The start of PaedForm - a pan-European Paediatric Formulary

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INTRODUCTION

The formulary will collect together on a pan-European level formulations for extemporaneous preparation currently described in national formularies, or those which are well-established in European countries, and make them freely available. Pharmacists and clinicians will be provided with formulations of appropriate quality to allow preparation when no licensed alternative is available on the market. The project has been launched by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the European Pharmacopoeia Commission (for which the EDQM provides the Scientific Secretariat).

CRITERIA FOR SELECTION OF MONOGRAPHS

Positive assessment for use of active substance including:
- is of therapeutic benefit
- relevant to current practice
- no safety signals

In addition:
- no authorised products with age-appropriate dosage form available
- excipients not harmful
- all excipients necessary and suitable for their intended use
- active substance and excipients comply with Ph. Eur.
- evidence on stability

SELECTED PARTS OF A PAEDFORM MONOGRAPH

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 mg of hydrochlorothiazide per mL of the hydrochlorothiazide label claim.

CONTENT OF METHYL PARAHYDROXYBENZOATE: 1.00 mg per mL.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per 107.7 g:
- Purified water 85.4 g
- Sucrose 20.16 g
- Disodium phosphate dodecahydrate 0.835 g
- Citric acid monohydrate 0.87 g
- Propylene glycol 0.275 g
- Methyl parahydroxybenzoate 0.077 g
- Essentiens aurantii 0.052 g
- Sodium formaldehyde sulfoxylate 20.16 g
- Purified water 85.4 g

ADDITIONAL INFORMATION

1. The formulation contains 1.00 mg of propylene glycol per mL.
2. The formulation contains 0.77 mg of methyl parahydroxybenzoate per mL.
3. The concentration of methyl parahydroxybenzoate is lower than 0.1% because of the risk of precipitation, and therefore the storage period is limited to 6 months.
4. The concentration of 0.5 mg/mL of hydrochlorothiazide is the maximum concentration that gives a clear liquid with a limited amount of co-solvent.
5. Grinding hydrochlorothiazide powder before preparation may shorten the dissolution time during manufacturing.
6. The concentration of 0.5 mg/mL hydrochlorothiazide is limited to 6 per cent, resulting in a negligible concentration of formaldehyde.
7. The pH value is set to 2.5 because of better taste and reduced hydrolysis.

PRODUCTION

Ingredients:
- Production steps:
1. Dissolve citric acid monohydrate and dixiodum phosphate in 70 g of purified water.
2. Mix a syrupus simplex FNA with this solution.
3. Dissolve in this mixture hydrochlorothiazide by heating the solution to 60°C and stirring.
4. Add methyl parahydroxybenzoate and propylene glycol concentrated solution to the warm solution.
5. Cool to room temperature.
6. Add 0.052 g of essentiens aurantii.
7. Add purified water to reach a final mass of 107.7 g and mix.

PROCESS control:

LABELLING

QUALITY CONTROL

Appearance: Clear, colourless liquid.
- Identification:
  - Assay: PH 2.2-3.0, 25-30°C.
  - Microbiological purity (2.1.4). Complies.
- Related substances: Liquid chromatography (2.2.29).
- Assay: Liquid chromatography (2.2.29) as described in the test for related substances.

STORAGE

REFERENCES

Source: Formulary of Dutch Pharmacists (FNA).

METHODS AND ONGOING WORK

- The dedicated PaedF working party comprises 17 experts from hospital pharmacists, academia and national authorities from 14 countries.
- The experts started with prioritisation based on paediatric needs published by the EMA Paediatric Committee and criteria for the formulary adopted by the CD-P-PH.
- The formulations available for a specific preparation of high priority will be screened and a final selection will be made.
- Draft texts will be made available by the EDQM for public consultation for 3 months (first ones foreseen by the end of 2018).
- The online formulary will be subsequently extended and regularly reviewed.

RESULTS

- The work on prioritisation is partly completed.
- The first two pilot monographs (Hydrochlorothiazide 0.5 mg/mL oral solution and Sotalol 20 mg/mL oral solution) are in final drafting stage before public enquiry.
- An explanatory text with general principles will be published together with the 2 monographs.
- 6 additional monographs have been added to the work programme.
  - Furosemide 80 mg/mL intravenous solution
  - Ranitidine 15 mg/mL oral solution

CONCLUSIONS

This project is still in its infancy. With the upcoming public enquiry of the first monographs in the end of 2018, it will be visible to a larger audience. With the aim of all stakeholders, the formulary can in future fulfil its aims: to be an easily accessible, science-based online tool with a collection of child-appropriate formulations that supports its users by promoting the health of children in all countries where no licensed medicine is available.

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