstances-Take-Home Doses**

If:	Then:
The patient has been treated for at least two months, not yet generally eligible for take-home doses, but is stable and is not considered high-risk for diversion.	<ul style="list-style-type: none"><li>• Give take-home doses on compassionate grounds only, e.g., a personal crisis</li><li>• Give no more than six take-home doses at a time.</li></ul>
The patient has been treated for at least two months, has had negative random urine drug screen (UDS) for at least four weeks and is approaching a stable methadone dose.	<ul style="list-style-type: none"><li>• Give take-home doses for sound personal reasons only e.g., vacation / holidays / family matters</li><li>• Give no more than six take-home doses.</li></ul>
The patient has demonstrated 12 months with no drug use, is clinically stable and already receiving three to six take-home doses per week.	<ul style="list-style-type: none"><li>• Give up to 13 take-home doses for travel purposes</li><li>• If more than 13 days of take-home doses are required Pharmacists should contact the physician to discuss.</li></ul>

**Discontinuation of /Refusal to fill Take-Home Doses**

A pharmacist may refuse to fill a prescription for a take-home dose if there is concern for the safety of the patient, or the safety of others. This decision must be communicated to the physician.

Take-home doses may be discontinued or decreased by the physician for one of many possible reasons including:

- The patient has failed to meet the terms of a physician treatment agreement.
- The patient has a sustained use of unauthorized drugs.
- The patient has produced an unacceptable urine sample or has tampered with the collection of the urine sample.
- The patient has approached another treated patient suggesting or proposing to sell, buy or share any urine sample or tamper with any urine sample.
- The patient has diverted, or permitted to be diverted any part of the methadone.
- The patient has approached another person suggesting or proposing to sell, buy or share medication.
- The patient shows disruptive behavior.

In such situations, take-home doses should not be reinstated until stability can be re-established objectively via weekly urine drug screening and other measures of clinical stability. This may take one month in patients whose drug use was sporadic and brief, and whose clinical

stability is not significantly compromised, or up to two months or more in patients who have had a longer relapse with loss of clinical stability.

Pharmacists may refuse to fill or withhold doses for any of the many reasons which may include:

- The patient fails to meet the terms of the Patient-Pharmacist agreement.
- The pharmacist suspects the patient is intoxicated when they arrive for their doses.
- The pharmacist has knowledge that the patient has diverted or attempted to divert doses.
- The patient has missed a number of doses outside these practice directives or within the physician-pharmacy agreement.

### **Monitoring Compliance with Take-Home Doses**

There are several ways that pharmacists can monitor a patient's compliance with take home doses which include:

**Take-Home Dose Audit:** Patients shall be advised that they may be asked at any time to return to the pharmacy with the remainder of their take-home doses and empty containers. This procedure, known as a “take-home dose audit”, may be used to deter patients from diverting their take-home doses. This audit may be initiated by either the physician or the pharmacist.

If there are issues of concern with the patient’s compliance with their take-home doses or evidence of diversion, the pharmacist should notify the physician immediately (see sample [Prescriber Notification Form in Appendix G](#)).

**NOTE:** When patients return their take-home dose containers to the pharmacy prior to receiving their next lot of take-home doses, pharmacists must ensure that the returned containers are disposed of in a manner that protects the public from diversion of any methadone remaining in the containers and that maintains the patient’s confidentiality. Bottles that are being disposed offsite from the pharmacy must be rinsed of any remaining methadone and patient labels removed.

## **Dosing in Special Circumstances: Divided Dosing**

Prescribers may authorize “split doses” for the following reasons:

1. A small proportion of patients may metabolize methadone rapidly.
2. Split dosing or dose increases may be necessary in the 3<sup>rd</sup> trimester of pregnancy in opioid dependent women and occasionally in the initiation phase of their treatment, after which the doses can be combined into a single daily dose.

## **Dosing in Special Circumstances: Missed Doses**

Missed doses may be handled by the pharmacist in accordance with the Physician-Pharmacist agreement ([Appendix F](#)). However, patients who miss 2 consecutive observed doses should have the remainder of their prescription suspended and the physician contacted to discuss next steps. Pharmacists will note the missed dose on the Patient Daily Methadone/Buprenorphine Witnessed Ingestion and Take-Home Dose Log and in the patient’s electronic record.

Since a clinically significant loss of tolerance to opioids may occur within as little as three days without methadone/buprenorphine, the prescriber should reduce the dose in patients who have missed three consecutive days. The dose can be rapidly increased once the response to the lower dose is assessed. See table 5. Guidance on Missed Methadone Doses for more information on making recommendations to prescribers on adjusting therapy for missed doses.

**Table 5. Guidance on Missed Methadone Doses**

Phase of Treatment	Missed Doses	Action(s)	Dose Change(s)
Early Stabilization	1 day missed	No dose change	Resume same dose  Do not increase dose until 3 consecutive days at the same dose
	2 consecutive days missed	Patient should be reassessed by physician in person  Remainder of prescription should be cancelled	Restart at initial dose (10-30 mg) for at least 3 days  Reassess after 3rd consecutive dose
Late Stabilization/ Maintenance	1-2 days missed	No dose change  Assess patient in 1-2 weeks to determine clinical stability	Resume same dose
	3 consecutive days missed	Patient should be reassessed by physician in person and every 3-4 days thereafter if dose is increased daily  Remainder of prescription should be cancelled	Restart at 50% of regular dose or decrease to 30 mg  Then increase dose by no more than 10 mg daily for maximum of 3 days, then reassess by day 3-4  Then increase dose by 10-15 mg every 3-5 days until 80 mg  Then increase by 10 mg every 5-7 days for dose increases above 80 mg
	4 or more consecutive days missed	Patient should be reassessed by physician in person  Remainder of prescription should be cancelled	Restart at 30 mg or less  Then increase dose by no more than 10-15 mg every 3-4 days until 80 mg  Then increase by 10 mg every 5-7 days for dose increases above 80 mg

CPSNS, Methadone Maintenance Treatment Handbook. May, 2012

### Administration Errors

In the event of a confirmed or suspected medication dosing error, the pharmacist must take appropriate and necessary action to minimize harm to the patient, ensuring transparency throughout the entire process. This includes prompt consultation with the patient’s other health care provider(s) for determination of appropriate action.

In addition to the following standards specific to methadone, it is expected that pharmacists will manage the error in accordance with the NAPRA Model Standards of Practice for Canadian Pharmacists and the individual pharmacy's medication error management policy.

### **Methadone Overdose**

- Tell the patient. If the patient has left the pharmacy, contact him or her by telephone. If the patient has no phone, you may need to contact the patient's prescriber or clinic to obtain a contact number or send police to the home.
- Advise the patient to seek medical attention immediately. If the patient refuses medical attention, document the time and details. Ask the patient to remain in the care of a friend or relative for the day;
- Advise the patient of the symptoms of overdose; including the possibility of euphoria and respiratory. Make follow-up contact with the patient throughout the day;
- Advise the patient's prescriber or clinic;
- Reassess the patient's health condition before administering the next daily dose.

### **Methadone Under dose**

- Advise the patient's prescriber or clinic and the patient as you would with an overdose.
- Once the patient is contacted, offer the patient the "difference" of methadone between the amount administered and the amount prescribed.
- Should the patient refuse to return for the methadone, advise them of the possibility of withdrawal and the symptoms related to opioid withdrawal.
- If the patient cannot be reached during business hours, advise them of the error at their next administration. (AADAC, 2007)



## Preparation and Administration of Dose Formulations

Pharmacists **must use a commercially available 10mg/mL** methadone solution when preparing individual patient doses because of:

- enhanced patient safety (fewer steps to be potentially impacted by human error);
- enhanced stability of commercial product;
- The expectation that large volume production is undertaken under the requirements of federal legislation governing manufacturing.

### Witnessed and Take-Home Dose Preparation

1. Calculations for the preparation of the patient's dose must be completed by a pharmacist. It is preferable if these calculations are checked using an independent calculation performed by another pharmacist or pharmacy technician/assistant.
2. Procedure:
  - i. Measure the amount of 10mg/mL methadone solution required to obtain the individual dose using an appropriate measuring device e.g. syringe, Methameasure<sup>®</sup> system.
  - ii. Perform independent double-check of quantity of methadone..
  - iii. Put measured solution in a child proof, amber, calibrated bottle.
  - iv. Add sufficient quantity of diluent to bring the final volume of the dose to 100mL
3. The final dosage volume for each individual dose must not be less than 100 ml, both for on-site consumption and for take-home doses (*e.g. a dosage of 80 mg requires 8ml of a 10 mg/ml solution, then qs to 100ml with diluent*). A consistent volume enables patients to more easily identify unanticipated changes in the taste of their solution [i.e. in the event of an error]). This volume is sufficiently large to ensure the dose is not retained in the mouth. Patients have been known to “cheek” their dose, spit it out later and then inject or divert it.
4. All individual patient doses will be bottled separately in 100 mL amber, childproof bottles.
5. When periodic auditing of unconsumed take-home bottles is being considered, the use of tamper evident seals is recommended.
6. If individual patient doses are prepared in advance of being processed for dispensing, they must be clearly labelled with at least: (1) strength and quantity of methadone (i.e.

methadone 8 mg in 100 mL of diluent) (2) prepared date/expiry date and (3) initials of preparing pharmacist. These doses must be stored securely in the fridge.

7. All doses provided to the patient (i.e. by witnessed ingestion or by witnessed ingestion + take-home doses) must be labelled in accordance with the provincial labelling requirements. In addition, the label of each dispensed doses must include the **total dose of mg of methadone contained in the bottle**.
8. Individual patient doses dispensed as take-home doses must also be labelled with :
  - a) The date of ingestion of take-home doses
  - b) The start date and the end date of the prescription
  - c) The auxiliary label "Keep in Refrigerator"
  - d) The auxiliary label " Keep Away From Children"
  - e) A notation "Drink entire contents of bottle" and one of the following auxiliary labels:
    - i. Methadone can be fatal when taken by individuals for whom it is not prescribed  
or,
    - ii. The contents of this bottle may cause harm or toxicity if taken by someone other than the person whose name appears on the prescription label

For security and safety reasons, it is recommended that the preparation of methadone occurs away from the high traffic area in the dispensary.

### **Storage and Stability**

When storing individual doses of methadone pharmacists must consider the following:

- The stability of commercially available methadone solution versus compounded methadone solution,
- Whether the individual doses have been diluted,
- The date the individual dose was prepared.

### **Stock Solutions**

An unopened bottle of Methadose™ or Metadol™ has a shelf life of approximately 4 years from the date of manufacture. The expiry date will appear on the bottle. Once opened, it can be stored at room temperature (15-30°C) for six months.

## Individual Patient Doses

The stability and sterility of Methadose™ diluted with a crystalline drink such as Kool-Aid, Tang, or Crystal Light, is unknown as published studies are not available. Available literature does not address the issue of sterility, which includes the likelihood of bacterial growth in prepared solutions stored under refrigerated or unrefrigerated conditions. Pharmacists are required to use best judgment to assign the beyond-use date for diluted products.

**All diluted Methadose™ products must be refrigerated** and carries are permitted a **maximum expiry date of 14 days from the date of dilution**. The dispensing staff must assign dates based on the earliest expiry of the ingredients used or 14 days refrigerated, whichever comes first. Dilution with fruit juices may require a shorter dating as an opened juice bottle may have a best before date that is earlier than 14 days.

Metadol is stable and sterile in crystalline diluents for 14 days.

Table 6. **Methadone stability in various diluents for carries**, identifies the stability of **solutions** according to the diluents used and storage condition.

This table is provided as the best existing guidance to allow you to user professional judgment when assigning best-before dates to diluted Methadose™.

**Table 6. Methadone stability in various diluents for take home doses**

Diluent	Stability Room Temperature 20-25°C	Stability Refrigerated 5°C	Period of acceptable sterility for oral consumption under refrigeration (i.e., bacterial or pathogenic growth)
Grape Flavored Kool Aid®	17 days	55 days	Unknown for dilution with Methadose™  14 days for diluted Metadol™
Orange Flavored Tang®	11days	49 days	Unknown for dilution with Methadose™  14 days for diluted Metadol™
Allen’s® Apple Juice	9 days	47 days	Unknown for dilution with Methadose™  7 days for diluted Metadol™
Grape Flavored Crystal Light®	8 days	54 days	Unknown for dilution with Methadose™  14 days for diluted Metadol™
Grape Flavored Crystal Light® with 0.1% Sodium Benzoate	29 days	--	Unknown for dilution with Methadose™

Medication-Assisted Treatment for Opioid Dependence: Guidelines for Pharmacists and Pharmacy Technicians.  
2015. Alberta College of Pharmacists

## Administration of doses

### Providing Witnessed Doses

The pharmacist is required to witness the ingestion of the dose. This function may not be delegated to a pharmacy technician or any other member of the pharmacy team. Prior to releasing the witnessed dose to the patient, the pharmacist must:

- i. Positively identify the patient. If uncertain as to the patient's identity, photo identification must be requested.
- ii. Assess the patient for signs of intoxication or sedation. If it is determined that the patient is intoxicated or sedated, it is be advisable to withhold the dose. If such determination is made, the physician must be notified immediately (see sample [Prescriber Notification Form in Appendix G](#)).
- iii. Review the patient's profile and Administration Log for notes, missed doses, documentation of returned bottles (if applicable), or any other applicable information.
- iv. Counsel the patient appropriately (for complete patient counselling information, see the relevant product monograph).

Once it has been determined to be appropriate to release the witnessed dose, the pharmacist must:

- i) Directly observe the patient ingesting the medication;
- ii) Engage the patient in brief conversation to ensure the entire dose has been swallowed; and
- iii) Appropriately document the dose on the Administration Log ([Appendix H](#))

### **Providing Take-Home Doses.**

When providing take-home doses to the patient, the pharmacist must:

- i) Positively identify the patient. If uncertain as to the patient's identity, photo identification should be requested.
- ii) Review the patient's profile and Administration Log for notes, missed doses, documentation of returned bottles (if applicable), or any other applicable information.
- iii) Counsel the patient appropriately.
- iv) Appropriately document the provision of the take-home doses on the Administration Log.

## **Take-home Doses released to patient's agent (Exceptional Circumstance)**

Best practice would indicate that methadone take-home doses are released to the patient when their observed dose is provided. Only in exceptional circumstances should the pharmacists deviate from this practice and only when the physician's consent is obtained and documented.

## **Doses in the event of Storm**

Storm days pose a significant challenge to pharmacists dispensing opioid dependence treatment. Pharmacists should not provide take-home doses unless directed by the prescriber. Acceptable forms of communications from prescribers include:

- A new Methadone Prescription Fax Form faxed to the pharmacy with directions for take-home doses
- A notation within special instructions directing the pharmacists to provide a take-home dose in the event of a storm.

Pharmacist should not provide an observed dose or a take-home dose to patients that do not regularly obtain doses at their pharmacy, even after consulting the provincial drug information system. Variations in the method of billing in each pharmacy may lead to double dosing of patients.

## **Dosing in Special Circumstances: Vomited Doses**

When a patient reports that they have vomited their dose, the dose should not automatically be replaced. Vomited methadone doses should not be replaced unless a health professional directly observes the emesis. If the emesis was witnessed by the health professional and it occurred less than 30 minutes after consumption, best practice indicates that the dose can be replaced at no more than 50% of the regular dose. The prescriber is to be notified and provided with as much information as possible about the incident (time the dose was taken, time of vomiting) so that a decision can be made regarding replacement doses. Pharmacists may use the Prescriber Notification Form to document the incident and provide follow up to the prescriber for their records.

For pregnant patients or patients with serious underlying conditions (e.g. cancer or HIV), the prescriber should be contacted promptly as he or she may decide to prescribe a replacement dose even if the pharmacist or staff did not directly observe the emesis.

## Dosing in Special Circumstances: Intoxicated Patients

In most methadone related deaths, concurrent use of sedatives such as benzodiazepines and alcohol were found to have contributed to the cause of death. (CPBC, 2007)

Prior to dispensing methadone pharmacists must assess all patients for signs of intoxication methadone including but not limited to:

- slurred speech
- incoordination
- smelling of alcohol
- unusual behavior
- ataxia

To assess a patient for intoxication or sedation, consider their general demeanor and behavior in comparison to what you know as their usual behavior. If necessary:

- Ask the patient to remove sunglasses and observe their eyes for pin-point pupils, alertness or sedation.
- Talk to the patient, asking questions to determine if they are slurring or incoherent.
- Ask the patient to walk to the counter and observe their gait.

If an intoxicated patient presents at the pharmacy asking for their methadone dose, **the dose will be withheld** and the pharmacist will inform the prescriber immediately using the Prescriber notification form. If the patient returns within 8 hours of their scheduled dose that was refused and is no longer intoxicated, the pharmacist can provide the dose.

It is safer to refuse to dispense a patient's methadone than to medicate an intoxicated patient. Opioid withdrawal, while uncomfortable, is not life threatening - but adding methadone to the other drugs already consumed by an intoxicated patient may be.

The handling of such situations will have been made clear to the patient well in advance, by means of a pharmacist-patient agreement. In such a situation, the pharmacist will:

- Try to avoid confrontation with the patient by explaining that it would be dangerous to medicate at this time.
- Warn the patient against driving a car.

- Inform the prescriber that the patient appeared intoxicated in your pharmacy.
- Clearly document the rationale and the parameters around their decisions to withhold the dose. (Isaac, 2004)

### **Methadone Discontinuation**

Opioid dependence treatment programs focus on maintaining patients on methadone for as long as they continue to benefit from treatment. While some patients may want to reduce their methadone dose or stop using methadone entirely; these outcomes are not the exclusive emphasis of most programs. (Health Canada, 2002)

Although achieving a sustained drug-free state is an optimal treatment goal most individuals who are dependent on opioids cannot achieve this. Programs with a long-term maintenance philosophy have better retention rates than programs with a short-term maintenance philosophy. (Health Canada, 2002)

Patients may express an interest in tapering off methadone and leaving the program. The wish to taper off methadone may be influenced by several factors (Health Canada 2002):

- the patient's unrealistic expectations for recovery
- pressure from family and friends who may not recognize that recovery is a long-term process
- the patient's sense of stigma in being associated with the program
- their concern over the cost of the treatment
- the inconvenience of regular attendance at appointments

Since the likelihood of relapse is high, patients should be advised that tapering off methadone is an option, but that it is possible to continue on opioid dependence treatment and lead a fulfilling life. (Health Canada, 2002)

If a patient starts a "self-taper" by drinking only a portion of their daily methadone, this will be recorded on the patient dose log with a note of the estimated dose consumed. The pharmacist must discuss the taper with the prescribing physician. This discussion provides a chance to work together to determine a strategy for future prescribed doses. Slower tapering has shown to be more successful, with a maximum taper of 5 mg per week being suggested. (ACP, 2007) (CPBC, 2007)

The last part of the taper process is the most difficult, and therefore should be done slowly and cautiously. Many patients can only tolerate decreases of 1 mg every one to two weeks at this



point. Abrupt discontinuation is discouraged as withdrawal symptoms can be severe and long-lasting. (ACP, 2007)

If the patient is insistent on discontinuing their methadone treatment, the patient should be made aware of the consequences and risk of relapse to illicit drug use. Other members of the health care team should be informed of the patient's decision and status. (ACP, 2007)

Medication for the symptoms of withdrawal should be considered (clonidine, loperamide, NSAIDs, dimenhydrinate), and counselling on other appropriate resources should be made available. (ACP, 2007)

## **Special Populations**

### **Pregnancy**

Pregnancy in opioid-dependent women is an urgent indication for inclusion into an opioid dependence treatment program. (ACP, 2007)

Compared to the risks associated with continued opioid use, the use of methadone during pregnancy is preferred for both the mother and the fetus. Studies have shown that MMT improves both maternal and neonatal outcomes in pregnant opioid-dependent women. (CPSO, 2011)

Some of the advantages of methadone treatment in pregnant, opioid-dependent women include:

- better prenatal care and nutrition
- improved birth weight
- decreased infant mortality(Isaac, 2004)

Split dosing may be necessary in the third trimester due to changes in the woman's body composition. Pregnancy may cause the effects of methadone to abruptly change and therefore close monitoring is required. (ACP, 2007)

Pregnant women should not miss a dose of methadone, as the withdrawal symptoms associated with missing a dose may cause fetal distress. (NLPB, 2007)

### **Guest Dosing**

There are occasions, such as a vacation or business travel, when a methadone patient might ask to be medicated on a temporary basis at another pharmacy. Guest dosing generally involves situations in which the patient cannot be provided with sufficient take-home doses for the period of absence. Such situations may arise when the patient:

- Is not considered functionally stable enough to be given take-home doses for the time period.

- May be away for a long period that prevents issuing sufficient take-home doses. For example, juice will spoil, it is not practical to travel with a large number of containers, or concern exists about loss or theft of a large number of containers.

With the patient's consent, the pharmacist can facilitate identifying a conveniently located pharmacy that would be willing to dispense methadone on a temporary basis. Health care professionals may contact the PEICP to identify pharmacies dispensing methadone in PEI. Addiction Treatment Centers in other provinces can often facilitate identification of opioid dependence treatment physicians and pharmacies in their province. The name of a dispensing pharmacy will not be provided to a patient without the prior consent of that pharmacy.

The patient or pharmacist will inform the methadone prescriber of the name and address of the temporary pharmacy. If the prescription at the usual pharmacy is still valid for the time the patient will be away, the physician should cancel the remainder of that prescription and write a new one for the temporary pharmacy.

The pharmacists at both pharmacies must communicate clearly with one another at the beginning and end of the guest-dosing period, so that everyone understands where and when the patient is receiving the methadone. This communication is imperative to prevent double-dosing or missed dosing. (Isaac, 2004)

# Opioid Dependence Treatment with Buprenorphine

## Establishing Relationships

### Collaboration- Pharmacist and the Prescriber

**Verbal Discussion.** It is strongly encouraged that the physician and pharmacist have a verbal discussion outlining the details of the physician’s treatment agreement with the patient along with his or her expectations regarding missed doses and intoxication, among other things, prior to dispensing buprenorphine to the patient. This may or may not be followed up with documentation of these issues being sent to the pharmacist by the physician.

### Pharmacist – Patient Relationship

#### Verbal Discussion

Pharmacists should arrange for an initial meeting with the patient to discuss the services that they will provide, along with the obligations and expectations of both the pharmacy staff and the patient within this relationship. The patient should be given the opportunity to ask questions and relevant written information should be made available to supplement the discussion.

#### Written Agreement

A written Pharmacy-Patient Agreement serves to outline the roles, expectations and obligations of both parties and can go a long way to prevent and/or handle any misunderstandings that may occur in the future. It is strongly recommended that such an agreement be developed by the pharmacy and read and signed by both the patient and the pharmacist prior to buprenorphine for opioid dependence being dispensed.

## Assessing the Prescription

### Prescriber Eligibility

Physicians in PEI are required to submit a “Commitment by Physicians who Undertake Buprenorphine Treatment for Opioid Dependency” form to the College of Physicians and Surgeons of PEI (CPSPEI) as a requirement to prescribe buprenorphine. Prior to dispensing buprenorphine for opioid dependence, the pharmacist must first confirm that the physician is eligible to prescribe the medication for this purpose in accordance with the CPSPEI policy.

## Prescription Requirements

Unlike methadone, buprenorphine can be written on regular prescription pad and is not required to be written on the Methadone Prescription Fax Form.

**Required Information.** The prescription must be appropriately signed and dated by the physician and also specify:

- i) The daily dose of buprenorphine in milligrams, written in both numbers and words;
- ii) The start date and end date of the prescription;
- iii) The total number of witnessed doses of buprenorphine, written in both numbers and words and the days of the week that doses are to be witnessed; and
- iv) The number of take-home doses per week and the days of the week that the take-home doses are to be given.

## Buprenorphine Dosing

Buprenorphine dosing tends to be less variable than methadone dosing overall. Patients are generally given an induction dose when they are in a period of at least moderate opioid withdrawal and are then steadily increased according to the patient's needs over a period of a few days.

**Table 8. Buprenorphine Dosing During Phases**

Phase	Initial Dose	Dose Increases	Maximum dose
Induction	Single 2-4 mg dose	An additional 4 mg dose may be administered on the same day depending on the individual requirements  Second dose should be given only after physician assessment and not sooner than 3 hours after the initial dose	8 mg on Day 1
Maintenance	A dose equivalent to the total dose given on Day 1	Dose can be increased by 2-8 mg every 3-5 days to an average dose of 8-12 mg/day	24 mg/day

Pharmacists should assess each buprenorphine prescription to determine whether or not the dose falls within these practice directives. Generally speaking, these criteria should be adhered

to unless special circumstances exist. Once the patient is at a stable maintenance dose, consideration may be given to alternate day dosing (i.e. 16 mg every other day, instead of 8 mg daily) but these situations should be the exception and evaluated on a case by case basis.

If pharmacists see doses being prescribed outside of these guidelines or special circumstances, they should consult with the prescribing physician and document the rationale for the deviation in the patient record

### **Take-Home Doses**

Take-home doses are key to the success of treatment of opioid dependence. It has been demonstrated that not only do patients markedly reduce their use of opiates when given take-home doses, but it also helps to prevent the decline in treatment outcomes over time. Patients value take-home doses and treatment retention rates are lower in clinics with restrictive take-home policies.

**Typical Schedule:** In general, patients are eligible for their first take-home dose of buprenorphine if they meet specific criteria for clinical stability, have had at least two months of daily witnessed dosing and have demonstrated two months without substance use, as determined by history and urine drug screening. There should be a gradual increase in the number of weekly take-home doses (starting with just weekends and holidays) up to a suggested maximum of one to two weeks of consecutive take-home doses dispensed between observed doses.

**Accelerated Schedule:** While the Centre for Addictions and Mental Health (CAMH) guidelines do allow for the physician to prescribe take-home doses earlier than two months after treatment is initiated, they also advise that this would be considered “off-label” prescribing and the patient must be made aware of this as well as of the additional risks of starting take home dosing earlier than normal.

Again, this situation should be the exception and evaluated on a case by case basis. If pharmacists see take-home doses being prescribed outside of these criteria, they should consult with the prescribing physician and document the rationale for the deviation in the patient record.

### **Exceptional Circumstances**

There may occasionally be circumstances where the physician allows for exceptional take-home doses to be given in the case of travel for work, vacation or family crisis. The previous take-home dose schedule should be resumed after the period of exceptional take-home dose is completed.

If pharmacists see take-home doses being prescribed outside of these criteria, they should consult with the prescribing physician and document the rationale for the deviation in the patient record.

### **Suspending Take-Home Doses**

In certain circumstances, it may be advisable for the physician to suspend the patient's take-home doses. This generally occurs in response to the patient having a relapse to substance use, or in the following situations:

- i) There is reasonably strong evidence that the patient has diverted their dose, or has tampered with their Urine Drug Screen (UDS).
- ii) The patient has missed three or more doses (except in unavoidable circumstances such as hospitalization).
- iii) The patient has become homeless or has unstable housing, and can no longer safely store their medication.
- iv) The patient is actively suicidal, cognitively impaired, psychotic, or is otherwise at high risk for misuse of their medication.
- v) The patient has recently been released from jail when incarcerated for prolonged periods of greater than three months. In such situations, take-home doses should not be reinstated until stability can be re-established objectively via weekly UDS and other measures of clinical stability. This may take one month in patients whose drug use was sporadic and brief, and whose clinical stability is not significantly compromised, or up to two months or more in patients who have had a longer relapse with loss of clinical stability.

## Dispensing the Prescription

### Formulations

Buprenorphine-naloxone is available as a sublingual tablet with either 2 mg of buprenorphine and 0.5 mg of naloxone or 8 mg of buprenorphine and 2 mg of naloxone.

### Preparing Witnessed Doses

Buprenorphine-naloxone should be dispensed in a light-resistant vial labelled with:

- i) Patient's first and last name;
- ii) Prescriber's full name or first initial and last name;
- iii) Drug name (i.e. buprenorphine-naloxone or brand);
- iv) Amount of drug (in mg) contained in the vial to be consumed in a single dose;
- v) Local prescription number and DIS prescription number (if applicable);
- vi) Date of dispense;
- vii) Quantity of medication (part-fills) remaining (if applicable); and
- viii) Dispensing pharmacist's initials.

### Preparing Take-Home Doses

Take-home doses of buprenorphine-naloxone should be dispensed in the original foil packaging (if applicable) in a light-resistant vial with a child-resistant cap and labelled with:

- i) Pharmacy name, phone number and street address (if available, or, if not, a way of uniquely identifying the pharmacy location);
- ii) Patient's first and last name;
- iii) Prescriber's full name or first initial and last name;
- iv) Drug name (i.e. buprenorphine-naloxone or brand) and strength
- v) Total number of tablets in the vial;
- vi) Specific directions for use (such as "Take X tablets on (insert date or days of week);
- vii) Local prescription number;
- viii) Date of dispense;
- ix) Quantity of medication (part-fills) remaining (if applicable);
- x) Dispensing pharmacist's initials; and
- xi) Cautionary labels:
  - Keep out of reach of children
  - Special cautionary label such as: *"May be toxic or lethal if ingested by a child or adult other than the intended patient. Accidental ingestion is considered a medical emergency and requires immediate medical attention."*

## Releasing the Prescription

### Providing Witnessed Doses

The pharmacist is required to witness the ingestion of the dose. This function may not be delegated to a pharmacy technician or any other member of the pharmacy team. Prior to releasing the witnessed dose to the patient, the pharmacist must:

- i) Positively identify the patient. If uncertain as to the patient's identity, photo identification should be requested.
- ii) Assess the patient for signs of intoxication or sedation. If it is determined that the patient is intoxicated or sedated, it may be advisable to withhold the dose. If such determination is made, the physician must be notified immediately (see sample [Prescriber Notification Form in Appendix G](#)).
- iii) Review the patient's profile and Administration Log for notes, missed doses, documentation of returned vials (if applicable), or any other applicable information.
- iv) Counsel the patient appropriately (for complete patient counselling information, see the product monographs).

Once it has been determined to be appropriate to release the witnessed dose, the pharmacist must:

- i) Prepare the buprenorphine-naloxone dose by unwrapping each tablet, taking care to avoid skin contact, and placing them in a disposable single-use cup.
- ii) Directly observe the patient ingesting the dose. The patient should be instructed to place the contents of the cup under the tongue and stay within the sight of the pharmacist observing the dose since it can take 1-10 minutes for buprenorphine/naloxone tablets to dissolve completely;
- iii) Request that the patient to open their mouth and lift up their tongue to ensure the entire dose has dissolved; and
- iv) Appropriately document the dose on the Administration Log.

### Providing Take-Home Doses

When providing take-home doses to the patient, the pharmacist must:

- i) Positively identify the patient. If uncertain as to the patient's identity, photo identification should be requested.



- ii) Review the patient's profile and Administration Log for notes, missed doses, documentation of returned vials (if applicable), or any other applicable information.
- iii) Counsel the patient appropriately (for complete patient counselling information, see the product monographs).
- iv) Appropriately document the provision of the take-home doses on the Administration Log.

### **Monitoring Compliance with Take-Home Doses**

There are several ways that pharmacists can monitor a patient's compliance with take home doses which include:

Take-Home Dose Audit: Patients shall be advised that they may be asked at any time to return to the pharmacy with the remainder of their take-home doses and empty vials. This procedure, known as a "take-home dose audit", may be used to deter patients from diverting their take-home doses. This audit may be initiated by either the physician or the pharmacist.

If there are issues of concern with the patient's compliance with their take-home doses or evidence of diversion, the pharmacist should notify the physician immediately.

### **Responding to Special Circumstances**

#### **Intoxication**

Prior to dispensing buprenorphine, pharmacists must assess all patients for signs of intoxication methadone including but not limited to:

- slurred speech
- incoordination
- smelling of alcohol
- unusual behavior
- ataxia

To assess a patient for intoxication or sedation, consider their general demeanor and behavior in comparison to what you know as their usual behavior. If necessary:

- Ask the patient to remove sunglasses and observe their eyes for pin-point pupils, alertness or sedation.

- Talk to the patient, asking questions to determine if they are slurring or incoherent.
- Ask the patient to walk to the counter and observe their gait.

If there is evidence of intoxication or sedation, the pharmacist should withhold the dose from the patient to prevent a possible overdose. The physician must be notified within 24 hours that the dose has been withheld.

### Missed Doses

Missed doses may indicate a variety of problems, including relapse to alcohol or other drug use. Due to buprenorphine’s partial mu agonist properties and lower risk of overdose, re-titrating and adjusting patients’ doses likely does not require the same degree of vigilance as with the full mu agonist methadone.

Pharmacists **MUST** report **ANY** missed doses to the physician within 24 hours so that the physician can reassess the patient’s clinical stability. If a patient has missed five days or less of buprenorphine-naloxone, they may resume their previous dose. If the patient misses more than five days, the physician may adjust the dose according to the recommendations in Table 9 Missed doses with buprenorphine.

**Table 9. Missed Doses with Buprenorphine**

Buprenorphine Dose	Number of Consecutive Days Missed	New Starting Dose
> 8 mg	> 7 days	4 mg
> 8 mg	6-7 days	8 mg
6-8 mg	6 or more days	4 mg
2-4 mg	6 or more days	2-4 mg

Centres for Addiction and Mental Health, Buprenorphine/Naloxone for Opioid Dependence-Clinical Practice Guidelines. 2012

### Administration Errors

In the event of a confirmed or suspected medication dosing error, the pharmacist must take appropriate and necessary action to minimize harm to the patient, ensuring transparency throughout the entire process. This includes prompt consultation with the patient’s other health care provider(s) for determination of appropriate action.

In addition to the following standards specific to methadone, it is expected that pharmacists will manage the error in accordance with the NAPRA Model Standards of Practice for Canadian Pharmacists and the individual pharmacy’s medication error management policy.

### **Buprenorphine Overdose**

- Tell the patient. If the patient has left the pharmacy, contact him or her by telephone. If the patient has no phone, you may need to contact the patient's prescriber or clinic to obtain a contact number or send police to the home.
- Advise the patient to seek medical attention immediately. If the patient refuses medical attention, document the time and details. Ask the patient to remain in the care of a friend or relative for the day;
- Advise the patient of the symptoms of overdose; including the possibility of euphoria and respiratory. Make follow-up contact with the patient throughout the day;
- Advise the patient's prescriber or clinic;
- Reassess the patient's health condition before administering the next daily dose.

### **Buprenorphine Under dose**

- Advise the patient's prescriber or clinic and the patient as you would with an overdose.
- Should the patient refuse to return for the dose, advise them of the possibility of withdrawal and the symptoms related to opioid withdrawal.
- If the patient cannot be reached during business hours, advise them of the error at their next administration. (AADAC, 2007)

## Appendix A- Comparison of Methadone and Buprenorphine

Methadone	Buprenorphine
<p><u>General</u></p> <ul style="list-style-type: none"> <li>• A full opioid agonist with actions at the <math>\mu</math> (<math>\mu</math>) opioid receptor</li> <li>• No ceiling effect</li> </ul> <p><u>Pharmacology</u></p> <ul style="list-style-type: none"> <li>• Dose continues to accumulate over many days</li> <li>• Onset of action: within 30 mins</li> <li>• Peak effects: 2 - 4 hours</li> <li>• Elimination half-life: 22-28 hours</li> <li>• Steady state: 5-7 days</li> </ul> <p><u>Administration &amp; Availability</u></p> <ul style="list-style-type: none"> <li>• Available as a 10 mg/ml oral concentrate in a red, cherry-flavored hypertonic syrup and as a dye-free, sugar-free, unflavored clear concentrate.</li> <li>• Formulations allow for patient preferences in taste, and can accommodate for those with dye allergies</li> <li>• Titration to desired response is possible over a wide range of doses</li> </ul> <p><u>Advantages</u></p> <ul style="list-style-type: none"> <li>• No ceiling effects can mean better efficacy profile in those addicted to higher doses of opioid</li> <li>• Flexible dosing</li> <li>• Long history of use and clinical experience</li> <li>• Many resources for guidance on proper use</li> <li>• Considered a safer option to buprenorphine-naloxone in pregnancy</li> </ul> <p><u>Disadvantages</u></p> <ul style="list-style-type: none"> <li>• Titration to response may take longer than buprenorphine</li> <li>• Poses a greater danger of toxicity during the initiation phase</li> </ul>	<p><u>General</u></p> <ul style="list-style-type: none"> <li>• A partial opioid agonist at the <math>\mu</math> (<math>\mu</math>) receptor</li> <li>• Ceiling effect; effectiveness plateaus once serum level is reached</li> <li>• Product for opioid dependence include naloxone which has no pharmacologic purpose but is included to deter against diversion and injection abuse</li> </ul> <p><u>Pharmacology</u></p> <ul style="list-style-type: none"> <li>• Longer half-life than methadone so may be dosed every other day once stabilized</li> <li>• Onset of action: 30 - 60 minutes</li> <li>• Peak effects: 1 - 4 hours</li> <li>• Elimination half-life: 37 hours (20 - 72 hours)</li> <li>• Steady state: 7 - 10 days</li> </ul> <p><u>Administration &amp; Availability</u></p> <ul style="list-style-type: none"> <li>• Available in 2mg and 8mg unscored sublingual tablets</li> <li>• Dose range less flexible, ranging from 2 - 24 mg daily</li> <li>• Witnessed dosing can be prolonged as it can take from 2 - 10 minutes for sublingual tablet to dissolve</li> </ul> <p><u>Advantages</u></p> <ul style="list-style-type: none"> <li>• Partial agonist, therefore lower abuse potential</li> <li>• Ceiling effects on respiratory depression means better safety profile</li> <li>• Can be easier to prescribe; dosing is simple; rapid escalation to the maximal dose</li> <li>• Enhanced convenience; may allow for an increased number of carry doses due to reduced risk</li> <li>• Longer half-life means possibly more moderate withdrawal symptoms when weaning someone completely off treatment.</li> </ul>

<ul style="list-style-type: none"> <li>• Level of respiratory depression or sedation does not have ceiling effect and therefore may be fatal in overdose</li> <li>• More clinically significant drug interactions; increased need for close monitoring and appropriate prescribing</li> <li>• Requires routine ECG and monitoring</li> <li>• Greater toxicity to children and those who are opioid naïve; carry doses pose a greater danger to the public and require close monitoring and communication for proper storage</li> <li>• Difficult to wean completely off</li> </ul>	<ul style="list-style-type: none"> <li>• Lower prevalence of drug interactions than methadone</li> <li>• Less toxic; carry doses pose less danger to the public</li> </ul> <p><u>Disadvantages</u></p> <ul style="list-style-type: none"> <li>• Efficacy is limited by its ceiling effect; may be inadequate to control withdrawal symptoms in those dependent on higher doses of opioids</li> <li>• Generally more expensive than methadone</li> <li>• Newer drug for addiction; limited experience with use and/or long term safety</li> <li>• Not recommended in pregnancy due to the naloxone component</li> <li>• Not recommended for use while breastfeeding</li> </ul>
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## Appendix B- Methadone Treatment of Opioid Dependence: Cautions

### Adverse Effects

Methadone is generally well tolerated. Table 1 lists common adverse effects.

**Table 1: Common Adverse Effects**

Adverse Effects	Comments
Sedation <ul style="list-style-type: none"> <li>May occur at the start of treatment and when doses are increased</li> </ul>	<ul style="list-style-type: none"> <li>Patients generally become tolerant to this effect</li> <li>Caution should be exercised when performing activities that require alertness</li> <li>Avoid other substances that may contribute to sedation</li> </ul>
Sweating <ul style="list-style-type: none"> <li>Commonly reported (up to 50% of high dose patients)</li> <li>May be related to inappropriate dose</li> </ul>	<ul style="list-style-type: none"> <li>Reassure patient that it causes no medical problems</li> <li>Balance reduction of dose to address sweating with risk of opioid use relapse</li> </ul>
Constipation <ul style="list-style-type: none"> <li>Common to all opioids</li> <li>Reported to be less with methadone</li> <li>Results from interference with bowel</li> </ul>	<ul style="list-style-type: none"> <li>Recommend regular exercise and increased fluid intake</li> <li>Occasional osmotic laxative use may be recommended</li> <li>Regular use of stimulant laxative should be discouraged</li> </ul>
Weight Gain	<ul style="list-style-type: none"> <li>May be due to decrease drug use and improved nutrition as a result of methadone treatment</li> </ul>
Sexual Problems (libido)	<ul style="list-style-type: none"> <li>May increase or decrease</li> </ul>
Psychoactive Effects <ul style="list-style-type: none"> <li>Mild euphoria can occur in those given a dose slightly higher than their tolerance</li> </ul>	<ul style="list-style-type: none"> <li>Patient may complain of withdrawal when effect wears off</li> </ul>
Insomnia	<ul style="list-style-type: none"> <li>Tends to improve as patients are stabilized</li> <li>Educate patient with regard to good sleep hygiene techniques</li> </ul>

Less common adverse effects include muscle and bone aches, peripheral edema, change in menstruation, and flushing and itching.

(Isaac, 2004)

## QT Interval Prolongation

Administration of methadone is associated with QTc interval prolongation and torsades de pointes. The rate of this occurrence is not clear and while it seems to be dose-dependent, it is important to note that sudden cardiac death associated with methadone has been seen at dosages as low as 29 mg/day. This means that arrhythmia can occur in dosages commonly used in both analgesia and addiction treatment, and that dosage is just one consideration with regard to limiting arrhythmia risk. (Stringer, 2009) (Pearson 2005)

More information about QT prolongation including drugs known to cause QT prolongation can be found at [www.azcert.org](http://www.azcert.org)

*See Risk Factors for QTc Prolongation in Patients on Methadone, Appendix G*

## Methadone Intoxication and Overdose

Assessing a patient's clinical signs, and considering the feedback a patient provides on their symptoms, are important indicators in assessing the adequacy of their dose and the safety of continuing with their current methadone dosing schedule.

Overdose may occur as a result of:

- Too high a dose being prescribed
- Increasing the dose too quickly
- Drug interactions (especially alcohol, benzodiazepines and other opioids)
- Impaired metabolism due to hepatic/renal insufficiency
- Misuse of prescribed methadone therapy i.e. patients not taking carry doses as intended
- Accidental ingestion in a non-tolerant person\*
- Intentional ingestion in a non-tolerant person\*

**(\*Note: non-tolerant person includes a patient who has missed 3 or more doses of their daily methadone)**

Other risk factors include age (children are more susceptible to overdose), cardio-respiratory illness, use before onset of sleep, and concurrent use of sedative drugs. (CPSO, 2005)

Symptoms of methadone intoxication and overdose include but may not be limited to euphoria, sedation, dysphoria, motor retardation, pinpoint pupils, slowed speech, respiratory depression, circulatory collapse, bradycardia, cardiac arrest, death.

### Withdrawal and Methadone Underdose

With abrupt discontinuation of methadone, signs and symptoms of withdrawal are not usually observed until 36 to 48 hours after the last dose. They appear gradually and peak at about 72 hours after the last methadone dose. They may continue at this peak level for about two weeks. The withdrawal syndrome then declines very gradually. Symptoms may be experienced for months. Therefore, patients who are doing well and want to discontinue methadone treatment are generally encouraged to taper slowly. The rate of taper is usually guided by the patient. (Isaac, 2004)

Alternative explanations for the withdrawal symptoms should be sought if the patient:

- gives an inconsistent history of withdrawal symptoms;
- has one isolated symptom (such as insomnia or nausea);
- advises the onset of symptoms is not related to the time of the dose; or
- has been taking a stable dose and suddenly complains of withdrawal (see below).

A dose might be considered acceptable if the patient sleeps comfortably at night and only has mild withdrawal symptoms on awakening. (CPSO, 2007)

### Drug Interactions

Pharmacodynamic interactions can occur when drugs that have similar pharmacologic profiles are combined with methadone. Examples include an increase in CNS depression and sedation when methadone is combined with alcohol and/or benzodiazepines and an increased risk of constipation and urinary retention with the use of anticholinergic medications such as dimenhydrinate.

Methadone is metabolized mainly via the CYP 450 3A4 enzyme system and as a result, may interact with medications that either induce or inhibit these enzymes. (CPSO, 2011)

The sequence of administration of the drugs is key to evaluating the significance of the interaction. When a patient is stabilized on a drug that affects liver metabolism and methadone is introduced, the interaction may not be observed unless the first drug is discontinued. It is only if a patient is stabilized on methadone and an interacting drug is initiated or discontinued that an interaction may occur.

***\* Note: The following table contains examples of drug interactions affecting/ affected by methadone. Pharmacists must refer to a current reputable drug interaction reference for a comprehensive list.***



Drugs that may decrease methadone levels	Barbiturates Carbamazepine Various antiretroviral medications Chronic alcohol use Phenytoin Primidone Rifampin Urinary acidifiers St. John's Wort
Drugs that may increase methadone levels	Ciprofloxacin Fluconazole/ketoconazole Cimetidine Various antiretroviral medications Diazepam Acute alcohol use Fluvoxamine Urinary alkalinizers
Drugs whose levels may be affected by methadone	Desipramine Zidovudine
Interactions with food	Grapefruit juice may inhibit metabolism

Medications that might precipitate withdrawal syndrome for patients on methadone must be avoided. These are mainly opioid antagonists such as Naltrexone and partial agonist such as pentazocine, butorphanol, nalbuphine.

A more detailed discussion of methadone drug interactions may be found by consulting the Centre for Addiction and Mental Health (CAMH) publication: *Methadone Maintenance-A Pharmacists Guide to Treatment Second Edition* or by visiting the Addiction Treatment Forum at <http://www.atforum.com/SiteRoot/pages/rxmethadone/rxmethadone.shtml>



## Appendix C- Pharmacokinetics and Actions of Methadone and Buprenorphine

### Methadone

Dosing of methadone must be undertaken carefully, individually titrating the optimal dose for each patient. An effective dose for one patient can be a lethal dose for another. Many factors impact an individual's optimal vs. toxic dose including the individual's opioid tolerance, physiologic and metabolic response, and concurrent drug therapy; and the drug's pharmacokinetic activity.

#### Absorption

- When given orally, methadone is effectively absorbed from the gastrointestinal tract within approximately 30 minutes.
- Oral bioavailability is approximately 90 per cent.
- Peak plasma levels occur about two to four hours after oral ingestion.
- Blood levels of methadone continue to rise for five days after starting therapy or increasing a dose. Death from accumulated toxicity may be the result of increasing a dose before the full effect of the current dose is known (i.e. a dose that is barely adequate on day one can be toxic by day three to five). (CPSO, 2011) (Kleber, 2008)
- A dose as low as 40mg can be lethal by day three in a methadone naïve adult and single doses as low as 30mg have been fatal in children. (CPSO, 2005)

#### Distribution

- Methadone is extensively bound to plasma proteins.
- Volume of distribution is 4 – 5 L/kg of body weight.
- Elimination half-life ( $t_{1/2}$ ) of methadone averages 22 to 48 hours. This long half-life permits once-daily dosing for methadone. Its analgesic effects are not as long lasting, and dosing in pain is usually every six to eight hours. The long half-life also results in it taking longer (i.e. five to seven days) for plasma levels to reach steady state than most other opioids, and therefore doses must be titrated slowly.
- There is wide variability in plasma methadone levels among people prescribed the same dose. There is no consensus regarding interpretation of blood levels in clinical practice.
- In pregnancy, methadone passes through the placenta to the fetus.
- Methadone is excreted into breast milk in small amounts.



## **Metabolism**

- Methadone is metabolized in the liver through demethylation and glucuronidation.
- It is predominantly metabolized through the cytochrome P450 system, mainly by CYP 3A4.
- Active metabolites are produced in small amounts. The primary metabolite has no significant pharmacological activity.
- Metabolism by CYP3A4 is subject to induction and inhibition effects by many other drugs.

## **Excretion**

- Methadone is excreted in the urine and feces, both as unchanged methadone and as metabolites.
- Urinary excretion of methadone and metabolites is dose dependent. It becomes the major route of excretion when doses exceed 55 mg/day.
- Renal absorption of the parent compound increases as urine pH increases.

## **Physiological Effect**

- As a synthetic opioid agonist, methadone affects similar physiological functions as morphine and other opioids, although to varying degrees.
- Patients develop a tolerance for some of the physiological effects of methadone once stabilized on a dose, at which time cognitive skills and attention are not impaired.
- Physiological tolerance to methadone is lost very quickly. A patient who has missed 3 days of methadone doses may no longer be able to safely tolerate the dose to which they had been titrated, and therefore will not be given their current maintenance dose. (CPSO 2011)



**Table 2. Physiologic Effects of Opioids**

<p><b>Primary Actions</b></p> <ul style="list-style-type: none"><li>• Analgesia</li><li>• Sedation</li><li>• Respiratory depression</li><li>• Euphoria (oral methadone causes less euphoria than intravenous heroin)</li></ul> <p><b>Other Actions</b></p> <ul style="list-style-type: none"><li>• Decreased blood pressure</li><li>• Constriction of the pupils</li></ul> <p><u>Gastrointestinal tract actions</u></p> <ul style="list-style-type: none"><li>• Reduced gastric emptying</li><li>• Reduced motility</li><li>• Elevated pyloric sphincter tone</li><li>• Elevated tone of Sphincter of Oddi can result in biliary spasms</li></ul> <p><u>Skin actions</u></p> <ul style="list-style-type: none"><li>• Histamine release</li><li>• Endocrine actions including</li><li>• Reduced Follicle Stimulating</li></ul> <p><u>Hormone</u></p> <ul style="list-style-type: none"><li>• Reduced Luteinizing Hormone</li><li>• Elevated Prolactin</li><li>• Reduced adrenocorticotropic</li><li>• Reduced testosterone</li><li>• (Endocrine function may return to normal after 2-10 months on methadone)</li><li>• Elevated Anti Diuretic Hormone</li><li>• Antitussive</li></ul>	<p><b>Side Effects</b></p> <ul style="list-style-type: none"><li>• Sleep disturbances</li><li>• Nausea and vomiting</li><li>• Constipation</li><li>• Dry mouth</li><li>• Increased sweating</li><li>• Vasodilation and itching</li></ul>
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## **Buprenorphine**

### **Absorption**

- Buprenorphine has a low bioavailability when swallowed given its high rate of first-pass metabolism.
- Bioavailability when administered sublingually is 28-51%.
- Onset of action is 30-60 mins.
- Peak action occurs within 1 to 4 hours.
- Duration of action is dose dependent ranging from 4-12 hours for low doses, 24 hours for moderate doses (4-8 mg) and 2-3 days for higher doses (>8 mg).

### **Distribution**

- 96% of buprenorphine is bound to plasma proteins, primarily to alpha and beta globulins.
- Crosses the placenta.
- Volume of distribution is 4-5L
- Elimination half-life of buprenorphine in plasma is 48-72 hours.
- Time to steady-state is 5-10 days.

### **Metabolism**

- Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation through the CYP3A4 pathway.
- Norbuprenorphine, the major metabolite, can further undergo glucuronidation by the liver.
- Norbuprenorphine has 1/50<sup>th</sup> the analgesic potency of buprenorphine. Conjugated metabolites undergo extensive enterohepatic circulation which likely contributes to buprenorphine's long half-life..
- Caution should be used when CYP3A4 inhibitors are used with buprenorphine.



### **Excretion**

- Primarily eliminated in the feces and urine as both buprenorphine and its metabolite norbuprenorphine.

### **Physiological Effects**

- Buprenorphine is a partial mu receptor agonist with lower intrinsic activity at the receptor compared with full mu opioid receptor agonists such as methadone.
- Buprenorphine has a ceiling effect and the opioid agonist effects plateau.
- The risk of overdose is reduced compared with full opioid agonists.
- Adverse events associated with buprenorphine are similar to those experienced with other mu-agonists but may be less intense than those produced by full agonists.



## Appendix D- Methadone Prescription Fax Form

Methadone Prescription Fax Form For Patients on Methadone Maintenance Treatment						
Pharmacy Name:	Fax:					
Patient Name:	PHN:					
Rx Methadone _____ mg _____ Dose in words p.o. Once Daily (each dose to be individually bottled, labeled and mixed in juice)						
Start Date: _____ End Date: _____ Inclusive						
Total Doses: _____ Total Observed Doses: _____ Total Take-home doses (carries): _____						
Drink observed doses in the pharmacy on days circled:						
Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Special instructions:						
Hold prescription if two or more consecutive doses are missed and contact prescriber. Notify prescriber if a dose is missed or if there are any concerns about this prescription.						
_____ Physician Signature	_____ Print Name	_____ License #				
_____ Date						
Prescriber Certification This prescription represents the original of the prescription drug order. The pharmacy addressee noted above is the only intended recipient and there are no others. The original prescription has been invalidated or retained so that it cannot be re-issued. Verification: This certifies the above prescription has been transmitted only to the pharmacy indicated.						
Name of Sender: _____ Date Sent: _____						



## Appendix E- Patient Pharmacist Agreement Methadone or Buprenorphine

### Patient-Pharmacist Agreement

Name: \_\_\_\_\_ Address: \_\_\_\_\_

Tel#: \_\_\_\_\_ Postal Code: \_\_\_\_\_

Date of Birth: \_\_\_\_\_ Physician: \_\_\_\_\_

#### OUR COMMITMENT TO YOU:

*As your pharmacists, we believe in the principles of the opioid dependence treatment program, and the valuable role it can play in improving people's lives and their health. To help you succeed in the program we make the following promises:*

We will treat you professionally and respectfully at all times.

We are part of your health care team and will communicate with your physician when necessary. The kinds of issues we will discuss with your physician include:

- missing one or more doses,
- refusal to consume the full prescribed dose,
- being intoxicated or sedated when you arrive at the pharmacy,
- doses for replacement of lost, stolen or vomited doses, and
- visiting another physician and being prescribed mood-altering medications by another physician.

We will provide your dose to you exactly as your physician has prescribed it.

We are not able to give you extra doses, early doses, take-home doses unless your physician prescribes it.

We are required to watch you ingest your dose and have a conversation with you afterward, unless your physician specifically directs otherwise on your prescription. You may also be required to drink water after swallowing your dose.

We will not dispense your take-home doses to anyone other than you unless directed to do so by your physician on your prescription.





We welcome any comments or suggestions you may have in regards to our services.

*As our patient, we have a number of expectations of you, too*

### **YOUR COMMITMENT TO US:**

I will not arrive at the pharmacy before the pharmacy is open. I will arrive for my daily dose between the hours of \_\_\_\_ and \_\_\_\_ daily (preferably in the morning and should be a consistent time each day).

I will respect the pharmacy's neighborhood. I will ensure that all pharmacy packaging materials and litter are disposed of in the garbage containers provided.

I will be respectful of others, including staff, other patients, and neighbors of the pharmacy.

If I am prescribed take-home doses, I will store them safely and securely in my home.

I realize that I may be asked to present identification before receiving my first dose of methadone from the pharmacy and when receiving doses from any new pharmacist on staff.

I realize I may not be given my dose if I am under the influence of other substances.

I will not participate in any illegal activity at the clinic/office/pharmacy etc.

I will not abuse any staff person verbally or otherwise.

I realize that my doctor, pharmacist, nurse and other health professionals directly involved in my care may openly communicate with each other concerning any aspect of the opioid dependence treatment program.

I realize any drug abuse will be reported to the prescribing physician.

If I see a doctor other than the opioid dependence treatment program prescribing doctor, I will inform them that I am in the opioid dependence treatment program.

I agree to undergo supervised urine drug screening on a periodic basis, as may be required of my opioid dependence program.

I will not stock-pile my doses.

I will be observed swallowing my dose and this will be confirmed by speaking to the pharmacist after swallowing the dose and/or drinking water.



PRINCE EDWARD ISLAND  
COLLEGE OF PHARMACISTS

Member organization of National Association of Pharmacy Regulatory Authorities (NAPRA)

I will dispose of the container used to dispense my dose in the pharmacy.

I realize it is best to spread the time between doses by at least 16 hours. There will be no twice daily dosing.

I realize that all doses must be made up in Tang, unless specified otherwise by the prescriber on each prescription (methadone only)

I will ensure that all caps on all take home doses are tightly secured and that the doses will be kept in a secure place away from others, especially children.

I will confirm I have received the appropriate number of doses and sign for same.  
I may periodically be expected to present remaining carry bottles to the pharmacy.

I realize I require a valid prescription and no doses will be dispensed without one. It is my responsibility to make sure the prescription does not expire before a new prescription is presented to the pharmacy.

I realize that any doses vomited or any take home doses lost will not be replaced without a written prescription from the prescribing physician.

I realize that a missed day means a missed dose which will not be made up.  
If I am required to pay for my doses, I will pay at the time I receive the dose.

Failure to pay for my doses may result in discharge from the program.  
The pharmacist may obtain information about my medication use from other pharmacies.

I understand that failure to honor this agreement may result in my no longer being serviced at this pharmacy.

**I have read the above agreement and understand and agree with its content**

Patient Name: \_\_\_\_\_ Patient Signature: \_\_\_\_\_

Pharmacist Name: \_\_\_\_\_ Pharmacist Signature: \_\_\_\_\_

Date: \_\_\_\_\_



## Appendix F- Sample Prescriber-Pharmacist Agreement

Physician's Name and Clinic:

Address:

Phone:

Fax:

Dear Pharmacist,

My patient attends your pharmacy for Opioid Dependence Treatment with methadone. We encourage an active communication between pharmacist and physician.

I have already discussed the following safety measures, methadone dispensing practices, and clinic policies with the patient. Please feel free to contact me to discuss any of these matters or any further suggestions that your team may have for this patient's clinical care.

You may call/page me at \_\_\_\_\_ During regular office hours and \_\_\_\_\_ after hours. Please do not give this pager/phone number to the patient.

- Patients are required to drink methadone dispensed in approximately 100 mL of diluent in front of the pharmacist. You or a member of your team must witness ingestion of methadone every day for patients receiving daily prescriptions and on the day that patient's pick up their doses for patients receiving take-home doses. Ask the patient to speak after their dose to ensure that it has been swallowed or observe drinking water after ingestion of their dose.
- The pharmacy team shall inform me or another member of the clinic of any information or observed evidence of diversion of methadone.
- The pharmacist shall inform me or another member of the clinic of missed methadone doses by the patient
- If the patient misses \_\_\_\_\_ or more doses in a row, the pharmacist is to withhold the methadone dose from the patient to prevent an overdose and the prescribing physician is to be contacted. The prescribing physician must reassess the patient before methadone is restarted.
- If there is any evidence of intoxication, sedation, or impairment (slurred speech, stumbling gait, disorientation), the pharmacists must withhold the methadone dose from the patient to prevent a possible overdose. The pharmacy team must contact myself or another member of the clinic to inform them of the observation of concern. If the patient returns within eight hours of their originally scheduled witnessed ingestion, and the pharmacist is satisfied that



the patient is no longer intoxicated, sedated or impaired, the pharmacist may give the patient the withheld dose. However, the pharmacists must not release any take-home doses until reauthorized.

- If the pharmacist observes evidence of an overdose, they must advise the patient to receive urgent medical care. The pharmacist may call 911 for transport to the hospital. The pharmacist will contact myself directly to inform me of the overdose and treatment directives.
- Dispense take-home doses in childproof containers. Patients are advised to store any take-home doses in an impenetrable locked box to ensure community safety (i.e. to avoid misplacement/loss and consumption of methadone by someone other than to whom it is prescribed). The pharmacist may require that the patient present the locked box prior to issuing take-home doses.
- The start and end date recorded on the prescription are the first and the last day the patient is authorized to receive a dose for that prescription. The pharmacist must not dispense any methadone from that prescription after the end date, regardless of the fact that there may be doses remaining on that prescription.
- A patient may be authorized to receive take-home doses based on their clinical stability. Providing take-home doses to a patient before they are clinically stable puts them and the public at risk of overdose and diversion. Providing take-home doses for patients because the pharmacy is closed is a last resort when all other steps outlined in the *Treatment of Opioid Dependence-Practice Directives for Community Pharmacists* have been exhausted, and then only in accordance with the document.

Sincerely,

/Signature/

Name of physician

License number



## Appendix G-Opioid Dependence Treatment-Prescriber Fax Notification Form

**To:** \_\_\_\_\_  
Prescriber Name \_\_\_\_\_ Fax # \_\_\_\_\_

**Date:** \_\_\_\_\_

**RE:** \_\_\_\_\_  
Patient Name \_\_\_\_\_ PEI Health Card \_\_\_\_\_

**From:** \_\_\_\_\_  
Pharmacy Name \_\_\_\_\_ Pharmacist Name \_\_\_\_\_

\_\_\_\_\_ Phone # \_\_\_\_\_ Fax # \_\_\_\_\_

### Type of Incident

- The patient missed his/her dose on (date): \_\_\_\_\_
- The patient vomited his/her dose on (date): \_\_\_\_\_
- The patient reported a lost or stolen take-home dose on (date): \_\_\_\_\_
- The patient was refused his/her dose on (date): \_\_\_\_\_ due to the fact that he/she presented at the pharmacy in an intoxicated or sedated state.

### Additional Detail:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

### Follow-up Plan:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_



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### Appendix H-Patient Daily Methadone/Buprenorphine Witnessed Ingestion and Carry Log

Patient: \_\_\_\_\_

Physician: \_\_\_\_\_

Date	Rx#	Dose (mg consumed)	# of carry bottles/tablet given	# of take-home doses/tablets returned	Patient signature	Pharmacist signature

**This log must be maintained by the pharmacy as part of the patient file for 10 years**

If the patient does not arrive for their witnessed ingestion or carry doses, if the patient vomits their dose, refuses their dose or consumes a portion of their dose it must be noted on this log.



## Appendix I: Risk Factors for QTc Interval Prolongation

### Risk Factors for QTc Prolongation in Patients on Methadone

#### Risk Factors for QTc Prolongation in Patients on Methadone

Adapted from: Methadone – associated QTc prolongation: A case report and review of the literature. (Abramson DW, Quinn DK, Stern TA. Prim Care Companion J Clin Psychiatric 2008; 10(6): 470-476

Risk Factor	Example
Older Age Structural heart disease	Non-Opioid treatments Myocardial infarction, congestive heart failure, valvular disease, cardiomyopathy
HIV	HIV antivirals
Low Potassium Levels	On drugs that lower potassium (e.g. diuretics)
Low Prothrombin	
On medications that inhibit Cytochrome p450 3A4*	HIV antivirals e.g. Indinavir
	Antifungals e.g., Fluconazole, ketoconazole
	Calcium channel blockers e.g., Diltiazem, verapamil
	Antimicrobials e.g., Norfloxacin, ciprofloxacin
	Antidepressants e.g., SSRIs
	Contraceptives e.g., Mifepristone
	Food e.g. Grapefruit juice
Alcohol Use	
Cocaine Use	
Family or past history of long QT syndrome	History of syncope or sudden cardiac death in the family
On medications that prolong QTc*	Cardiac medications e.g., amiodarone, sotalol
	Antipsychotics e.g., quetiapine, aripiprazole, chlorpromazine, haloperidol, pimozide, thioridazine
	Antibiotics e.g., clarithromycin, erythromycin

\*NOTE: The drugs listed in this table are examples of drug interactions affecting / affected by methadone. Pharmacists must refer to a current reputable drug interaction reference for a comprehensive list. More information about QT prolongation including drugs known to cause QT prolongation can be found at [www.axcert.org](http://www.axcert.org)



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