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NOTICE: ADULT HOSPITAL LEVEL (AHL) APPENDIX IV: EXTEMPORANEOUS PREPARATIONS – MORPHINE REFORMULATION

Following the erratum which was circulated to external stakeholders regarding the corrected extemporaneous compounding formula for morphine oral solution on the 21 August 2023 (refer to Circular Number: 2023/08/21/EDP/01), the National Essential Medicines List Committee (NEMLC) reviewed the full guidance and updated the recommendations.
The updated recommendations were reviewed with input from palliative care experts.
In summary, NEMLC recommended the following updates for compounding morphine oral solution in adults and children above the age of 6 years old:

- Formulation:
  - The inclusion of sorbitol as an excipient was discouraged due to its high sugar content.
  - Additionally, sorbitol has laxative properties and concomitant use with other laxatives is a concern.
  - In the AHL Appendix IV: Extemporaneous Preparations, a commercial preparation of methyl parahydroxybenzoate, propyl hydroxybenzoate, alcohol and purified water (the components of nipastat, 0.15%) were recommended as an alternative to the sorbitol, if available.
  - In the 2020-4 AHL review cycle, NEMLC has therefore removed the sorbitol formulation and only recommended 0.15% nipastat solution (procured commercially as a premade solution) as diluent for the extemporaneous preparation of morphine oral solution.
- Concentrations:
  - The 1 mg/mL concentration of morphine oral solution is recommended for children and frail care patients where lower doses are required.
  - The 5 mg/mL and 10 mg/mL concentrations of morphine oral solution are recommended for adult patients.
  - The 20 mg/mL concentration of morphine oral solution is only recommended in patients with complex pain (e.g. opioid tolerant patients). This concentration will only be needed in oncology centres and specialist care settings.
  - For clarity, concentrations represented as a percentage (%) have been removed and concentrations expressed as mg/mL have been retained.

- Shelf life:
  - NEMLC noted that extemporaneous compounding is performed in accordance with section 14(4) of the Medicines and Related Substance Act (Act 101 of 1965) and the accompanying Regulations. General Regulation 3, as amended in December 2022, only allows the preparation of an extemporaneous solution to be used for no more than 30 consecutive days from the date of sale. In the public sector, the date of sale would be the date of issue by the pharmacy. To avoid wastage, especially at smaller facilities, NEMLC has recommended the inclusion of formulae for smaller final volumes of 100mL and 500mL of morphine oral solution.

Additionally, NEMLC recommended the following in **neonates, infants and young children (under the age of 6 years old):**

While the use of nipastat could be considered in children under the age of 6 years old, the high percentage of alcohol in this formulation is of concern in this group of patients. There is a lack of robust data on extemporaneous formulations for neonates, infants and younger children with available excipients and formulations. It is thus recommended that for this group of patients:

1. A diluted morphine intravenous formulation be used orally (in consultation with specialists in units and your pharmacy department); e.g. Add 1ml of 10mg/ml IV solution to 9ml normal saline (preservative-free), to make 1mg/ml concentration (to be stored in fridge for no longer than 7 days).
2. Alternative morphine extemporaneous formulations excluding the use of alcohol, for example use of the following excipients: Benzoic acid, propylene glycol, sorbitol and purified water can be considered.

Procurement of Nipastat 0,15%

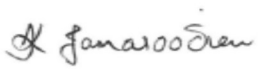
NSN	Product	Supplier	Contract
222001625	METHYLHYDROXYBENZOATE; 2.5G; PROPYLHYDROXYBENZOATE 1.25G; ALCOHOL (99%) 125 ML; PURIFIED WATER; 2.5L;1'S	Patient Focus Africa (Pty) Ltd	PPQ EDP-2024-02

Circular dissemination

Provinces and Healthcare facilities are requested to distribute and communicate this information in consultation with the Pharmaceutical and Therapeutics Committees for immediate implementation. Kindly share with all healthcare professionals and relevant stakeholders.

NOTE: Appendix IV: Extemporaneous preparations is currently under review, therefore the updated morphine, oral solution formulation guide will be published as part of the final Adult Hospital Level STG and EML 2024 edition, in due course. Refer to Annexure A for the complete guidance on the preparation of morphine oral solution.

Kind regards



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CHIEF DIRECTOR: SECTOR WIDE PROCUREMENT
DATE: 03 October 2024

ANNEXURE A

MORPHINE, ORAL SOLUTION FORMULATION GUIDE

Different concentrations of morphine can be compounded to make the oral solution. However, it is recommended that a standard concentration (mg/mL) is used per ward/facility to prevent dosing errors. The following standard concentrations should be used:

- 1 mg/mL
- 5 mg/mL
- 10 mg/mL

Lower concentrations (e.g., 1mg/mL) are used for children and frail care patients where lower doses are usually required. Dosing for adult patients is generally commenced using concentrations of 5mg/mL or 10mg/mL. Higher strengths (20mg/mL) may be required in patients with complex pain (e.g. oncology centres and specialist care, opioid tolerant patients).

The volume compounded is dependent on individual patient requirements. Any remaining unused solution must be discarded 30 days from the day of compounding, in keeping with legislation and the expected stability of oral morphine solutions. Therefore, in order to prevent wastage, compound a volume in line with expected usage in a 30-day period. Compounding is usually done for individual patients, but can be done in anticipation of demand, with due regard to the limited stability of oral morphine solutions. Large volumes cannot be prepared for bulk stock and kept in stock awaiting prescriptions. The same approach should be applied to stock prepared for use on hospital wards.

Tables 1 and 2 below show the amount (in grams) of morphine hydrochloride/sulphate required to make 100 mL and 500 mL morphine oral solutions, respectively, at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL, using nipastat 0.15% solution (procured commercially as a premade solution) as diluent. Varying volumes of nipastat 0.15% are combined with each fixed amount of morphine powder, in order to produce the final volume required. Please refer below for instructions for Neonates, infants and young children (under the age of 6 years old).

Table 1: Amount (in grams) of morphine hydrochloride/sulphate required to make a 100 mL oral morphine solution at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL

Formula:

Final morphine concentration	**1 mg/mL**	**5 mg/mL**	**10 mg/mL**
Morphine hydrochloride/sulphate	**0.1 g**	**0.5 g**	**1 g**
Nipastat 0.15% Solution*, make up to	To 100 mL	To 100 mL	To 100 mL

**Nipastat 0.15% Solution (2.5 L) procured as a pre-made solution contains methylhydroxybenzoate (2.5 g), propylhydroxybenzoate (1.25 g), alcohol 99% (125 mL), purified water to 2.5L*

Table 2: Amount (in grams) of morphine hydrochloride/sulphate required to make a 500mL oral morphine solution at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL

Formula:

Final morphine concentration	**1 mg/mL**	**5 mg/mL**	**10 mg/mL**
Morphine hydrochloride/sulphate	**0.5 g**	**2.5 g**	**5 g**
Nipastat 0.15% Solution*, make up to	To 500 mL	To 500 mL	To 500 mL

**Nipastat 0.15% Solution (2.5 L) procured as a pre-made solution contains methylhydroxybenzoate (2.5 g), propylhydroxybenzoate (1.25 g), alcohol 99% (125 mL), purified water to 2.5 L*

Neonates, infants and young children (under the age of 6 years old)

While the use of nipastat could be considered in children under the age of 6 years old; the high percentage of alcohol in this formulation is of concern in this group of patients. There is a lack of robust data on extemporaneous formulations for neonates, infants and younger children with available excipients and formulations. It is thus recommended that for this group of patients:

1. A diluted morphine intravenous formulation be used orally (in consultation with specialists in units and your pharmacy department) e.g. Add 1ml of 10mg/ml IV solution to 9ml normal saline (preservative-free), to make 1mg/ml concentration. (To be stored in fridge for no longer than 7 days).
2. Alternative morphine extemporaneous formulations excluding the use of alcohol for example:

Formula:

Declaration:

Active ingredient: Morphine hydrochloride/sulphate 1 mg/mL
Dosage form: Oral solution
Excipients: Benzoic acid, propylene glycol, sorbitol, purified water

	1 mg/mL
Morphine hydrochloride/sulphate	0.1 g
Benzoic acid solution 5%*	2 mL
Sorbitol 70%	30 mL
Sterile water, add to	100 mL
(Smaller volumes can be formulated - calculate proportions)	

Preparation:

Dissolve the morphine in approximately 40 mL of the purified water. Dissolve the benzoic acid solution 5% in this solution. Add the 70% sorbitol solution and a sufficient quantity of purified water to a volume of 100 mL and mix well.

Quality requirements:

Identity: as stated under the section "Declaration", above.
Content of morphine hydrochloride: 90–110% of the declared amount, calculated as the pure substance.
pH: ≤ 4
Appearance: The solution is clear and almost free of visible particles.

Storage: Glass amber bottle, below 25 °C with an expiry date of 1 month.

**To make the benzoic acid 5% solution:* Dissolve the benzoic acid in the propylene glycol, adding the hot purified water to a volume of 100mL.

Benzoic acid	5 g
Propylene glycol	75 mL
Sterile water, heated to ±60ºC, add to	100 mL

Storage: Glass amber bottle, below 25 °C with an expiry date of 1 month.