Clarithromycin: paediatric extemporaneous unlicensed formulations

Technical recommendation of the European Drug Shortages Formulary Working Party

Foreword

About the present document

In view of the recurring difficulties encountered by some member states with the supply of paediatric products containing clarithromycin and in line with its terms of reference, the European Drug Shortages Formulary Working Party (EDSForm WP) has compiled a list of existing licensed medicines, recommendations and unlicensed pharmaceutical preparations that have been or are being prepared to alleviate the lack of age-appropriate licensed products.

The present technical recommendation is the result of this compilation exercise and should be understood and used as an overview of current practices. 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 alone.

Use of information enclosed in this document

The aim of this technical recommendation is to assist healthcare professionals in their risk assessment and decision-making processes. The quality of the formulations listed has not been verified by the EDSForm WP, and they should only be used after the performance of a proper risk assessment that takes into account the level of evidence of the source, as well as the specific context concerning the shortage and regulatory landscape of the member state.

The EDSForm WP used predefined criteria to assess the level of supporting evidence for the unlicensed pharmaceutical preparations that are described below. Three levels of evidence – high, medium and low – were assigned (see below), and formulations that did not satisfy the minimum criteria (e.g. potential safety considerations, absence of critical data) were not included in the technical recommendation.

- High-evidence formulation: the formulation described in the bibliographical source can be easily implemented (national regulatory requirements notwithstanding) and is supported by validated data from a reliable or standardised source.

- Medium-evidence formulation: the data supporting the formulation described in the bibliographical source contain several gaps, which should be included in the risk assessment carried out by the pharmacist or responsible person.

- Low-evidence formulation: the formulation described in the bibliographical source contains significant gaps in the data, contains non-validated data or has not been tested. These gaps should be included in the risk assessment carried out by the pharmacist or responsible person.

The data given in the tables and related appendices below are reproduced from the original sources in part only. Users are advised to refer to the source for more comprehensive information and are reminded to check that the data presented in this document or in other documents to which it refers comply with their own local/national requirements.

Although every care has been taken in compiling and checking the information contained in the tables and appendices below, neither the EDSForm WP nor the EDQM can be held responsible for any errors or inaccuracies they may contain.

Use of unlicensed pharmaceutical preparations

The EDSForm WP and the EDQM emphasise that the use of licensed medicines should always be preferred to unlicensed pharmaceutical preparations. However, as stated in the European Pharmacopoeia (Ph. Eur.) 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.

The terms "stock preparations" and "extemporaneous preparations" are used as defined in Ph. Eur. general monograph *2619*.

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Information on licensed products

Licensed clarithromycin oral suspensions are indicated in children or in adults who are unable to swallow tablets. It has been reported that these products are in short supply in several of the member states in which they are authorised.

The products whose composition is given below are provided either as an example or because they are used as starting materials in the unlicensed preparations described later in this document. Some of these unlicensed pharmaceutical preparations may use licensed products as starting materials; examples of the composition of these licensed products are provided. Other compositions are possible, and users should always verify that the composition of the licensed product they intend to use is appropriate.

Licensed medicines - Oral suspension			
Product [(1)]	**Strength**	**Excipients**	**Ref.**
Klacid 125 mg/5 mL, granules for oral suspension	After reconstitution as directed, each 5 mL or sachet contains 125 mg clarithromycin, 2.75 g **sucrose** and 3.22 mg **virgin castor oil**	Carbomers, povidone K 90, hypromellose phthalate, **virgin castor oil**, silicon dioxide, **sucrose,** xanthan gum, fruit punch flavour, potassium sorbate, citric acid, titanium dioxide (E171), maltodextrin	(1)
Klacid 250 mg/5 mL granules for oral suspension	After reconstitution as directed, each 5 mL or sachet contains 250 mg clarithromycin, 2.275 g **sucrose** and 4.32 mg **virgin castor oil**	Carbomers, povidone K 90, hypromellose phthalate, **virgin castor oil**, silicon dioxide, **sucrose,** xanthan gum, fruit punch flavour, potassium sorbate, citric acid, titanium dioxide (E171), maltodextrin	(2)
Licensed medicines – Tablets			
Klacid 250 mg film-coated tablets	Each tablet contains 250 mg clarithromycin	Tablet core: croscarmellose sodium, pregelatinized starch, microcrystalline cellulose, silicon dioxide, povidone, stearic acid, magnesium stearate, talc, quinoline yellow aluminium lake (E104) Tablet coating: hypromellose, hydroxyproplycellulose, propylene glycol, sorbitan oleate, titanium dioxide (E171), sorbic acid, vanillin, quinoline yellow aluminium lake (E104)	(3)
Klacid Forte 500 mg film-coated tablets	Each tablet contains 500 mg clarithromycin	Tablet core: croscarmellose sodium, microcrystalline cellulose, silicon dioxide, povidone, stearic acid, magnesium stearate, talc Tablet coating: hypromellose, hydroxypropylcellulose, propylene glycol, sorbitan oleate, titanium dioxide (E171), sorbic acid, vanillin, quinoline yellow aluminium Lake (E104)	(4)

[(1)] Klacid is available in various pharmaceutical forms, and strengths and names in different member states, marketed under different brand names and also as generic formulations (5).

Pharmaceutical preparations containing clarithromycin: general considerations

Regarding clarithromycin

Clarithromycin is practically insoluble in water and shows high permeability (BCS class II) (6). It is therefore expected that the handling of the pharmaceutical forms (crushing of tablets, etc.) during preparation of the formulation will have an impact on bioavailability.

The very strong, bitter taste of clarithromycin makes it difficult to produce oral liquid formulations.

If using a suspension, the bottle must be shaken well before measuring each dose.

Based on the literature and current recommendations, in the absence of a licensed powder for oral suspension and if the dose is easily obtained from a tablet, it is possible to crush the tablet immediately before administration and to mix it with a spoonful of yoghurt or apple puree or disperse it in 10-20 mL of water (7).

Regarding the handling of clarithromycin

Safety precautions: when crushing the tablets or handling the active substance, healthcare professionals should take appropriate measures to **prevent exposure to the potentially harmful active substance** (e.g. using dedicated or disposable equipment, following appropriate cleaning procedures and protecting from dust by wetting with suspension vehicle and careful trituration). An example Safety Data Sheet for clarithromycin can be found here.

The clarithromycin active substance should not be handled by people with a clarithromycin allergy.

Other relevant information

Monographs describing analytical procedures for the quality control of clarithromycin-containing preparations can be found in British Pharmacopoeia and United States Pharmacopeia.

Existing unlicensed pharmaceutical preparations: overview

Formulations listed in national formularies or sanctioned by national pharmacopoeia authorities

Denomination	Pharmaceutical form	Strength	Starting material	Excipients/ vehicle	Stability	Assigned shelf life	Comments	Level of evidence	Ref.
Source: French National Agency for the Safety of Medicines and Health Products (ANSM)									
ANSM capsules	Capsules	Each capsule contains 250 mg or 500 mg clarithromycin	Clarithromycin (active substance)	Gelatin capsule, no excipient	In-use or microbiological stability data not available	**1 month** ambient temperature	See Appendix 1	High	(8)

Formulations listed in other sources

Denomination	Pharmaceutical form	Strength	Starting material	Excipients/ vehicle	Stability	Assigned shelf life	Comments	Level of evidence	Ref.
Source: Fagron									
SyrSpend® SF PH4 NEO Formulation	Oral suspension	Each mL contains 25 mg clarithromycin	Clarithromycin (active substance)	SyrSpend® SF PH4 NEO, purified water	Stability data not available	**7 days** 2-8 °C	See Appendix 2	Low	(9)
Source: Handbook of Pharmaceutical Manufacturing Formulations, Third edition, Vol. 3, 2020									
Handbook of Formulations oral suspension	Granules for oral suspension	Each mL contains 25 mg clarithromycin	Clarithromycin (active substance)	Carbopol® 974P NF, polyvinyl pyrrolidone K 90, purified water, hydroxypropyl methylcellulose phthalate HP55, castor oil, potassium sorbate, sucrose, maltodextrin, xanthan gum, flavouring agent, dry, silicon dioxide, citric acid, titanium dioxide, maltodextrin, sucrose	Stability data not available		Wet granulation. Only for suitably equipped pharmacies. See Appendix 3	Low	(10)

Appendices

Appendix 1: ANSM capsules

Source: [Monograph published by the ANSM](#) (in French) **– 10/2024**

Data from the original source only partially reproduced herein. Users are advised to refer directly to the source for further information.

1. Formulation

CLARITHROMYCIN 250 MG PAEDIATRIC CAPSULES

Composition	For one capsule
Clarithromycin (active substance**)**	**250 mg**
Empty gelatine capsule shells	**N/A**

CLARITHROMYCIN 500 MG PAEDIATRIC CAPSULES

Composition	For one capsule
Clarithromycin (active substance**)**	**500 mg**
Empty gelatine capsule shells	**N/A**

2. Preparation

For one batch of capsules:

1. Comply with all applicable health and safety rules and regulations.
2. Work under a fume cupboard or equivalent, in accordance with national requirements.
3. Prepare the workstation and check that the equipment is clean and disinfect with a suitable product.
4. Define the number of capsules to be produced.
5. Install the capsule-filling machine and add the empty capsule shells.
6. Weigh the clarithromycin on an appropriate and qualified balance in a suitable container.
7. Triturate until a fine powder is obtained.
8. Pour the powder into a suitable container.
9. Fill the capsules volumetrically and remove the excess powder.
10. Verify the number of capsules filled and that each capsule is clean and has been evenly filled.
11. Check the uniformity of mass according to Ph. Eur. general chapter *2.9.5*.
12. Transfer the preparation to a suitable container.
13. Label the container.

3. Other information

During the development of the source monograph, capsule sizes 2 and 00 were found to be suitable for strengths of 250 mg and 500 mg, respectively. Users are recommended to check that the capsule size selected is compatible with both the particle size and strength of the active substance prepared.

Appendix 2: SyrSpend® Formulation

Source: Fagron Document – Drug shortages Innovation in the preparation of oral pharmaceutical suspensions in the pharmacy

1. Formulation

CLARITHROMYCIN 25 MG/ML ORAL SUSPENSION

Composition	Quantity (g) or volume (mL) Per 100 mL of preparation
Clarithromycin	2.5 g
SyrSpend® SF PH4 NEO	1 unit
Purified water	q.s. 100 mL

2. Other information

Storage conditions: 2-8 °C.

Shelf life: 7 days.

Appendix 3: Handbook of Formulations – (granules for) oral suspension

Data from the original source only partially reproduced here. Users are advised to refer directly to the source for further information.

Source: CRC PressNiazi SK. Handbook of Pharmaceutical Manufacturing Formulations, Third Edition, Vol. 3, Liquid Products. Boca Raton, USA: CRC Press; 2020.

1. **Formulation**

   CLARITHROMYCIN 125 MG/5 ML, GRANULES FOR ORAL SUSPENSION

Composition	Quantity (g) or volume (mL) Per 1kg of preparation
Clarithromycin	35.47 g
Carbomer, 974P NF	21.28 g
Povidone, K 90	4.96 g
Purified water	145 mL
Hypromellose phthalate HP55	43.17 g
Castor oil	4.56 g
Acetone	approx. 172 mL
Ethanol	approx. 164 mL
Potassium sorbate	5.96 g
Sucrose	600.80 g
Maltodextrin	67.58 g
Purified water	10 mL
Xanthan gum	1.08 g
Flavouring agent, dry	10.14 g
Silicon dioxide	1.42 g
Citric acid	1.20 g
Titanium dioxide	10.14 g
Maltodextrin	13.50 g
Sucrose	q.s. to 1 kg

2. **Note:**

   Users are advised to refer to the source for detailed information on the manufacturing process.

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