Working group “Psycho-Social Care from Fetus to Adult” of the Association for European Paediatric Cardiology (AEPC)

Health and insurance aspects for CHD-patients in Europe

**Safer drugs for CHD-patients**

Prof. Dr. Stephanie Läer

Department of Clinical Pharmacy and Pharmacotherapy, Heinrich-Heine-Universität Düsseldorf, Germany

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**Drug development**

- Quality
- Safety
- Efficacy
Paediatric regulation EU

Improve health of children in Europe by:

- Facilitating development and availability of medicines
- Ensuring medicines for use in children are of high quality, ethically researched and authorised appropriately
- Improving availability of information on use of medicines

Drug Development Paradigm and Point of Consideration for Paediatric Studies

Off-label use

Definition

Off-label Use
A use of the drug that is outside of its authorized product license as defined in the Summary of Product Characteristics (SmPC)

Unlicenced Use
A use of a drug which is not licensed (in the country)

Drug use in children

Off-label use in Germany

Children and adolescents in outpatients: about 15%

In patients university clinic: about 30%

Premature and neonates: 70%

Off-label use is higher in small and young patients
High unlicensed and off-label use of medicines in children in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Setting/population</th>
<th>Unlicensed and off-label use of prescriptions of children</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Children’s hospital</td>
<td>25 % 36 %</td>
<td>Turner et al 1998</td>
</tr>
<tr>
<td>UK, S, D, I, NL</td>
<td>Children’s hospitals</td>
<td>46 % 67 %</td>
<td>Conroy et al 2000</td>
</tr>
<tr>
<td>UK</td>
<td>General practice</td>
<td>11 % 65 %</td>
<td>McIntyre et al 2000</td>
</tr>
<tr>
<td>F</td>
<td>Office based paediat</td>
<td>33 % 56 %</td>
<td>Chalumeau et al 2000</td>
</tr>
<tr>
<td>NL</td>
<td>Children’s hospital</td>
<td>66 % 90 %</td>
<td>’t Jong et al 2001</td>
</tr>
<tr>
<td>IR</td>
<td>District hospital ward</td>
<td>23 % 43 %</td>
<td>Craig et al 2001</td>
</tr>
</tbody>
</table>

*Unlicensed = Not licensed for children at all.*
*Off-label = Prescribed outside the terms of the product license (not licensed for the age group, not licensed formulation, not licensed route of administration)*

Off-label use - the problem

- Lack of age-related dosing guidelines
- Lack of age-related adverse effect profiles

Pharmacotherapy in children?

Is there a relation between off-label use and adverse events?
Off-label use and adverse events

<table>
<thead>
<tr>
<th>In patients</th>
<th>Out patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events due to label use</td>
<td>3.9%</td>
</tr>
<tr>
<td>Adverse events due to off-label use</td>
<td>6%</td>
</tr>
</tbody>
</table>


Heart failure in children

Pediatric and adult heart failure: epidemiology and drug treatment

Enalapril Maleate

- marketed in Europe since 1983
- prolonging survival in adult patients with hypertension, cardiac failure, and chronic renal disease
- first-line treatment for chronic heart failure (CHF) in children
  (European Medicines Agency Expert Group Meeting on Paediatric Heart Failure)
- only labelled for children >20 kg
- no licensed formulation suitable for children or for patients who cannot swallow a capsule or tablet in Europe:
  problems with chemical stability in solutions
- => included in the priority list for studies of off-patent paediatric medicinal products for CHF, hypertension, and chronic renal disease
  (EMA 2012).

Enalapril suspension – a problem for small children

Absorption, distribution, metabolism and elimination of enalapril in adults: prodrug for enalaprilat

In adults:
- Conversion rate = 70% Tmax 3-4 h

**Effect of maturation and growth for enalapril?**
Orodispersible mini-tablets

Progress in pharmaceutical development of paediatric formulations – practical examples

A real opportunity for children with heart failure

Thank You!

Stephanie.laeer@uni-duesseldorf.de
http://www.pharmazie.uni-duesseldorf.de/Institute/klin_pharm