Aprepitant: Expert opinion on extemporaneous formulations

Expert opinion of the European Drug Shortage Formulary (EDSForm) Working Party

Foreword

In view of the current shortage of paediatric products containing aprepitant faced by some member states and in line with its terms of reference, the EDSForm Working Party (WP) has compiled a list of existing licensed medicines, recommendations and extemporaneous preparations that have been or are being used to alleviate the lack of age-appropriate licensed products.

The present document is the result of this compilation effort and should be understood and used as an overview of the state of the art on this specific topic. Its content has not been formally approved by the European Pharmacopoeia Commission or by the European Committee on Pharmaceuticals and Pharmaceutical Care and represents the opinion of the experts of the EDSForm WP. It is intended to assist healthcare professionals in their risk assessment and decision-making processes.

The EDSForm WP and the EDQM emphasise that the use of licensed medicines is always preferable to the use of unlicensed pharmaceutical preparations. However, as stated in the European Pharmacopoeia general monograph *Pharmaceutical preparations (2619)*, "when deciding to use an unlicensed preparation all health professionals involved (e.g. the prescribing practitioners and/or the preparing pharmacists) have, within their area of responsibilities, a duty of care to the patient receiving the pharmaceutical preparation". The healthcare professionals concerned remain fully responsible for the assessment of the risks and benefits for each patient.

Although every care has been taken in compiling and checking the information contained in this table, neither the EDSForm WP nor the EDQM is liable for any mistakes, incompleteness or inaccuracies.

Expert Opinion

Aprepitant: General information	Ref.
EMEND® 125 mg powder for oral suspension is the only licensed product containing aprepitant that is appropriate for paediatric patients under age 12. It has been reported that this product is in short supply in several of the member states in which it is licensed. Aprepitant has poor water solubility and low bioavailability (BCS class IV). Therefore, it is expected that the oral bioavailability of the substance is closely dependent on its particle size and the formulation concerned. To improve the bioavailability of aprepitant, the commercially available capsules and the powder for oral suspension are both composed of nanoparticle-coated beads. A review of the literature indicates that, in a paediatric population, the bioavailability of an extemporaneous oral suspension produced by grinding the contents of EMEND® capsules is comparable to that of the capsules. In adults, the bioavailability of the same extemporaneous formulation was evaluated to be 82.3% relative to that of the oral capsules. In accordance with the literature and other recommendations, and in the absence of a licensed powder for oral suspension, licensed capsules may be opened and their contents either compounded into an extemporaneous oral suspension or mixed with water or food for immediate oral administration. Safety precautions: when opening the capsules, appropriate measures should be taken to prevent inhalation of the potentially harmful active ingredient.	1,4,5,7

Information on licensed product and existing unlicensed formulations					
Product	**Strength**	**How to formulate**	**Excipients**	**Comments**	**Ref.**
Licensed medicines - Powder for oral suspension					
EMEND® 125 mg, powder for oral suspension. MSD	After reconstitution, each 1 mL contains 25 mg aprepitant, 25 mg **sucrose** and approx. 93,7 mg **lactose** (anhydrous substance)	---	Hydroxypropylcellulose (E463), sodium laurylsulfate, **saccharose**, **lactose** (anhydrous substance), red iron oxide (E172), sodium stearyl fumarate	---	2
Licensed medicines – Capsules					
EMEND® 125 mg capsules EMEND® 80 mg capsules MSD (originator products)	Each capsule contains 80 mg / 125 mg aprepitant and 80 mg /125 mg **sucrose**	---	Sucrose, microcrystalline cellulose (E460), hydroxypropylcellulose (E463), sodium laurilsulfate	---	2
Generic aprepitant capsules are widely available under a number of brand names (e.g. Aprepilor, Aprepitant Accord, Aprepitant Alpha-medical, Aprepitant Aurobindo, Aprepitant Biogaran). The composition of the generic products may vary from that of the originator products.					
Extemporaneous preparation - Oral suspension					
Formulation #1 20 mg/mL extemporaneous preparation (as described in Dupuis et. Al, see Appendix 1)	1 mL contains 20 mg aprepitant and 20 mg **sucrose**	Produce one bottle at a time. Use 4 EMEND® 125 mg capsules and 25 mL of ORA-BLEND®	ORA-BLEND®	Storage: up to 2 months in an amber glass bottle; stable in a fridge (2-8 °C) and at room temperature (20-25 °C). Up to 2 months in a PET bottle; stable in a fridge (2-8 °C). No in-use or microbiological stability data available. **In adults, the relative bioavailability of this extemporaneous suspension was evaluated to be 82.3% to that of capsules. In children, the bioavailability of this extemporaneous suspension was deemed comparable to that of capsules.**	3 4
Formulation #2 20 mg/mL extemporaneous preparation (formulation used in Denmark, see Appendix 2)	1 mL contains 20 mg aprepitant	Produce one bottle at a time. Use 8 EMEND® 80 mg capsules with 32 mL of extemporaneous pharmaceutical vehicle	Extemporaneous pharmaceutical vehicle (see Appendix 2)	Storage: up to 1 month in an amber glass bottle in a fridge (2-8 °C). No in-use or microbiological stability data available. **No data on bioavailability.**	6
Other information					
Some guidelines state that the beads should be stable if removed from the capsule and placed in water or on food for immediate oral administration. The capsules should only be opened at the time of administration, not in advance.					7

Appendix 1: 20 mg/mL extemporaneous preparation #1

1. **Formulation:**

Composition	Quantity (g) or volume (mL) Per 25mL of preparation
EMEND® 125 mg capsules	4 capsules i.e. 0.500 g of aprepitant
ORA-BLEND®	25 mL

2. **Preparation:**

For one bottle:

1. Empty and weigh the contents of 4 EMEND® 125 mg capsules.
2. Grind the contents of the capsules to a fine powder using a mortar and pestle; this will take 10 to 15 min. Do not add ORA-BLEND® to the capsule contents before grinding.
3. Add a small amount of ORA-BLEND® to the fine powder and triturate to a smooth paste; ensure that there are no lumps.
4. Add more ORA-BLEND® to make a liquid and transfer to a graduated cylinder.
5. Rinse out the mortar with ORA-BLEND® and add to the graduated cylinder.
6. Make up to a final volume of 25 mL with ORA-BLEND®.
7. Fill into a PET or glass bottle.
8. Label and assign the expiry date (no longer than 2 months).

3. **Additional physico-chemical data:**

pH = 4.7+/-0.5

Osmolality = 1600 mOsm/kg

4. **Other information:** ORA-BLEND® contains purified water, sucrose, glycerine, **sorbitol**, berry citrus flavour (contains FD&C Red #40), microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, **carrageenan**, calcium sulfate, trisodium phosphate, citric acid and sodium phosphate as buffers, **dimethicone**, **methylparaben** and potassium sorbate.

Appendix 2: 20 mg/mL extemporaneous preparation #2

1. Formulation:

Composition		Quantity (g) or volume (mL) Per 35.6 g of preparation
EMEND® 80 mg capsules		8 capsules, i.e. 0.640 g of aprepitant
Extemporaneous pharmaceutical vehicle	2.5% carmellose sodium solution (2.5 g of carmellose sodium in 100 mL of purified water)	6.4 g
	50% citric acid solution (50 g of citric acid in 100 mL of purified water)	0.32 g
	85% glycerol	3.2 g
	Simple syrup	9.6 g
	Purified water	14.3 g

35.6 g of preparation = 32 mL of preparation

2. Preparation:

For one bottle:

1. Empty and weigh the contents of 8 EMEND® 80 mg capsules.
2. Grind the contents of the capsules to a fine powder using a mortar and pestle.
3. Weigh all the ingredients of the extemporaneous pharmaceutical vehicle and mix them together in a glass bottle.
4. Mix the powdered capsule contents with the extemporaneous pharmaceutical vehicle to form a suspension.
5. Pour the suspension into a suitable recipient and stir for 5 min.
6. Transfer 30 mL into a 30 mL amber glass medicine bottle, discard the rest.
7. Label, assign the expiry date (no longer than 1 month) and refrigerate.

3. Other information:

- **2.5% carmellose sodium solution:** for 100 g:
  Carmellose sodium (*F* x 2.5 = X g). *F*-value of viscosity will be on the CoA from the supplier/contract laboratory.
  Purified water (warmed to 80 °C) 90 g
  Purified water qs 100 g
  Dissolve carmellose sodium in warm purified water by vigorous stirring. Qs to final weight with purified water.
  Shelf life: 5 days in a fridge (2-8 °C).
- **50% citric acid solution:** for 1000 g:
  Citric acid monohydrate 500 g
  Purified water 500 g
  Dissolve citric acid monohydrate in purified water by stirring for at least 20 min. Filter through a disposable filter.
  Shelf life: 2 years at room temperature (20-25 °C).

- **Simple syrup:** for 1000 g:

Sucrose	630 g
Purified water	370 g
Purified water	qs 1000 g

  Dissolve sucrose in purified water by heating and stirring. Filter through a filter or gauze. Qs to final weight with purified water and stir for minimum 20 min. Bottle the solution while still warm (75–85 °C).

  Shelf life: 1 year at room temperature (20-25 °C).

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