COMMERCIALLY AVAILABLE METHADONE FOR OPIOID AGONIST THERAPY (OAT): PHARMACIST INFORMATION

August 2022 (Updated: April 13, 2023)

Table of Contents

EXECUTIVE SUMMARY

Important Changes to Methadone Formulations Used as Opioid Agonist Therapy (OAT):

As of September 1, 2022, three commercially available methadone 10 mg/mL oral concentrates were added as listed benefits on the Formulary of the Saskatchewan (SK) Drug Plan and Extended Benefits Branch (DPEBB). These products were already listed on the Non-Insured Health Benefits (NIHB) Drug Benefit List.

After November 30, 2022, compounded methadone will not be a SK Formulary benefit of the DPEBB. Prescribers may submit additional clinical information that may be considered on a case-by-case basis for patients who experience severe allergic reactions to the commercially available products.

All people taking compounded methadone will require a new prescription to transition to a commercially available product before November 30, 2022. As per the Saskatchewan College of Pharmacy Professionals (SCPP), Level A pharmacies may continue to compound methadone, with risk mitigation precautions in place, until people taking compounded methadone are transitioned to the new products, or November 30, 2022, whichever occurs first. After November 30, 2022, all pharmacies that compound methadone for exceptional circumstances must be permitted as a Level B or C pharmacy through SCPP.

Summary of Key Points

- Two commercially available methadone 10 mg/mL concentrated formulations are available as a first choice for opioid agonist therapy (OAT) in SK:
  1) Metadol-D® (recommended option) or
  2) Methadose™ Sugar-Free
- Methadose™ Cherry-Flavoured is also on both the SK DPEBB and NIHB Drug Benefit Lists; however, it is not being recommended as a first choice at this time, due to its documented serious risk of lack of effect causing clinical destabilization.
- Only 10 mg/mL concentrates may be used for dispensing commercially available methadone as OAT.
- These commercially available methadone products are not interchangeable. There are differences between methadone brands, and also between brand formulations.
- A new prescription is required to switch from compounded to commercially available methadone.
  - The product brand and formulation must be specified on each prescription.
  - The prescribed dose is the same when converting from one methadone product to another.
- When dispensing Metadol-D® or Methadose™ Sugar-Free products, they must still be diluted to 100 mL.
  - If dispensing Methadose™ Cherry-Flavoured (not recommended as a first choice), dilution is not required but is strongly recommended.
- Pharmacies are not able to submit claims for compounding fees to the SK DPEBB for commercially available methadone.
- Follow up by clinicians together with people taking methadone is strongly recommended after the change to ensure clinical stability is maintained.
- Communication and collaboration is required to make the change safely.
  - Encourage people taking methadone to discuss any concerns they have with their prescriber and/or pharmacist as early as possible (before and after the change).

Disclaimer: This document is intended to communicate the key points associated with the change from compounded methadone to commercially available methadone products in Saskatchewan and is a supplement, not a replacement, for any regulatory standards or documents. Readers are encouraged to review the Saskatchewan College of Pharmacy Professionals Opioid Agonist Therapy Standards for additional information regarding dispensing opioid agonist therapy in Saskatchewan.

BACKGROUND AND REASONS FOR THE CHANGE

- Methadone hydrochloride is used for pain management and/or as opioid agonist therapy (OAT) for opioid use disorder (OUD).
- When used for OUD, pharmacists in SK have traditionally compounded a stock solution from methadone powder and water, which was stored in the fridge. The prescribed dose of this solution was diluted with a suitable diluent (a liquid vehicle, such as Orange Tang™).
- As of September 1, 2022, three commercially available methadone 10 mg/mL oral concentrates were added as listed benefits on the SK DPEBB Formulary. These oral concentrates were also already on the NIHB Drug Benefit List.
- Compounded methadone will only be approved by the SK DPEBB in exceptional circumstances after November 30, 2022.

Reasons for the Change

- Commercially available products are available that:
  - are consistently prepared and standardized products resulting in enhanced safety and quality control,
  - are recommended by the Institute for Safe Medication Practices Canada (ISMP Canada),
  - do not require refrigeration (before dilution),[i,ii]
  - may be associated with less wastage (due to the 14-day beyond-use date of the compounded stock solution if not preserved),
  - have an assigned drug identification number (DIN) which enables pharmacy management systems to utilize the integrated drug interaction checkers to improve clinical decision-making and patient safety, and,
  - must be used rather than compounded solutions, per Health Canada Policy, whenever they are readily available.[iii]
- Regulatory changes to compounding standards in SK were implemented on August 31, 2022 which seek to ensure the safety of both patients and the personnel involved in compounding, as well as establish additional quality controls. After this date, numerous pharmacies (i.e., those who have not declared as being Level B or C) are no longer authorized to compound complex non-sterile compounds, such as methadone.
- By removing the safety risks associated with compounding, and simplifying the preparation process for methadone, more pharmacies in Saskatchewan may begin dispensing OAT, reducing barriers to access for people taking methadone.
- All other jurisdictions in Canada have already transitioned away from using compounded methadone and are using the commercially available products as the preferred products.
  - Aligning the availability of products across provinces and territories, allows people taking methadone to maintain consistency of the product when they move between jurisdictions.
- The reasons for the change are believed to all be important and, ultimately, to be in the best interest of people taking methadone for improving safety.

Methadone for Pain

- The information in this document does not address methadone used for the indication of pain. Clinicians who prescribe and dispense methadone must also ensure people receiving compounded methadone exclusively for pain are transitioned to the appropriate commercially available product.
- The commercially available methadone brand for pain is Metadol®.
  - Metadol® is listed on the SK DPEBB Formulary (under the EDS Program) and the NIHB Drug Benefit List (prior approval is required) as tablets, a 1 mg/mL solution, and a 10 mg/mL concentrate.

PRODUCT AVAILABILITY

Compounded Methadone

- As per Health Canada Policy, once commercially available methadone products are listed on the SK DPEBB and NIHB Drug Benefit Lists, "Compounding should only be done if there is a **therapeutic need** or **lack of product** availability…".[iii]
- After November 30, 2022, compounded methadone will not be a SK Formulary benefit of the DPEBB. It will only be approved by the SK DPEBB in exceptional circumstances.
    - Prescribers may submit additional clinical information that may be considered on a case-by-case basis for patients who experience severe allergic reactions to the commercially available products.
- Additionally, effective August 31, 2022, the SCPP requires that pharmacies must meet NAPRA Model Standards for Pharmacy Compounding.
- Methadone falls under the Level B requirements for compounding in SK (i.e., pharmacies must have a separate room that is ventilated or a containment device).
    - Methadone is considered a complex non-sterile compound because the Workplace Hazardous Materials Information System (WHMIS) classifies methadone as a highly toxic substance. Proper facilities with personal protective equipment are required to ensure the pharmacy staff is protected and the environment is not contaminated during product preparation.
- **Pharmacies that meet Level A requirements and who would only require Level B for the purposes of compounding methadone, may continue to compound methadone, with risk mitigation precautions in place, until November 30, 2022, or until all people taking methadone have been transitioned to commercially available methadone products, whichever occurs first.**
    - This "grace period", from September 1 to November 30, 2022, allows time for pharmacies to obtain a new prescription to switch people to commercial methadone, as well as to establish safe policies and procedures to prepare and dispense the commercially available methadone products.
- Communication from the SCPP Certified Compounding Inspector – Field Officer has indicated that, "*…Level A pharmacies… can continue compounding methadone solution in the interim while waiting for the formal announcement from the drug plan, however ensuring that they have additional risk mitigation strategies in place to manage potential exposure to staff. These additional measures should be documented on the master formula for methadone solution and could include strategies such as wearing an N95 mask or respirator instead of surgical mask and compounding it at a time of day when the dispensary is least busy (i.e., first thing in the morning or at the very end of the day), and ensuring the surrounding area is appropriately cleaned following compounding*" (B. Sharkey, personal communication, June 23, 2022).
- After November 30, 2022, all pharmacies that compound methadone for exceptional circumstances must be permitted as a Level B or C pharmacy through SCPP.

Commercially Available Methadone Concentrated Products

- As shown in Table 1, two brands of methadone concentrates (i.e., Metadol® and Methadose™) and three specific formulations (i.e., Metadol-**D**®, Methadose™ **Sugar-Free**, and Methadose™ **Cherry-Flavoured**) are listed benefits of the SK DPEBB for use as OAT after September 1, 2022. These are also already on the NIHB Drug Benefit list.

Table 1: Specifying the Methadone Brand and Formulation

Brand	Formulation
Metadol®	- D
Methadose™	Sugar-Free
Methadose™	Cherry-Flavoured

- In accordance with the SCPP OAT Standards, **Methadose™ Cherry-Flavoured use should be limited to patient request due to the risk of contributing to destabilization.**[iv]
- To reduce the chance of dosing errors, pharmacies are **required to dispense only the 10 mg/mL commercially available oral concentrates for OAT**.
- Pharmacies are encouraged to proactively order approximately one to three weeks of the anticipated volume of the desired brand and formulation, to ensure availability is secured from the distributor and reduce concerns associated with insufficient supply.
- It is important to recognize **there is risk of potential error when pharmacies carry different products of the same medicinal ingredient**. There is also risk to people taking methadone when they are not offered choice regarding their medication treatment.
    - Pharmacies are encouraged to actively engage with people taking methadone and their prescribers, to offer medication-related information and recommendations (see Product Selection), while also not creating barriers to access to specific brands and formulations.

Table 2: Commercially Available Methadone Concentrated Products Available on the SK DPEBB and NIHB Drug Benefit Lists

Methadone 10 mg/mL Oral Concentrates [a,b]	Benefit of SK DPEBB	Benefit of NIHB	Preferred for OAT in SK	Rationale for Recommendation [c]
Metadol-D®	Yes	Yes	Yes	Person unlikely to notice a difference from compounded methadone. May be preferred by people taking methadone.
Methadose™ Sugar-Free	Yes	Yes	May use, but caution advised	Unknown if person will notice a difference (i.e., lack of effect) compared to compounded methadone. Published reports have been specific to the Cherry-Flavoured formulation; however, some anecdotal reports (low-quality evidence) suggest lack of effect with this formulation contributing to clinical destabilization.
Metadol®	Yes	Yes	No	Indicated for pain only.
Methadose™ Cherry-Flavoured	Yes	Yes	No [d]	Documented reports of a serious risk of contributing to lack of effect and clinical destabilization. Note: it also has a different colour, taste, and viscosity.

[a] As of September 1, 2022.
[b] Other generic formulations of commercially available methadone concentrates are available on the Canadian market; however, they are not anticipated to be listed on the SK DPEBB Formulary and NIHB Drug Benefit Lists and should not be used at this time.
[c] Recommendation by medSask/Continuing Professional Development for Pharmacy Professionals (CPDPP) based primarily on observational studies and anecdotal reports of people taking methadone and clinicians experienced with these products at this time, given the lack of high-quality formal studies comparing the products. See section, Product Selection, for more information.
[d] Not recommended as a first choice. SCPP OAT Standards indicate use should be limited to prescriptions written on the specific request of a person taking methadone.[iv] Ensuring informed consent is documented is advised.

PRODUCT SELECTION

Considerations to support the decision regarding which product to select should include factors such as relative effect, safety, formulation properties, convenience, cost, as well as patient perceptions and preferences.
Please see Table 3 for an overview of the product characteristics, particularly those which compare the formulation properties and differences which people may notice.

Relative effect and safety:

- **The commercially available methadone products for OAT are not interchangeable in Saskatchewan.**
- In 2020, Health Canada released a risk communication, which identified a potential risk of lack of effect (i.e., causing the person to experience opioid withdrawal symptoms) and clinical destabilization when switching between different methadone products.[v] Reasons for this difference in effect are unclear. Health Canada did not indicate a specific brand or formulation of concern.
- The Methadose™ Cherry-Flavoured brand and formulation has been described in the literature as causing lack of effect and clinical destabilization (e.g., people taking methadone becoming "dope sick" or experiencing "withdrawals"), which can be a serious safety concern. (See Exploring the Reports of Clinical Destabilization for more information.) For this reason, SCPP OAT Standards indicate use should be limited to patient request.[iv]
- It is unknown whether the lack of effect associated with the Methadose™ Cherry-Flavoured formulation is similar with the Sugar-Free formulation.
    - The literature does not report on the Sugar-Free formulation and no randomized controlled trials or head-to-head analyses have been performed to compare the formulations.[vi] Anecdotal reports suggest some people taking the Methadose™ Sugar-Free formulation have experienced lack of effect and clinical destabilization.
- Comparatively, in a Commentary written by clinicians in BC, it was reported that, "Fortunately, offering Metadol-D® as an alternative to Methadose™ appears to be greatly beneficial." [vii]
- It may also be safer if clinicians preferentially recommend, prescribe, and dispense a single methadone product, to further reduce the chance of confusion and error in the prescribing and dispensing processes.

Formulation Properties:

- Metadol-D® and Methadose™ Sugar-Free are most similar to compounded methadone in their taste and appearance.
- Methadose™ Cherry-Flavoured has a distinct taste, color, and thickness, which may decrease palatability.
- Metadol-D® contains dextrose while Methadose™ Sugar-Free does not.
    - Communication with the manufacturer indicates that Metadol-D® contains dextrose in a concentration of 125 mg/mL (Paladin Labs, personal communication, July 6, 2022). This concentration is low enough that it is unlikely to have clinical significance for people, such as those with diabetes or fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) intolerance. E.g., a Metadol-D® 100 mg PO daily dose = 10 mL = 1.25 g of dextrose = 4.25 calories.

Convenience:

- All products should initially be prescribed at the same dose and interval as the person previously received.
- If particular products do not last for twenty-four hours (e.g., "wear off" early), as has been described in the literature with the Methadose™ Cherry-Flavoured formulation, this may lead to clinical destabilization. Destabilization can result in the need for the person to make more frequent healthcare visits, lose authorization for take-home doses, and/or require split dosing at the pharmacy.
- Additionally, if a single product is used preferentially in SK, this will support people taking the product who might require "guest dosing" from a different pharmacy due to unexpected circumstances (e.g., travelling for a funeral, family emergency, rapidly changing living situations).

Cost:

- At the time of initial product listing (September 1, 2022), there were no cost differences between the Metadol-D® and Methadose™ products. Subsequent listing prices may be modified by the manufacturers. Pharmacy professionals should consult current listing prices in circumstances when the cost becomes

significant for people taking methadone (e.g., those not receiving provincial or federal drug plan benefits and without third party insurance).

Perspectives and Preferences of People Taking Methadone Alongside Clinical Experience:

- Patient perspectives and experiences, particularly for structurally vulnerable individuals, are at times under-represented in the medical literature.
- Clinicians should be aware that the Methadose™ brand as a whole has been associated with negative experiences and public perception.
    - Board members from an advocacy group comprised of people with lived experience in British Columbia (e.g., the British Columbia Association for People on Opioid Maintenance) have advised to, "Avoid Methadose. Choose Metadol-D." (L. Shaver, personal communication, June 21, 2022 and G. Mullins, personal communication, July 7, 2022).
    - A podcast by people with lived experience has supported the use of Metadol-D®, reporting that it, "… seems to work better" (than the Methadose™ Cherry-Flavoured) and, "…doesn't have a dose-holding problem." [viii,ix]
    - Regarding the reports of Methadose™ Cherry-Flavoured wearing off early, people have been quoted as describing it as, "It doesn't haven legs!".[ix]
    - Also anecdotally, some have suggested that the lack of documented reports in Canada outside of BC may be related to having fewer organized activist groups to speak to these issues.
- An electronic mailing list, META:PHI, composed of clinicians involved in addiction medicine, has provided a forum for some comments regarding experiences with the methadone products.
    - Some clinicians in Canada have described having patients experience withdrawal, particularly after switching to a Methadose™ product (reported with both the Cherry-Flavoured and the Sugar-Free formulations), often alongside a preference for Metadol-D®.
- Patients may prefer Metadol-D® because it has been reported more favourably by some people taking methadone and clinicians in other parts of the country, in terms of relative effect and safety, and because it has a comparable appearance and taste to the compounded methadone.

medSask/CPDPP Recommendations Based on these Considerations

- Providers should collaborate with people taking methadone to discuss options for transitioning to a commercially available methadone product. Engaging people in their own health care decision-making can improve the outcomes associated with change.
- There are unfortunately no high-quality studies to direct the treatment choice at this time. In the absence of robust clinical trials to draw from, lower quality observational trials and anecdotal information provide the only information on which to base decision-making at this time. Lived experience is an important consideration.
- **Metadol-D® may be preferred by people taking methadone and clinicians and is recommended by medSask/CPDPP as a first choice.**
    - There are potentially serious safety concerns associated with Methadose™ related to lack of effect which have been anecdotally reported by some people taking methadone and clinicians in Canada. Given this risk, even though not yet clearly established in the scientific literature, alongside reports that Metadol-D® has been preferred by people and clinicians with experience, it may be prudent to use this product preferentially until further evidence becomes available.
    - Another benefit of Metadol-D® is that people are unlikely to notice a difference in the taste and appearance, as compared to compounded methadone.
    - From a logistical perspective, recommending this as a single methadone product may also improve safety, by simplifying processes in the steps relating to prescribing and dispensing, as well as supporting people taking methadone who may require "guest dosing".
- **Methadose™ Cherry-Flavoured is not recommended as a first choice in SK** when changing from compounded methadone. However, it may be appropriate to continue this product if a person has already been stabilized on it elsewhere and wishes to continue taking it. Use should be limited to prescriptions written on the specific request of a person taking methadone, after ensuring informed consent is provided and documented.[iv]

Table 3: Characteristics of the Commercially Available Methadone 10 mg/mL Oral Concentrates for OAT on the SK DPEBB and NIHB Drug Benefit Lists

Brand Name and Formulation		Metadol-D®	Methadose™ Sugar-Free	Methadose™ Cherry-Flavoured [a]
DIN		02244290	02394618	02394596
Concentration (All are oral concentrates)		10 mg/mL [b]	10 mg/mL	10 mg/mL
Package Size(s) Available		100 mL and 1000 mL	1000 mL	1000 mL
Properties	**Flavour**	Unflavoured	Unflavoured	Cherry-Flavoured
	Sweetener	Dextrose (125 mg/mL) [c]	None	Sucrose (400 mg/mL)
	Dye	Colourless	Colourless	Red (FD&C Red No. 40, D&C Red No. 33)
	Viscosity	No viscosity enhancers added	No viscosity enhancers added	Viscous/thickened (hypertonic, poloxamer 407 added)
Dilution – to decrease ability to inject the liquid as well as to mask the bitter taste of the methadone		Dilute to 100 mL with suitable diluent.	Dilute to 100 mL with suitable diluent.	Dilution is not required for deterring injection, however diluting to 100 mL is recommended.[d]
Suitable Diluents		The same diluents used for compounded methadone solution (typically coloured, flavoured crystalline drink mix) may be used with these products. Examples: Orange Tang™, Grape Kool-Aid™, Grape/Lemonade/Tangerine-Grapefruit Crystal Light™. Diluting with plain water is not acceptable, as per the SCPP OAT Standards.[iv]		
Stability in Diluents		May be stored refrigerated in suitable diluent for up to 14 days.[iv]	The period of acceptable sterility for oral consumption under refrigeration is unknown. No information is provided in the product monograph (Professional judgement required).	
Differences people may notice - compared to compounded solution *Assuming the same diluent is used.		People are not expected to notice a difference in taste or appearance. People taking methadone have reported this product to be most similar to the compounded methadone product.[viii,ix]	People are not expected to notice a difference in taste or appearance. May be a lack of effect associated with clinical destabilization, based on anecdotal reports. Low-quality evidence, not well established.	The colour, flavour and viscosity will be different. Documented reports of the dose wearing off after 14-16 hours rather than 24 hours. See *Exploring the Reports of Clinical Destabilization* for more information.
Interchangeability		**These products are not interchangeable.** If a lack of clinical effect occurs with one brand and formulation, this may resolve with a change to a different brand and/or formulation; however, a new prescription will be required.		

[a] **Methadose™ Cherry-Flavoured is not recommended as a first choice for the switch from compounded methadone in SK.**

[b] Metadol-D® is also available as a 1 mg/mL solution; however, **only the 10 mg/mL concentrate is approved for use as OAT in SK.**[iv] Maintaining a consistent single concentration decreases the potential for dosing errors.

[c] This dextrose concentration is low enough that it is unlikely to have clinical significance for people, such as those with diabetes or fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) intolerance (e.g., a Metadol-D® 100 mg dose provides 1.25 g of dextrose).

[d] Dilute to retain consistent final volume among products and to reduce viscosity and "stickiness" (and therefore, potentially reduce adhesion to the vessel). The final diluted product will likely still be more viscous than the compounded and other available formulations of methadone. The dispensing cup should be rinsed and liquid consumed to ensure the full dose is given.

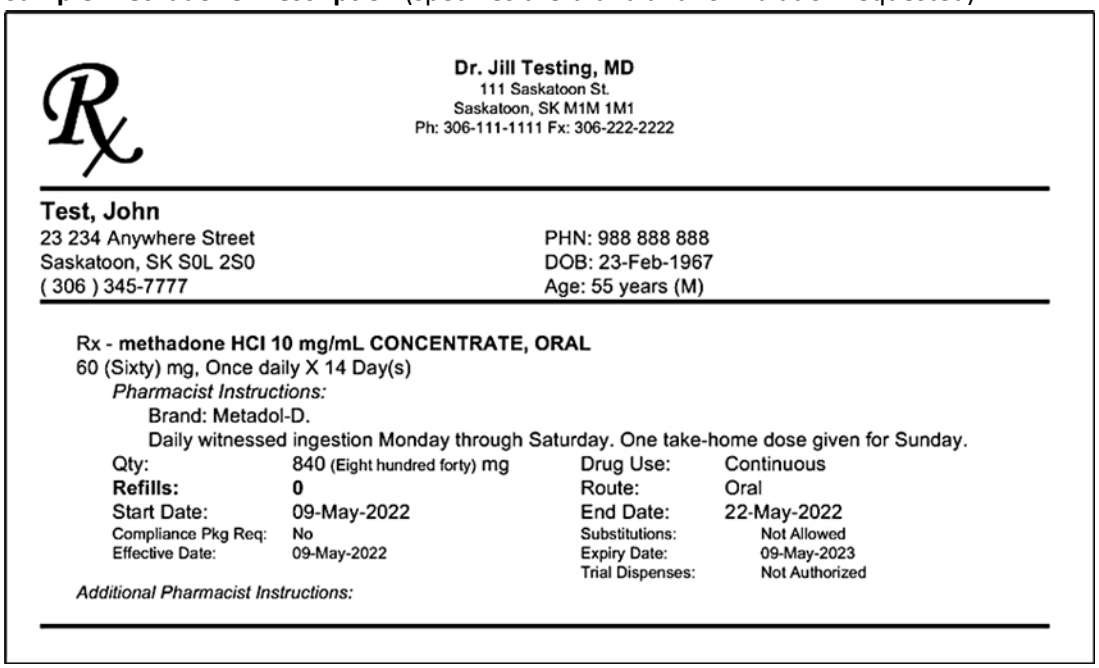
PRESCRIBING INFORMATION

- When converting from one methadone product to another, **continue the same dose** (e.g., 60 mg of compounded methadone = 60 mg of the commercial methadone concentrate).
- Prescriptions must be written in milligrams (mg).
- Since commercially available methadone products are not interchangeable, **the product selected must be prescribed by brand and formulation**.
    - E.g., If selecting Metadol-D®, ensure the prescription includes the "-D" (plain Metadol® is for pain only).
    - E.g., If selecting Methadose™, ensure the prescription specifies the Sugar-Free formulation (Methadose™ Cherry-Flavoured is not recommended as a first choice).
- Under the Section 56 Exemption, pharmacists are not authorized to prescribe for the change of prescription. A verbal order may only be accepted after every effort has been made to obtain a written or e-prescription.
- Collaboration, communication, and coordination between prescribers, pharmacists, and people taking methadone will be needed to establish the best date on which to change, in order to facilitate a safe transition.
    - It is strongly recommended that prescriptions are coordinated to start the new brand and formulation on a day when the person receives a witnessed dose. This will allow for the pharmacist to discuss any concerns or questions the person has at the time of taking their first dose. It will also allow for the subsequent take-home doses (if applicable) to be prepared and dispensed as a single formulation.
    - Plan to start the new brand and formulation early in the week (e.g., Monday or Tuesday), whenever possible, to enhance access to providers for follow up or changes, if needed.
- While it is not required, changes to take-home doses may be desired following the methadone switch to facilitate enhanced contact, monitoring, and communication with a pharmacist. This may be particularly relevant for those people who have very recently entered the maintenance phase of taking methadone.
    - Pharmacists are encouraged to discuss any concerns regarding take-home doses with prescribers.
- If there is particular concern, anxiety, or distress associated with making this change, people taking methadone may benefit from proactively having a prescription for pharmacological opioid withdrawal adjuncts logged on file at the pharmacy. This may include medications such as clonidine, loperamide, and non-steroidal anti-inflammatory drugs (note: see RxFiles "*Prescription for Managing Opioid Withdrawal*" available through SHIRP).
    - If opioid withdrawal occurs a few days after the methadone switch, this provides the person taking methadone an option to help manage their symptoms until the methadone prescription can be reassessed by the prescriber (See Responding to Clinical Destabilization).
- Once stabilized, keeping the prescribed product consistent is recommended for all subsequent fills.
    - If the prescriber and person taking methadone have deemed a brand and/or formulation switch may be necessary/beneficial, the change must be clearly communicated on a new prescription.

Communication with Prescribers

- A summary of this information has been developed for distribution to physicians and nurse practitioners who prescribe OAT in the province. Additional information for prescribers may also be found here.
- Prescribers have been asked to proactively communicate with pharmacists with regard to the availability of prescribed methadone products and the desired date of the switch in advance of sending the prescription to the pharmacy.
- Please see the template at the end of this document that might be used by pharmacists wishing to communicate with prescribers regarding the change to commercially available methadone products. This template also provides the pharmacist the opportunity to make a specific recommendation for the prescription when preference has already been discussed together with the person taking methadone.

Sample Methadone Prescription (specifies the brand and formulation requested):



Dr. Jill Testing, MD
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Test, John
23 234 Anywhere Street
Saskatoon, SK S0L 2S0
(306) 345-7777

PHN: 988 888 888
DOB: 23-Feb-1967
Age: 55 years (M)

Rx - **methadone HCl 10 mg/mL CONCENTRATE, ORAL**
60 (Sixty) mg, Once daily X 14 Day(s)
Pharmacist Instructions:
Brand: Metadol-D.
Daily witnessed ingestion Monday through Saturday. One take-home dose given for Sunday.

Qty:	840 (Eight hundred forty) mg	Drug Use:	Continuous
Refills:	**0**	Route:	Oral
Start Date:	09-May-2022	End Date:	22-May-2022
Compliance Pkg Req:	No	Substitutions:	Not Allowed
Effective Date:	09-May-2022	Expiry Date:	09-May-2023
		Trial Dispenses:	Not Authorized

Additional Pharmacist Instructions:

PREPARATION AND DISPENSING

- **Be aware that the 10 mg/mL methadone concentration may be a change from what the pharmacy has been compounding.** Methadone is a high-alert medication. Medication errors causing harm related to inadvertently giving ten times the prescribed methadone dose have been known to occur as a result of changing methadone concentrations (e.g., from a 1 mg/mL to a 10 mg/mL concentration).[x]
    - Ensure processes and procedures are in place to reduce the potential for error with concentration changes.
    - For example:
        - limit pharmacy inventory to a single concentration whenever possible (pharmacies may find it helpful to compound a 10 mg/mL concentration to help reduce potential dosing errors through the transition period),
        - ensure order-entry systems reflect the concentration being used,
        - ensure processes implement independent double checks during preparation and administration of every dose, and
        - add warning labels to the methadone containers to alert staff to changes in concentration.
- **Small variations in the volume of methadone concentrates can result in significant changes in clinical effect of the dose.** Pharmacy staff must ensure accurate, dedicated, and calibrated measuring devices are consistently used, and that are confirmed to have an error rate of no greater than +/- 0.1 mL.
    - Oral syringes may not be re-used.
    - Ensure processes and procedures are in place to reduce the potential for error associated with having more than one methadone product being dispensed.
    - For example:
        - prepare different commercially available methadone products and compounded methadone at different times, separate from one another in time and/or physical location, if feasible, and
        - label measuring devices with “ONLY USE FOR METHADONE”, a poison auxiliary label, and clearly specify the brand and formulation for which it is being used.

- Undiluted commercially available methadone products may be stored at room temperature.
- **When dispensing Metadol-D® or Methadose™ Sugar-Free, products must be diluted to 100 mL.**
    - The size of the dispensing bottles and caps that have been used for dispensing compounded methadone should be maintained and kept the same through this transition.
    - Aim to keep the diluent the same when changing methadone products.
    - Methadone doses should be diluted as close to the time of dispensing as is safe and feasible to optimize stability and sterility and to reduce the potential for dispensing errors.
    - Diluted commercially available methadone doses must be refrigerated.
- Upon receipt of a prescription for a Methadose™ Cherry-Flavoured product, pharmacists are advised to ensure people taking methadone are fully informed about the serious risk of lack of effect and clinical destabilization (see Exploring the Reports of Clinical Destabilization) and that the person's informed consent is documented on their medication profile.
    - Even though it is not required in the product monograph, pharmacists are strongly encouraged to dilute this product to 100 mL to retain a consistent final volume, and to reduce the viscosity and "stickiness" (and therefore, potentially also adhesion to the dispensing vessel), which helps ensure the full dose is administered. Diluting may also assist with palatability.
- Pharmacies must ensure policies and procedures are in place which safe-guard against medication errors that may occur as a result of carrying more than one commercially available methadone brand and/or formulation (See the Summary of Tips for Preparing in the Pharmacy to Help People Safely Switch to Commercial Methadone Products (checklist)).
- **Ensure individual privacy and confidentiality is maintained** throughout all processes and procedures established to help navigate the change in methadone to different brands and formulations.
- Offer all people taking methadone with a take-home naloxone kit if they do not already have one available. Pharmacies are encouraged to register to become a Naloxone Training and Distribution Site.
- Please refer to the SCPP OAT Standards, for additional information regarding stability, using appropriate and accurate equipment for dispensing and dilution, as well as documentation requirements.[iv]

Billing and Prescription Cost

- At the time of initial product listing (September 1, 2022), there were no cost differences between the Metadol-D® and Methadose™ products. Subsequent listing prices may be modified by the manufacturers. Pharmacy professionals should consult current listing prices in circumstances when the cost becomes significant for people taking methadone (e.g., those not receiving provincial or federal drug plan benefits and without third party insurance).
- The majority of people will see no change in their prescription cost, though some may see a decrease or increase. If people experience an increase in cost, encourage them to speak with a pharmacist for assistance. Some people may benefit from reassessment of their medication costs through the Special Support Program.
- While commercially available methadone must be diluted, it is not considered a compound. Therefore, pharmacies will not be able to submit claims for compounding fees to the SK DPEBB for commercially available methadone.
- Pharmacists may continue to bill the SK DPEBB for the *Methadone Managed Care Fee* (pseudoDIN 00951326 for on-site witnessed managed care fee). Billing for NIHB does not change.
- When billing to the DPEBB and to NIHB, pharmacies should ensure the commercially available methadone **quantity submitted is in milliliters dispensed** prior to any further dilution.
    - E.g., If Metadol-D 80 mg PO daily each day is prescribed, the claim submission would indicate a quantity of 8 mL of Metadol-D 10 mg/mL oral concentrate per day.
- Please refer to the *Proprietor Agreement*, any relevant DPEBB SK Ministry of Health Bulletins, and the Guide for Pharmacy Benefits: Non-Insured Health Benefits for additional billing information.

Labelling and Transmission to the Pharmaceutical Information Program (PIP)

- Dispensed methadone products must follow the *Labelling Requirements* set out in the SCPP OAT Standards.
- When entering the medication into the pharmacy management system, the commercial product name, formulation, and concentration should be used.
- Best practice suggests that the SIG should be filled out using the same format every time, to ensure important prescription and dispensing information is clearly reflected on PIP. This may help to reduce the potential for error, particularly with prescription transfers and transitions of care.
    - The SIG field should include three main areas, including the:
        1. instructions for use: directions for the patient to consume the entire contents of the bottle, **the total milligrams of methadone to be ingested in a single dose**, and a notation that indicates the drug product has been diluted,
        2. dates for which the prescription is valid, and
        3. witness and take-home dose schedule.
- The intended ingestion date for any take-home doses should also be is clearly indicated on the prescription bottles. This may be printed electronically or neatly handwritten on the bottle. This date must be distinct from the dispensing date and any other dates on the bottle.

Sample Diluted Commercially Available Methadone Label*

Pharmacy name: ABC Pharmacy
Pharmacy address: 123 Rx St.
Pharmacy phone number: (306) 333-3333

Patient name: John Test — Prescription number: 1234567

Metadol-D 10 mg/mL (DIN 02244290)
Qty: 6 mL

Drink the ENTIRE contents of this bottle containing 60 mg of Metadol-D mixed in Tang™ to a total volume of 100 mL once daily. Prescription valid from May 9 to May 22, 2022. All days are witnessed except for one take-home dose Sundays. (Consume this bottle on May 15)

KEEP REFRIGERATED IN A LOCKED AND SAFE AREA AWAY FROM THE REACH OF CHILDREN.

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.

RETURN ALL USED/EMPTY AND UNUSED/FULL BOTTLES TO THE PHARMACY.

Date dispensed:	Expiry date of bottle:	Prescriber's name:
May 9, 2022	May 22, 2022	Dr. J. Testing

*** Note:** warning labels, beyond-use dates, and ingestion dates may be provided as auxiliary labels.

MONITORING

- Monitor people taking methadone for lack of effectiveness and safety concerns regarding their regimen following transitions between products. See the SCPP OAT Standards, the College of Physicians and Surgeons of Saskatchewan (CPSS) OAT Standards and Guidelines, and specific product monographs for monitoring parameters.[i,ii,iv,xi]
- Some people taking methadone in Canada have reported severe withdrawal symptoms (lack of effect of the methadone) typically within a few days following the switch to a commercially available product (the literature specifically describes this happening with the Methadose™ Cherry-Flavoured product).
    - Symptoms of lack of effect reported include sweating, insomnia, tremor, agitation, nausea/vomiting/diarrhea (i.e., feeling more "dope sick" or "withdrawals"), increase in pain, increase in cravings and/or feelings of needing to supplement with other opioids.
    - If symptoms develop, consider utilizing COWS or SOWS scoring for monitoring and assisting with the establishment of symptom severity.
- Ensure any concerns are communicated to the prescriber. It is important for people to know they are supported through this transition by their team of providers.

RESPONDING TO CLINICAL DESTABILIZATION

- **There is a risk of destabilization with any change of OAT.**
    - Serious destabilization has been associated with the Methadose™ Cherry-Flavoured product, though high-quality evidence to establish causality is not available. The best available evidence that speaks to this association includes a qualitative study (N=34), a survey (N=405), a cohort study (N=331), and anecdotal reports.[vii,xii, xiii,xiv] All published reports have come out of British Columbia, and therefore the severity or extent of impact related to this change in other jurisdictions is also not well established.
    - It is unknown if there is a difference in destabilization risk between formulations.
    - Health Canada has identified a potential risk of lack of effect (i.e., causing the person to experience opioid withdrawal symptoms) and clinical destabilization when switching between different methadone products.[v] Health Canada did not indicate a specific brand or formulation of concern.
- Validate, reassure, and address the concerns of people who report a lack of effect in the first few days after switching to a new methadone formulation.
- **If withdrawal or destabilization occurs, the prescriber is encouraged to consider one of the following modifications to the methadone prescription as early as possible:**
    - Switch to a different methadone brand and formulation (i.e., from Methadose™ Sugar-Free to Metadol-D®). **Switching to Metadol-D® is the recommended approach** by some people with lived experience. There are no reports to suggest benefit related to changing the brand if the person is already taking Metadol-D®. Alternative management strategies as below are advised.
    - Divide the methadone dose, such as to split the total daily dose to twice daily (e.g., methadone 100 mg PO daily could be divided to 50 mg PO BID). This approach **may not be feasible** if take-home doses are deemed unsafe in the clinical circumstance and/or the person is unable to attend the pharmacy twice in a day.
    - Trial an increase in the methadone dose (e.g., by 5-10 mg, no more often than every 5-7 days). There is concern that if the medication is wearing off in advance of 24 hours, a dose increase **may not be sufficient** to overcome this effect.
- If clinical stability cannot be achieved with these methadone adjustments, or if the person wishes to explore a different option, consider whether an alternate form of OAT, such as a buprenorphine product, might be appropriate (note: buprenorphine may be less effective than methadone for people who use high opioid doses, e.g., large amounts of fentanyl regularly). Consult with an expert in prescribing OAT and/or addiction medicine as required.

- All people experiencing withdrawal and/or destabilization will require closer follow up and possibly reassessment of the take-home dose authorization (if applicable), until re-establishment of clinical stability on OAT.
- **If a pharmacist becomes aware that a person is experiencing opioid withdrawal and/or clinical destabilization, the pharmacist must ensure this information is communicated to the prescriber** so the prescription may be reassessed.
    - If inter-dose withdrawal is experienced and the person's primary prescriber cannot be reached (e.g., on a weekend), the pharmacist might consider the following strategies to attempt to address the individual's symptoms and risk:
        - Assess the person's level of distress and offer reassurance of the ability to offer support.
        - Assess the severity of opioid withdrawal (e.g., using COWS or SOWS scoring) and consider whether any over-the-counter or prescribed pharmacological options to address the physical symptoms of withdrawal may be accessible (note: see RxFiles "*Prescription for Managing Opioid Withdrawal*" available through SHIRP).
        - Consider referral to an alternate OAT prescriber if available in a local primary or tertiary care centre (e.g., a Rapid Access Addictions Medicine Clinic). Services in SK may be found listed in the "*Mental Health and Addictions Services Directory*" on the Mental Health and Addiction Support Services in Saskatchewan page of the *Government of Saskatchewan* website.
        - If a methadone dose is wearing off early and no OAT prescribers or alternatives are available, the pharmacist will need to use their best professional clinical judgement and discretion to support the person, recognizing there can be serious consequences and risks to patient safety associated with opioid withdrawal.
- **Any changes in clinical response associated with a commercially available product, including withdrawal symptoms soon after the transition, or other serious or unexpected adverse reactions in people taking methadone, should be reported to Health Canada** to support ongoing monitoring of the safety of commercially available products.[v]

Exploring the Reports of Clinical Destabilization

- **High-quality clinical evidence to establish causality is not available; however, it is important to take reports of changes in effect seriously** (i.e., getting "dope sick" or having "withdrawals") **since clinical destabilization can be life-threatening.** Lack of effect may result in people "topping up" with opioids from the illicit drug supply which are often contaminated and potentially lethal.
- In British Columbia, where this was primarily reported starting in the first few days after people were switched from compounded to the commercially available methadone in 2014, the lack of effect leading to opioid withdrawal was associated with the Methadose™ Cherry-Flavoured concentrate.
- Researchers in British Columbia published a study in 2016, in which 405 people who had been switched to the Methadose™ Cherry-Flavoured product were surveyed. Of the respondents, **56% (202/358) reported feeling more dope sick and 54% (193/358) reported more pain** after the formulation change. Also following the switch, **50% (181/360) of people surveyed reported supplementing with other opioids**, and 33% (107/320) had an increase in their methadone dose.[xii]
- Another observational study quoted a participant as saying, regarding the switch to the Methadose™ Cherry-Flavoured concentrate, "*It's not agreeing with my body. I can feel a little bit of the effects of it* [alleviation of withdrawal symptoms]. *Other than that… the pain seems to be a lot more than it was when I was taking the regular methadone. I still don't understand this* [obscenity]*, but I don't think I really wanna be on it* [Methadose®]. *In the middle of the night, I feel nauseated, whereas before I was always fine…I get my methadone at 6:30* [am] *and by about eight or nine o'clock at night, my body aches a lot more.*" [xiii]
- The exact reason for the reported difference in effect is not known.

- Theories regarding the potential difference in effect of the Methadose™ Cherry-Flavoured formulation include:
    - Differences in viscosity and volume – This product is thicker and does not require dilution. As such, the smaller and "stickier" amount may adhere more readily to the dispensing container resulting in a partial loss of the more concentrated dose.
    - Potentially different ratio of enantiomers – Methadone is a chiral molecule. Given that its R- and S-enantiomers may not fit into the receptors in the same way, a change in their relative amounts could cause a change in effect.
    - Psychological effects – The smaller (undiluted) dispensed volume, feelings of loss of control secondary to imposed changes, and a disagreeable taste/consistency may all contribute to lack of effect of the medication.
- In consideration of the observational and anecdotal reports, **Methadose™ Cherry-Flavoured is not recommended as a first choice when transitioning people to a new methadone formulation at this time**.
    - Also, since the differences between the Sugar-Free and Cherry-Flavoured formulations are not known, and in keeping with what is recommended by some people with lived experience, **people are encouraged to consider using Metadol-D preferentially at this time**.
- Any change can be difficult, and it is important for providers to follow up with people who are making the transition. People who feel supported and are well-informed about this change along with the potential implications will be more likely to return to their prescriber early on to communicate any concerns.

TIPS FOR PROACTIVE COMMUNICATION WITH PEOPLE TAKING METHADONE

- Start the conversation early regarding the change itself and what differences and similarities to expect.
    - Reassure that the diluent and appearance of the product and bottle can stay the same.
    - Emphasize that the person will be prescribed the same initial methadone dose.
    - It may be helpful to reassure people taking buprenorphine products that they will not be affected by this change.
- Let people know the reason the change is happening – to help make it safer for both the person taking methadone and the dispensing pharmacy.
    - Examples of how these products are safer from a pharmacy perspective include:
        - Avoids compounding errors which may occur during the preparation process (such as preparing the incorrect concentration, which can result in unintentional over- or under-dosing of the methadone).
        - Commercially available products are manufactured with more stringent quality control measures to optimize sterility and stability of the products, which reduces the likelihood of the product being contaminated and increases the likelihood that the dose will be consistent from dose to dose.
        - Avoids exposure of pharmacy personnel and the pharmacy environment to the methadone powder, which is classified by WHMIS as a highly toxic substance.
        - Allows pharmacy software systems to utilize automated drug interaction checkers (important since methadone can have significant drug interactions with numerous other medications).
        - Aligns with what other provinces and territories are offering, so that the dispensed product can consistently be maintained when a person taking methadone moves between jurisdictions.
- Consider sharing the medSask/CPDPP information poster with them, and/or using it as a tool to support discussions. People may also be directed to find more information here.

- Communicate the two products that are being offered, emphasize the person's choice in the decision, and consider recommending Metadol-D® while acknowledging the strength of the recommendation is limited by low-quality evidence associated with the Methadose™.
- Acknowledge the difficulties that some people in other parts of the country had when methadone was switched (e.g., documented reports from British Columbia).
    - Reassure that the challenges experienced in British Columbia were associated with the Methadose™ Cherry-Flavoured product, and that this product is not being recommended as a first step for the change in SK.
    - Advise that members of an advocacy group comprised of people with lived experience in Canada (i.e., the British Columbia Association for People on Opioid Maintenance) have advised to, "Avoid Methadose. Choose Metadol-D."
    - Encourage that many people have switched in other parts of the country (SK is the last province to make this change), and numerous people have experienced a continued beneficial effect of their methadone.
- Remember to treat each person as an individual, with respect and dignity, and acknowledge that any changes can directly impact their life.
- Emphasize the importance of continuity of care, that all pharmacies are making this change, and encourage the person to stay with the same methadone prescriber and pharmacist, whenever possible, through the transition.
- Commit to helping each person create a treatment plan that meets their own goals, values, and preferences.
- It may be helpful to explain the difference between compounded products and dilution, reiterate that diversion risks remain, and that people must safely store their medication and not share or sell it to others.
- Invite people to discuss any medication concerns early on with their care provider - including concerns before and after the change in methadone formulation – and offer reassurance that steps will be taken to partner with them to maintain and/or regain clinical stability after the formulation change.

PREPARING IN THE PHARMACY TO HELP PEOPLE SAFELY CHANGE TO COMMERCIAL METHADONE PRODUCTS (checklist)

- ☐ Proactively order in sufficient volume of the anticipated desired brand and formulation of the 10 mg/mL concentration to secure supply for approximately a one- to three- week period to reduce the risk of and vulnerability to insufficient supply from the distributor.
    - ⌂ If planning to bring in more than one product, pharmacies must ensure processes are in place to keep these products separate from one another, from other commercial methadone products (e.g., Metadol® for pain may be a 1 mg/mL concentration), as well as from compounded methadone during the transition period (e.g., store on separate shelves, consistently mark stock bottles with different warning labels/stickers). Plan to maintain this distinction throughout the storage, documentation, and dispensing processes.
- ☐ Obtain accurate calibrated measuring devices and equipment (e.g., oral calibrated devices, manual/electric pumps) to support the need for preparing and dispensing the methadone products.
    - ⌂ If using more than one product, measuring devices must be clearly labeled and stored separately from one another.
    - ⌂ Note that commercially available methadone products come in 1000 mL bottles.
- ☐ Verify that the drug files are set up appropriately in the pharmacy computer software system.
    - ⌂ The methadone product quantity submitted to the DPEBB and NIHB should be in “mL”.
- ☐ Implement procedures to reduce the chance of error when dispensing using two concurrent processes (e.g., dispensing compounded and commercial methadone, or dispensing different commercial methadone products).
    - ⌂ Carry and utilize a single methadone concentration in the pharmacy whenever possible (e.g., carrying and compounding 10 mg/mL concentrations only).
    - ⌂ Ensure order-entry systems reflect the concentration being used.
    - ⌂ Implement independent double checks for preparation and administration of each dose.
    - ⌂ Separate the processes in time and space (e.g., prepare formulations on different days or in different areas, store doses in different parts of the fridge, consider using different coloured signing sheets or baskets).
    - ⌂ Maximize individual privacy and confidentiality through process changes (e.g., being mindful to avoid colour-coding person-facing products or documentation).
    - ⌂ Review the SCPP OAT Standards to verify any differences in product stability once diluted. The stability chart may be helpful as a printed document with easy access for pharmacy staff.
- ☐ Communicate and create awareness regarding these new products and all new processes and procedures for pharmacy staff.
- ☐ Consider the pharmacy’s methadone prescription volumes and determine the most appropriate timelines for the date (or week) for proceeding with the switch.
    - ⌂ If possible, some pharmacies may find it is safer to seek to change the prescriptions over to the new product(s) at the same date/time. Other pharmacies may determine it is feasible to switch on an individual basis.
    - ⌂ Consider staffing levels and ability to ensure safe concurrent processes when planning for the change date(s).
    - ⌂ Ensure plans for preferred timelines are communicated to and coordinated with prescribers.

- ☐ Have conversations with people taking methadone early on to let them know what aspects of methadone will be changing, and what aspects will stay the same, along with the anticipated timelines.
    - ⌂ Ensure they are alerted that there is **choice** as to which product they switch to, and communicate any recommendations or considerations for making that choice. When considering all of the information (documentation in the literature, alongside reports from people with lived experience), pharmacists are encouraged to consider preferentially recommending Metadol-D®.
    - ⌂ Use the information sheet for people taking methadone to support the discussion (obtain print copies to hand out and refer to during discussions), and refer to the Tips for Proactive Communication with People Taking Methadone.
    - ⌂ Emphasize the importance of continuity of care, that all pharmacies are making this change, and encourage the person to stay with the same methadone prescriber and pharmacist, whenever possible, through the transition.
    - ⌂ It may be helpful to explain the difference between compounded products and dilution, reiterate that diversion risks remain, and that people must safely store their medication and not share or sell it to others.
    - ⌂ Confirm they have a take-home naloxone kit that is not expired, and provide a new/replacement kit whenever necessary.
- ☐ Review the current prescriptions for people taking methadone to determine when a new prescription will be required.
    - ⌂ Use the template to communicate an individual's brand and formulation choice and the preference for the start date to the prescriber, as appropriate.
    - ⌂ Proactively consider if some individuals may be better supported with changes to their take-home dose schedule (e.g., people who have very recently entered/will be entering the maintenance phase of taking methadone), as there may be benefit in pausing with expanded take-home dose authorization through this transition. Communicate these considerations with people taking methadone and their prescribers.
- ☐ Obtain a new prescription for all people taking methadone, confirming the dose remains the same, while the brand and formulation are also clearly indicated.
    - ⌂ Ensure people taking methadone receive their first dose of the new brand and formulation as a witnessed dose, and that any take-home doses provided are all the same brand and formulation.
    - ⌂ Consider adding an auxiliary label to the bottles in the first dispense (e.g., the witnessed dose and take-home doses, if applicable) as an additional strategy to help communicate the change.
    - ⌂ Plan to keep the diluent and bottle type and size the same to maintain the person's familiarity with the dose.
- ☐ Consider requesting a prescription for pharmacological opioid withdrawal adjuncts logged on file at the pharmacy if a person taking methadone is particularly concerned, anxious, or distressed in anticipation of making this change.

Pharmacist Letter to Prescriber Re: Changing from Compounded to a Commercial Methadone Product

TO: (Prescriber information)	FROM: (Pharmacy information)
Name:	**Pharmacy Name:**
Address:	**Address:**
Phone Number:	**Phone Number:**
Fax Number:	**Fax Number:**

RE: (Patient information)	
Name:	**Date:**
PHN:	
DOB:	

Dear Dr./N.P.: _____,

Our mutual patient, _____(name),

is taking methadone _____ mg (dose) PO _____ (interval).

As you may already be aware, all patients on compounded methadone must be switched to a commercially available methadone concentrated product prior to November 30, 2022. More information regarding this change may be found here: https://medsask.usask.ca/professional-practice/methadone--information-for-people-healthcare-providers.

A new complete prescription is needed which specifies the selected brand and formulation, in addition to the current requirements.

☐ I, the pharmacist, have spoken with this patient about their methadone options, and they prefer to switch to the brand and formulation indicated below. Please fax a new complete prescription for the following brand and formulation (the dose and interval remain the same) to the fax number indicated at right above.

☐ Metadol-D® OR ☐ Methadose™ Sugar-Free (in a 10 mg/mL concentration)

*Please specify to start this prescription on _____ (requested date).

OR

☐ I, the pharmacist, have not spoken with the patient about their methadone options.
Please discuss the change with them at your next scheduled appointment to determine together which methadone brand and formulation to change to. Supporting resources may be found at the medSask website.

*Please call the pharmacy in advance to ensure we have the requested product in stock and to confirm the desired start date. Then, send a new complete prescription to reflect the change, including the brand and formulation (the dose and interval remain the same).

Additional comments:

Thank you for your attention to this request. Please call if you have any questions about this change.
Regards,

(Pharmacist name and credentials)

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