

European Paediatric Formulary

Criteria for inclusion and evaluation of monographs

Authorised medicines which have been assessed by a regulatory agency are to be preferred before considering the use of unlicensed pharmaceutical preparations.

Priority should be given to the inclusion and evaluation of monographs that serve the unmet therapeutic needs of many or that increase safety of treatments of paediatric patients.

The decision to include an active substance and a preparation in the European Formulary requires careful consideration of some or all of the following criteria and a judgement based on risk and benefit to children. Active substances with a low therapeutic index (narrow therapeutic range) require particular attention to ensure that a risk assessment is positive and that quality measures provide confidence that the prepared product will be safe and effective.

To decide on evidence level for every indication would be ideal, but is not feasible as data are incomplete or even unavailable and for some preparations there may be more than one indication and dose. Restrictions on the use of a preparation should be flagged in the monograph.

The preparations to be described in the European Paediatric Formulary will meet the requirements laid down in the Ph. Eur. monograph Pharmaceutical preparations (2619) and the following criteria should be read in conjunction with this monograph. Therefore the criteria are arranged in the same order and under the same headers.

Explanations are distinguished by italic type.

DEFINITION

The definition of each preparation states the active moiety with specific salt, dosage form and strength. If appropriate, several different salts may be described in one monograph.

ETHICAL CONSIDERATIONS AND GUIDANCE IN THE PREPARATION OF UNLICENSED PHARMACEUTICAL PREPARATIONS

THERAPEUTIC RELEVANCE AND CLINICAL JUSTIFICATION

Active substance

An active substance can be included if an overall assessment of the substance considers its use to be positive.

Assessment elements include

1. Safety of the active substance

- signals from national and international pharmacovigilance systems,
It is acknowledged that active substances may have been withdrawn from the market or restrictions placed on their use, but may still be of importance for particular group of patients, e.g. codeine, chloral hydrate.
- concerns about active substances with a low therapeutic index (e.g. regarding age, pharmacokinetics etc.).

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2 *Restrictions are flagged in the monograph, if the active substance is still seen as appropriate*
3 *and necessary for a dedicated group of patients.*

4 2. Efficacy of the active substance

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6 – therapeutic benefit and relevant to current practice,

7 *A preparation can be included if the paediatric use is established and it is not considered*
8 *obsolete. This means that the active substance is included in, for example, two or more*
9 *national formularies or there is evidence that its use is not confined to a specific locality.*

10
11 – availability of authorised products.

12 *Authorisation of a medicinal product in Europe suggests that there may be therapeutic benefit*
13 *from the active substance in children. However an age-appropriate preparation may not be*
14 *available. Off-label use in children may be documented in the literature or information may be*
15 *available from regulatory authorities or manufacturers.*

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18 Preparation

- 19 1. A preparation can be included if there is not an appropriate authorised product available for
20 the targeted patient group in all member states.

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22 *The principle of providing easily accessible information on alternative authorised products with*
23 *the same active substance is strongly endorsed.*

- 24
25 2. A preferred preparation has the following features:

- 26 - Appropriate dosage form for the target age group with evidence of acceptability,
27 - appropriate administration volume for the target population which can be measured with
28 sufficient accuracy.
29 - Dose recovery and compatibility has been investigated, if administered through feeding
30 tubes.
31 - pH and osmolality have been investigated and must be appropriate for the route and
32 method of administration and the age of the target group.
33 - Bioavailability data is available.

34 *Bioavailability data is especially important for products with a low therapeutic index.*

35 *The monograph should clearly state, if bioavailability data is available.*

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37 3. If the therapeutic index is low, great importance is given to ensuring that application of suitable
38 quality criteria provides confidence that the prepared product will be safe and effective.
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40 Excipients

41 Excipients should be risk-assessed in relation to the patient group, severity of the disease,
42 exposure and the availability of alternative treatments for example by using the decision tree of the
43 EMA guideline on pharmaceutical development of medicines for paediatric use
44 (EMA/CHMP/QWP/805880/2012 Rev. 2).

45
46 *Restrictions occurring from the use of specific excipients are flagged in the monograph, if the*
47 *monograph is still seen as appropriate and necessary for a dedicated group of patients.*
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1 PRODUCTION

1. The preparation process is described in a way to assure the quality of the product according to the corresponding Ph. Eur. dosage form monograph.
2. The description of the process enables the reproducibility of the preparation process.
3. Suitable in process controls may be implemented after critical steps of the preparation process to check that the quality is maintained.

7 Formulation

1. All excipients are necessary and suitable for their function and compatible in the final product.
2. A monograph states the qualitative and quantitative composition (active substances, excipients and their amount).

11 Active substances and excipients

1. Active substances or excipients used in the preparation meet the requirements of the Ph. Eur. monograph Substances for pharmaceutical use (2034).
2. Active substances or excipients used in the preparation which have a substance-specific Ph. Eur. or national monograph are to be preferred. Other active substances or excipients are to be considered on a case by case basis taking into account the intended paediatric use and involved risk.

19 TESTS / ASSAY

Some general explanations about analytical testing are recommended to be given to the users e.g. in a preface to the formulary. For stock preparations analytical testing of the product is essential. Where it is not practical to carry out the tests (e.g. batch size, time restraints), other suitable methods may be implemented to ensure that the appropriate quality is achieved in accordance with the risk assessment carried out and any local guidance or legal requirements.

The extent of the analytical methods described in a monograph may help to distinguish between several similar monographs in existing formularies.

1. A monograph may comprise suitable analytical test methods and acceptance criteria. Tests, that are applicable to many preparations, are appearance, identity, dissolution and purity tests, uniformity, and assay for quantitative analysis.
2. Analytical testing may be performed according to the dosage forms monographs and related chapters on analytical methods of the European Pharmacopoeia; other suitable methods can be used to ensure that the pharmaceutical quality is guaranteed.

33 STORAGE

Assessment elements should include the following items.

1. For containers and container closure systems material of pharmacopoeial quality are used if a corresponding monograph is available. The container system may be stated in the monograph.
2. The chemical, physical and microbiological stability of preparations are evaluated. Shelf life and storage conditions with the container closure system used are stated, if available.
There must be evidence at least, e.g. by testing on retention samples at the end of shelf life (but not necessarily in a climate chamber, or stability tests according to ICH standards). Literature including data for exact formulation needs at least to be available. Stability data is given in combination with the used container system.
3. Data for in-use stability may be provided.