Publication of the first texts in the European Paediatric Formulary

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What was done?

The European Paediatric Formulary was launched at the end of 2019. It is a freely available online publication for pharmacists and clinicians that is intended to provide guidance on the use and preparation of standardised paediatric medicines of an appropriate quality when a suitable licensed medicinal product is not available. The first two monographs and two explanatory texts of the European Paediatric Formulary have now been published by the European Directorate for the Quality of Medicines & HealthCare (EDQM).

Why was it done?

Formularies for extemporaneous formulations of paediatric medicines of appropriate quality are currently available in some regions or countries, but no pan-European equivalent exists. Some formulations in use are not appropriate due to a lack of knowledge of best practices. The idea behind the new formulary is to collect, review and then select the most appropriate formulations currently used in Europe which meet today's requirements.

How was it done?

- Criteria for selection and evaluation of formulations were developed by 2015. Since then the work has been carried out by the European Paediatric Formulary Working Party under the supervision of the European Pharmacopoeia Commission and the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH). The EDQM provides the scientific secretariat.

- Monographs for development were prioritised based on patient need. Many formulations currently described in national formularies and other well-established formulations have been gathered from stakeholders throughout Europe.

- The information available for the most appropriate formulation was transferred into a common format with full quantitative composition details, extemporaneous preparation instructions, validated test methods for quality control and storage conditions.

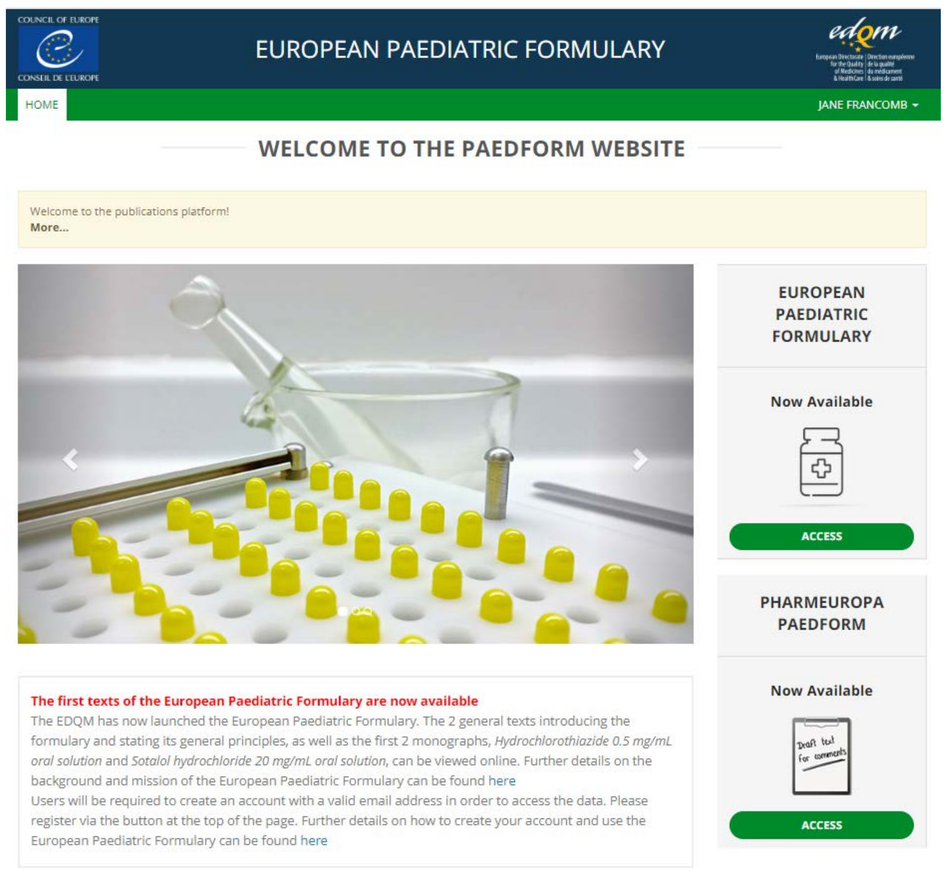

Fig. 1: European Paediatric Formulary website https://paedform.edqm.eu/home

What has been achieved?

Monographs published at the end of 2019:

- ✓ Hydrochlorothiazide 0.5 mg/mL oral solution and
- ✓ Sotalol hydrochloride 20 mg/mL oral solution

These were accompanied by an introduction and general principles which describe the purpose and content of the European Paediatric Formulary.

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HYDROCHLOROTHIAZIDE 0.5 MG/ML ORAL SOLUTION

Route of administration: oral.

DEFINITION

1 mL of hydrochlorothiazide 0.5 mg/mL oral solution contains 0.5 mg of hydrochlorothiazide (Ph. Eur.).

Content: 90.0 to 110.0 per cent of the hydrochlorothiazide label claim (0.45 to 0.55 mg/mL). *Content of methyl parahydroxybenzoate*: 90.0 to 110.0 per cent of the nominal content (0.69 to 0.85 mg/mL).

ATC classification:

C03AA03 - Low ceiling diuretics, thiazides.

QUALITATIVE AND QUANTITATIVE COMPOSITION

100.0 mL / 107.7 g of the oral solution are composed of:

Hydrochlorothiazide (Ph. Eur. *0394*)	0.050 g
Methyl parahydroxybenzoate	0.077 g…

ADDITIONAL INFORMATION

The formulation contains at least 2.75 mg of propylene glycol per mL. Natural orange flavour…

Compatibility with feeding tubes: no data available.

Bioavailability: no data available. Tablets about 70 per cent (adults), BCS class IV.

Acceptability: no data available.

pH: about 3.2.

Osmolality: no data available.

Refractive index: about 1.364 at 20 °C.

PRODUCTION

INGREDIENTS

107.7 g / 100 mL of the oral solution are composed of:

Hydrochlorothiazide	0.050 g
Citric acid monohydrate	0.870 g…

PRODUCTION STEPS

1. Dissolve citric acid monohydrate and disodium phosphate dodecahydrate in 70 g of…

IN-PROCESS CONTROLS

Appearance: clear, colourless liquid. Visual observation after steps 3 and 5.

PACKAGING

Multidose container (amber glass bottle or polyethylene terephthalate bottle….

INFORMATION FOR THE PATIENT

Patient information: available in Dutch (*see source monograph*).

QUALITY CONTROL

Appearance: clear, colourless liquid.

Identification:

Examine the chromatograms obtained in the assay…

pH (Ph. Eur. *2.2.3*): 2.5 to 3.5.

Microbiological purity (Ph. Eur. *5.1.4*). Complies.

Related substances. Liquid chromatography (Ph. Eur. *2.2.29*)…

Assay. Liquid chromatography (Ph. Eur. *2.2.29*) as described in the test for related substances with the following modifications…

Methyl parahydroxybenzoate. Liquid chromatography (Ph. Eur. *2.2.29*) as described in the test for related substances with the following modifications...

STORAGE

Expiry time:

- *overall shelf-life*: 6 months (including in-use period);
- *in-use shelf-life*: not determined experimentally, 6 months suggested [5].

Storage conditions: below 25 °C, protect from light, do not store in fridge or freezer. Not tested at higher temperatures or under different conditions (e.g. exposure to light).

REFERENCES

Main source: Dutch Pharmacist's Formulary (FNA), Royal Dutch Pharmacists Association (KNMP), Laboratory of Dutch pharmacists (LNA), the Netherlands.

Date of source monograph: 2008 (last revision: 2013).

Additional references:

1. Mollica JA, Rehm CR, Smith JB. Hydrolysis of Hydrochlorothiazide. *Journal of Pharmaceutical Sciences*. 1969;**58**(5):635-6…

Fig. 2: Abbreviated version of Hydrochlorothiazide 0.5 mg/mL oral solution monograph https://paedform.edqm.eu/app/epf/content/default/F0001E.htm

What next?

Monographs currently under development:

- ➢ Azathioprine oral suspension
- ➢ Chloral hydrate oral solution
- ➢ Furosemide oral solution
- ➢ Isoniazid oral solution
- ➢ Omeprazole oral suspension
- ➢ Phosphate oral solution
- ➢ Ranitidine oral solution
- ➢ Oral vehicle

Further prioritised items will be added as they are completed. Draft monographs for public consultation and final texts will be made available on https://paedform.edqm.eu.

Fig. 3: Current status of the PaedForm project

Possible new additions:

Etoposide oral solution
Ethambutol oral solution
Lorazepam oral solution
Midazolam nasal spray
Pyrazinamide oral solution
Other dosage forms

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