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17 October 2023

Distributed to:
Chief Executives
Directors of Clinical Governance
Director, Regulation and Compliance Unit

Action required by:
Chief Executives
Directors of Clinical Governance

We recommend you also inform:
Directors, Managers and Staff of:
- Palliative Care
- Pain Services
- Oncology/Cancer Care
- Neonatal/Paediatric Departments
- Maternity Services
- Alcohol and Other Drugs Services
- Intensive Care Units
- Emergency Departments
- Nursing/Midwifery Services
- Pharmacy Services
- Medical Services
- Drug & Therapeutics Committees

All other relevant clinicians and clinical departments where morphine oral liquid is prescribed, stored, and administered.

Expert Reference Group
Content reviewed by:
Medicine Shortage Assessment and Management Team
Medication Safety Expert Advisory Committee

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Discontinuation of all strengths of immediate-release morphine hydrochloride trihydrate (Ordine®) oral solution in Australia

Situation

All strengths of immediate-release morphine hydrochloride trihydrate (Ordine) oral solution are being discontinued from the Australian market. Stock is expected to be depleted between November 2023 and May 2024. Currently, there are no other Australian registered brands of morphine oral solution available. Other forms of morphine (including immediate-release tablets, controlled-release tablets and capsules, and ampoules for injection) continue to be available.

Background

Immediate-release morphine oral solution is indicated for the short-term management of moderate to severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain. It also has accepted, off-label indications for:

- neonatal pain and sedation, including during assisted ventilation
- neonatal abstinence syndrome (NAS) secondary to maternal opioid dependency
- iatrogenic opioid withdrawal secondary to infant opioid infusions
- pain and dyspnoea in patients receiving palliative/end-of-life care.

Assessment

Alternatives to immediate-release morphine hydrochloride trihydrate (Ordine) oral solution are available and can be utilised after consideration of the below precautions and safety issues.

Australian registered immediate-release oral morphine tablet alternatives

- Morphine sulfate pentahydrate (Sevredol®) 10 mg and 20 mg tablets – ARTG 47543 and 21089, respectively.

Australian registered immediate-release opioid oral solution alternatives

- Oxycodone hydrochloride (OxyNorm®) oral liquid 1 mg/mL, 250 mL bottle – ARTG 77464.
- Hydromorphone hydrochloride (Rhodes®) 1 mg/mL oral solution, 473mL bottle – Available under Section 19A (S19A) of the Therapeutic Goods Act 1989.

Opioid conversion tools (e.g., ANZCA Opioid Calculator, eviQ Conversion Calculator) should be used to guide switching opioids and to determine a suitable starting dose. Specialist advice should be sought if there is limited experience with opioid conversions. Careful monitoring is required until the patient is stabilised on a dose of an alternative opioid.

S19A immediate-release morphine oral solution alternatives

The Therapeutic Goods Administration (TGA) have released a web statement regarding the discontinuation and supply of Section 19A (S19A) alternatives. For updates on the S19A alternatives, refer to the TGA Section 19A approvals database.

The following S19A alternatives can be accessed by clinicians from 1 December 2023 until 31 July 2025:

- Morphine sulfate pentahydrate (Hikma) 2 mg/mL oral solution available from Medsurge Healthcare.
- Morphine sulfate pentahydrate (Martindale Pharma) 10 mg/5 mL oral solution available from Link Healthcare.
- Morphine hydrochloride trihydrate (Streuli Pharma AG) 10 mg/mL oral drops available from Medsurge Healthcare.

Other alternatives

There may be additional alternatives from other sponsors available in the future. For example, Phebra intends to make three strengths of immediate-release morphine oral solution available as alternatives for Ordine oral solution. Supply arrangements have not been determined, however, initial supply under Schedule 5A of the Therapeutic Goods Regulations 1990 is an option under consideration. Phebra is currently in communication with the TGA and Pharmaceutical Benefits Scheme (PBS) and will provide additional information once available.

Safety considerations

There are differences between Ordine oral solution and the S19A immediate-release morphine oral solution alternatives that clinicians need to be aware of, including (see **Table 1** below for a detailed comparison):

- **Different morphine salt** – two of the S19A alternatives contain morphine sulfate **pentahydrate**, while Ordine oral solution contains morphine hydrochloride **trihydrate**, however there is no difference in efficacy.
- **Excipients** – there are important differences in excipients in the S19A alternatives that may not be appropriate in some patient groups, including **sucrose** and **alcohol**. The amount of alcohol in the alternate product is an important consideration if the patient is pregnant or breast-feeding, has a history of alcohol use, has long term (chronic) liver problems or epilepsy, or if the patient is a child. The alternative products also contain parahydroxybenzoates (E216, E217, E218 and E219) as excipients which may cause allergic reactions in some patients.
- **Packaging** – there are differences in the form, packaging, and appearance of the products.
- **Storage** – there are differences in storage requirements and expiration dates once the bottle is opened.

Table 1. Comparison between the Australian registered product and S19A alternatives of morphine oral solution.

Product	*ARTG listed product*	*S19A alternatives*		
	Morphine hydrochloride trihydrate (Ordine) oral solution	**Morphine sulfate pentahydrate (Martindale Pharma®) oral solution**	**Morphine sulfate pentahydrate (Hikma®) oral solution**	**Morphine hydrochloride trihydrate (Streuli Pharma AG®) oral drops**
Country of origin	Australia	UK	USA	Switzerland
Supplier	Mundipharma	Link Healthcare	Medsurge Healthcare	Medsurge Healthcare
S19A approval	Not applicable	1 December 2023 until 31 July 2025		
Active ingredient and strength(s)	Morphine hydrochloride trihydrate 1 mg/mL, 2 mg/mL, 5 mg/mL, 10 mg/mL	Morphine **sulfate** pentahydrate **2 mg/mL**	Morphine **sulfate** pentahydrate **2 mg/mL**	Morphine hydrochloride trihydrate **10 mg/mL**
			Note: Both alternative products available from Medsurge Healthcare are also available in other strengths internationally. Only the strengths mentioned above are approved for supply under Section 19A.	
Form	Oral solution – colourless	Oral solution – colourless	Oral solution – **blue-green colour**	Oral drops – colourless (**Note:** 20 drops is equal to 1 mL)
Excipients	Anhydrous citric acid, sodium citrate, glyctransierol & disodium edetate with sodium methyl hydroxybenzoate 0.23% w/v as preservative, water for injections.	**Sucrose (2.25 g/5 mL), sodium methyl hydroxybenzoate (E219), sodium propyl hydroxybenzoate (E217)**, disodium edetate, raspberry flavour, hydrochloric acid, purified water.	Citric acid monohydrate, edetate disodium, FD&C Green No. 3, glycerin, methylparaben, propylparaben, sodium benzoate, sorbitol, water.	**Methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216).** (**Note**: No added flavours – may be taken with fruit juice to mask bitter taste)

Product	Morphine hydrochloride trihydrate (Ordine) oral solution	Morphine sulfate pentahydrate (Martindale Pharma®) oral solution	Morphine sulfate pentahydrate (Hikma®) oral solution	Morphine hydrochloride trihydrate (Streuli Pharma AG®) oral drops
Alcohol content	Nil	**Alcohol** 0.4 mL/5 mL	Nil	**Alcohol** 0.01 mL/1 mL (20 drops)
Specific patient considerations (as per the respective Product Information leaflets)	Not recommended for children under 1 year old. May be used in neonates under the direction of a neonatologist.	Not recommended for children under 1 year old.	Not indicated in children under 2 years old.	Use with extreme caution in children under 1 year old.
	Note: Immediate-release morphine oral solution may be used in neonatal and paediatric patients under the supervision of a relevant specialist for accepted, off-label indications such as neonatal abstinence syndrome. See Australasian Neonatal Medicines Formulary (ANMF) monograph for more information.			
Storage	Store below 30°C. Protect from light.	Store below 25°C.	Store between 20-25°C. Protect from moisture.	Store between 15-25°C in the original packaging. Protect from light.
Expiry	Discard 6 months after opening.	Discard **90 days** after opening.	Discard **90 days** after opening.	Discard **8 weeks** after opening.
Appearance	200 mL brown polyethylene terephthalate bottle	100 mL, 250 mL, 300 mL or 500 mL **amber glass bottles**	5 mL, 10 mL and 50 mL **amber plastic bottles**	20 mL **amber glass bottle**
Outer packaging artwork				
Bottle image/ artwork				
Labelling language	English	English	English	**French and German** (**Note**: the active ingredient and strength are identifiable in English. Further information will be provided in English with each product.)

Recommendations

To effectively manage the discontinuation of Ordine oral solution:

- Remaining stock of Ordine oral solution in each facility should be assessed, ensuring all locations of stock are identified. Orders for alternative products should be placed by Pharmacy Departments in advance to ensure the timely receipt and ongoing supply of morphine oral solution.
- Facilities should select an appropriate alternative(s) considering individual product specifications and requirements in relation to the intended patient populations and clinical indications. Prescribing clinicians must also consider individual product specifications (such as alcohol content) and appropriateness for each patient prior to prescribing.
- Clinicians should refer to the Australasian Neonatal Medicines Formulary (ANMF) monograph for information regarding morphine sulfate pentahydrate (Hikma®), which has been recommended as the preferred alternative immediate-release morphine oral solution for use in neonates. The monograph includes important information including specific dosing, preparation and administration requirements.
- Actions to prepare for the safe transition to the alternative morphine oral solution product should be implemented with liaison between representatives from the local Pharmacy Departments, Drug and Therapeutic Committees, and relevant clinicians.
- Clinicians should be made aware of the change in product and provided with education regarding the alternative products and any specific requirements, such as the product's expiry date after opening. This information should be documented on the dispensing labels and communicated to clinical areas when distributing as ward stock.
- Clinicians should take extra precaution when prescribing, dispensing and administering alternative oral morphine solutions, and when communicating medicine information during transitions of care.
- Patients and caregivers should be provided with appropriate education on the alternative morphine oral solution being prescribed including any specific requirements, and this information should be clearly documented during transitions of care (for example, on discharge).
- Pharmacy departments should take extra precaution when dispensing and storing the morphine hydrochloride trihydrate (Streuli Pharma AG) oral drops. Appropriate cautionary and advisory labels should be applied in English. Where possible, clinicians are encouraged to use an appropriately sized oral syringe (rather than the product's medicine dropper) to draw up and administer this product to ensure accuracy of dosing. Clinicians should refer to the Australian Product Information for Ordine oral solution and other evidence-based reference texts for dosing information.
- Governance committees should liaise with local electronic Medication Management (eMM)/ICT teams to update configurations (for example, order sentences and product catalogues) in eMM systems where required to reflect the change in product. Where eMM systems are in use, mechanisms are to be built to prevent selection errors at the point of prescribing.
- Drug registers and automated dispensing cabinets (ADCs) should be reviewed and updated to include the alternative product and reflect appropriate stock counts.
- Clinical guidelines and protocols that include morphine oral solution should be reviewed and updated to reflect any changes associated with the use of the alternative product(s).

In accordance with NSW Health Policy Directive Medication Handling PD2022_032:

- Morphine must be stored in the Schedule 8 drug safe/cabinet in the original packaging until immediately prior to use.
- Clinicians should adhere to local policy regarding safe and accurate medication administration, including independent second person checking procedures. The independent second check includes (but is not limited to) carefully reading the medicine name and concentration to confirm they are correct rather than relying on package/label recognition. While the policy does not mandate a second person check when administered by an authorised prescriber, it is strongly recommended.

In accordance with NSW Health Policy Directive High-Risk Medicines Management PD2020_045:

- Naloxone (reversal agent) must be available in all patient care areas where opioid medicines are used.
- Where possible, only store one strength of an oral morphine solution in a patient care area. If more than one strength of oral morphine solution is required, strategies must be in place to reduce selection error (for example, storing on different shelves or in clearly labelled tubs).

Required actions for the Local Health Districts/Networks

1. Distribute this Safety Notice to all relevant clinicians, clinical departments where immediate-release morphine oral solution is stocked, prescribed, and administered, and include this Safety Notice in relevant handovers and safety huddles.
2. Undertake a local risk assessment and incorporate the above recommendations to manage this discontinuation.
3. Ensure a system is in place to document actions taken in response to this Safety Notice.
4. Report any incidents associated with this disruption to supply into the local incident management system (e.g., ims+).
5. Confirm receipt and distribution of this Safety Notice **within 72 hours** to CEC-MedicationSafety@health.nsw.gov.au.