EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on the Standard EudraVigilance Paediatric Query

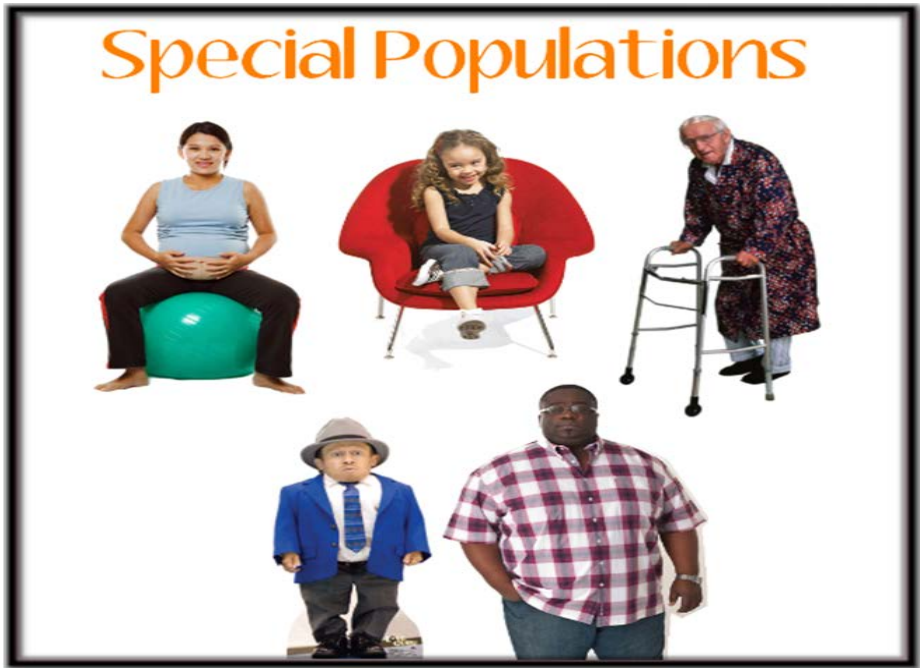
Paediatric workshop – 28 April 2014

Presented by: Cosimo Zaccaria
Signal Management – Pharmacovigilance Department

An agency of the European Union

- *Safety in the Special population*
- *PhV obligations*
- *EudraVigilance overview*
- *Paediatric queries*
- *Future implications and usefulness of EV paediatric queries*
- *Conclusions*

Introduction



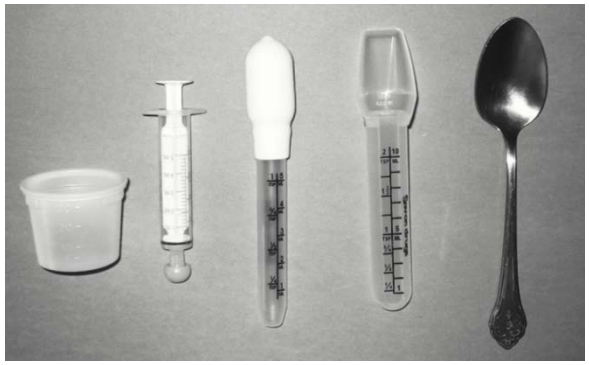
- Paediatric population: age ≤ 18 y/o
- Pregnant women
- Elderly population
- Population with genetic conditions
- Groups with specific disease
- Etc…

Would the presence of this special condition alter the effects of the drug producing more or different adverse events?

Off-label use of medicinal products in children

Use in children despite a relative lack of information on how to prescribe safely:

- Dosing error – medication error



- More severe ADRs or different from what is known in adults.

- Higher underreporting in children vs adults

- Risk/benefit balance in children could change

How to improve the health in children

- Increase high quality, ethical **research** into medicines for children
- Increase **availability** of authorised medicines for children
- Pharmacovigilance : Improve **Paediatric Signal Detection**
- Increase **information** on medicines

Achieve the above:

Without unnecessary studies in children

The EU Paediatric Regulation 1901/2006

New obligations for Pharmacovigilance: it is essential to ensure that PhV mechanisms are adapted to meet the specific challenges of collecting safety data in the paediatric population, including data on possible long-term effects.

1. **Obligations for new applications (PIP/waivers/Deferrals)**

2. **Obligations for approved products: Article 45 & 46** aiming at not repeating studies that have previously been performed. Impact in reducing ADRs

Main aim: improve paediatric health without delaying authorization for adults

Monitoring of drugs in the paediatric population

Pharmacovigilance

1) **Standard Paediatric query**

2) **Paediatric Signal Detection**

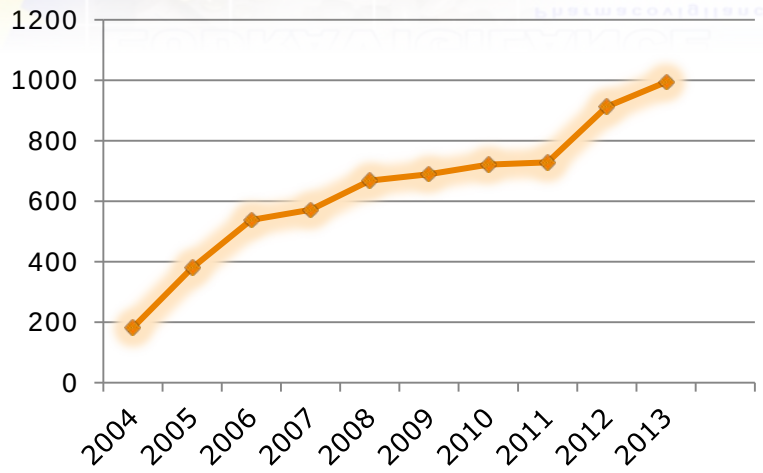
Post-Authorisation reports (ICSRs): EVPM

- Children:249 .776 **98 %**
- Adult: 3.094.729 **93.5 %**

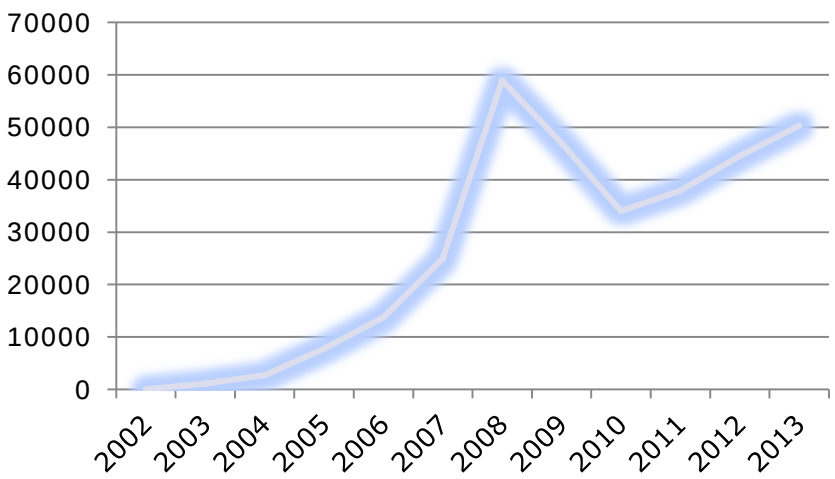
Clinical Trial reports (SUSARs): EVCT

- Paediatrics: 6.684 **2 %**
- Adults 216.164 **6.5 %**

Paed. EVCT overtime

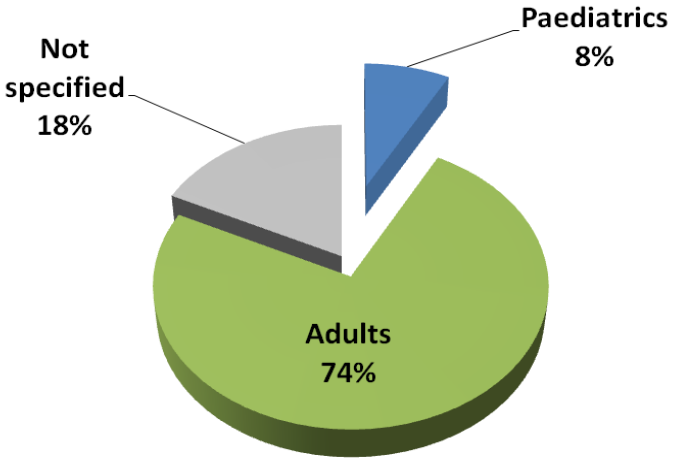


Paed. EVPM overtime

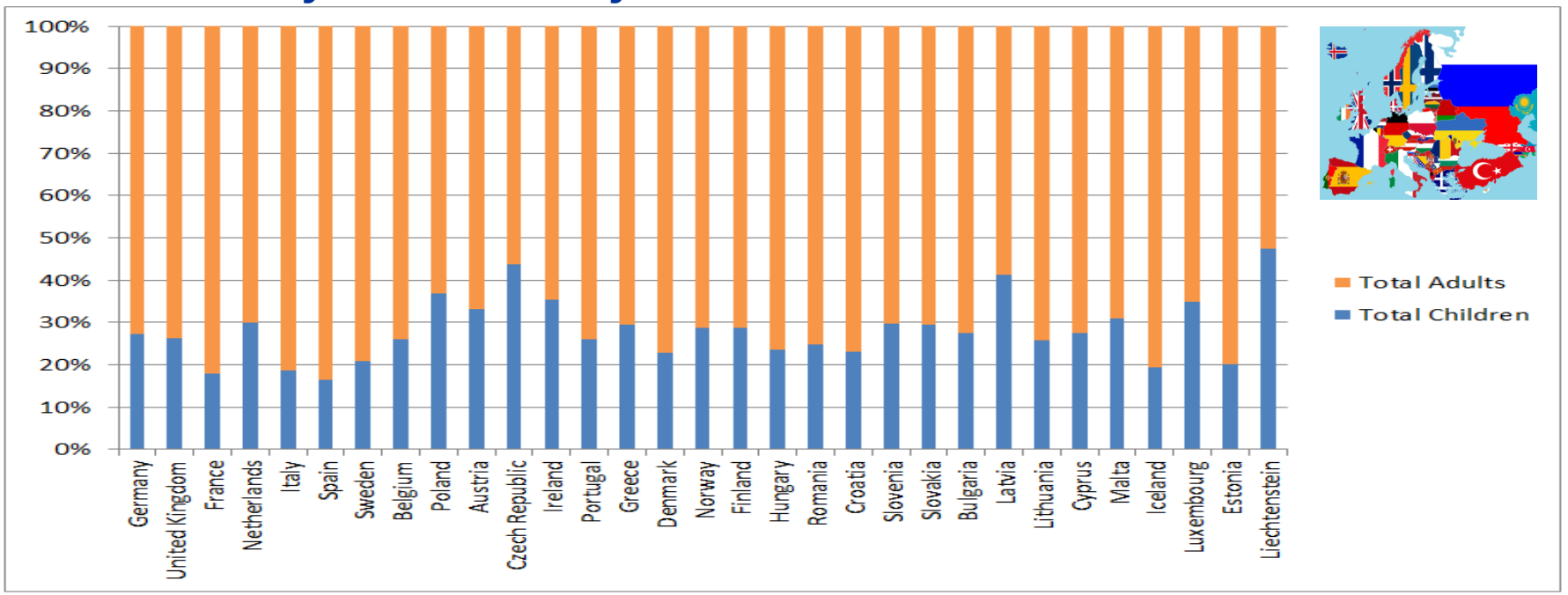


Children vs Adults

TOTAL EV = ~4.5 million ICSRs



Tot ICSRs by EEA Country



Access Policy – external requests

- Written requests (including emails) for access to any document originated, received or held by the Agency
- Proactive disclosure of EMA documents through website or other sources
- Protection of commercial and confidential information, personal data and conflicting interest+

Standard EV paediatric query – internal requests

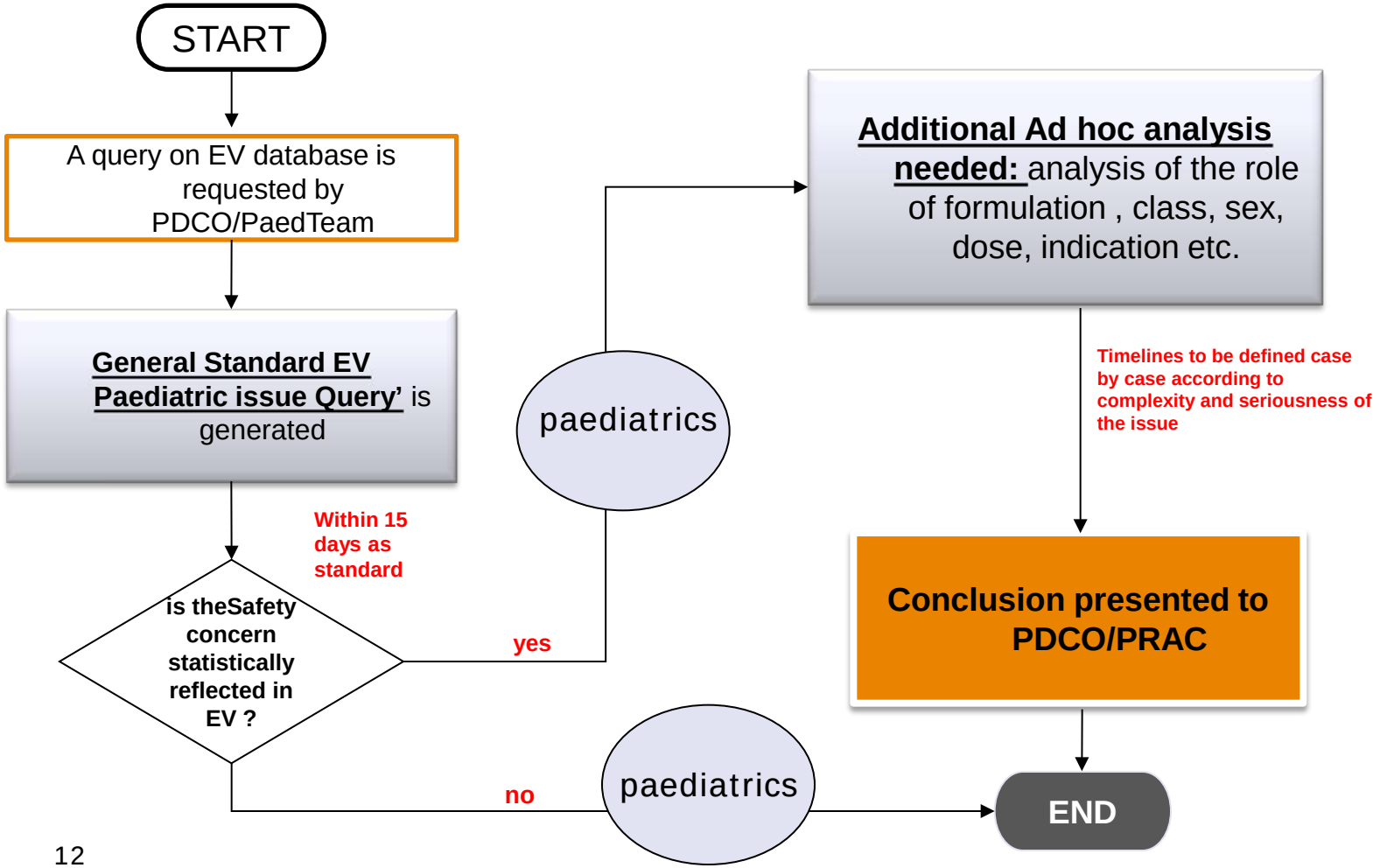
"General" standard EV paediatric query (routine)

- **any evidence of the rumour in the paediatric profile reported in EV in the paediatric population?**
- **any differences as compared to the adult population ?**
- **any specific paediatric age group at risk taking in account the progressive maturation of the organ involved?**

" Detailed "standard EV paediatric query (ad hoc query)

- issue specific to the product/substance or exists for the all **class**?
- role of the specific **formulation**(s) used in the paediatric population?
- any specific paediatric age group at risk taking in account the progressive maturation of the different **functions of the organ** involved
- Any other paediatric specificities ? **Dose? Duration? Indication?** …(ad hoc)

General Standard EV Paediatric Query (SEVPQ) triggered by PDCO



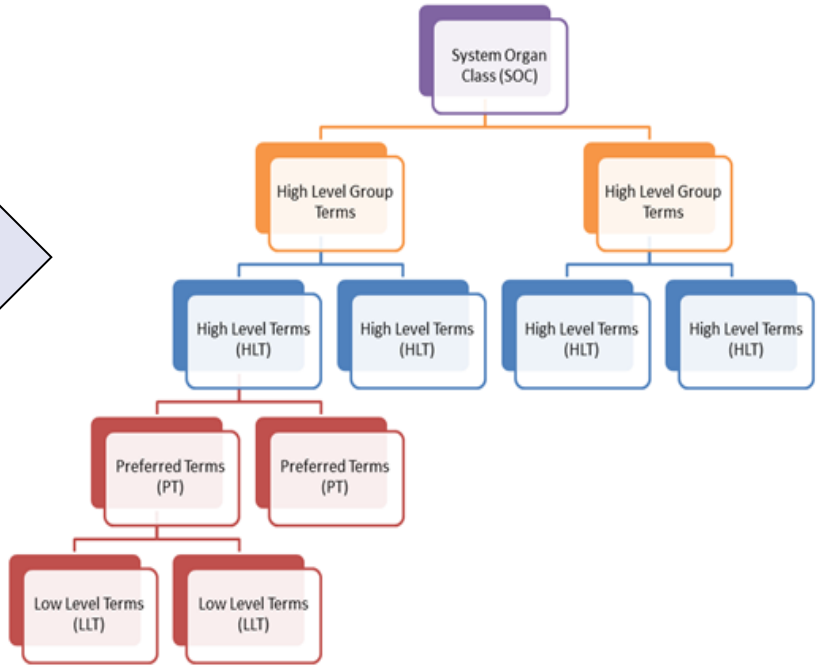
Request of a Standard EV paediatric query

Template for internal request

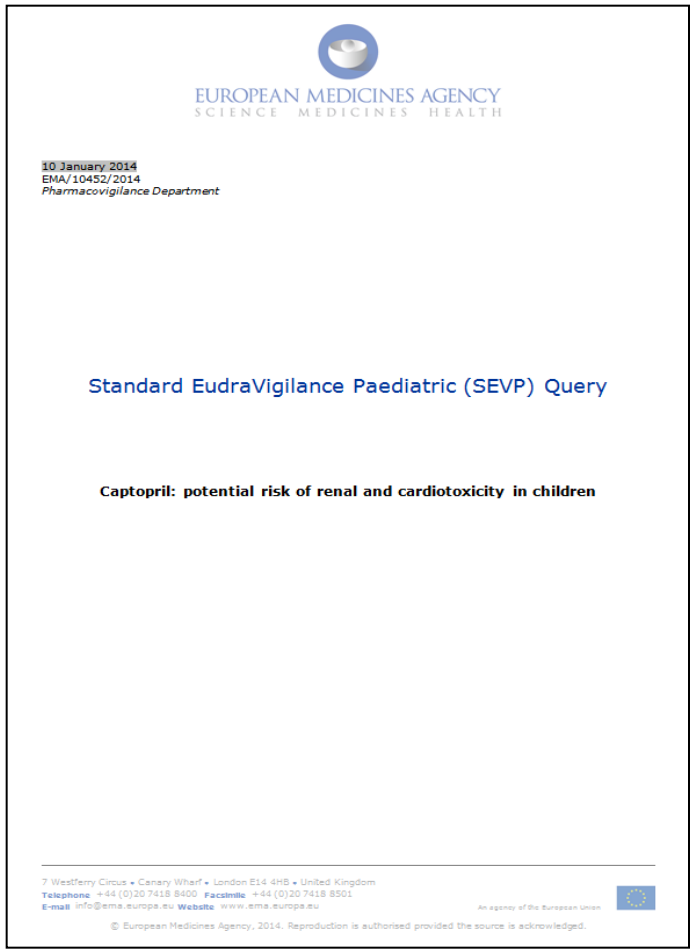
Request for Standard EudraVigilance Paediatric Query

EMA Contact points:
Request to be sent by email to P-PV-Helpdesk@ema.europa.eu in specifying "standard EV paediatric query" in the title of the message
To be completed by Paediatric Medicines section contact point:
Date of the request: 25 Nov 2013 Deadline for results: 15 Jan 2013 (apologies for the short deadline but the next PDCO takes place on 4-6 Dec and the Committee really needs these data so your quick help would be much appreciated!)
Active substance: captopril Medicinal Product(s): all Pharmacological class: ACE inhibitor ATC code : CO9AA01 Indications considered for the PIP: Treatment of heart failure Description of the Issue/Rumour (main safety issue and detailed characteristics if any) *Animal data suggests that the substance has a potential for renal and cardiovascular toxicity, particularly in neonates.* Is it related to any adverse drug reaction already known for this medicinal product/active substance in adults? Yes ☐ No ☒ Please specify: <text> Basic information about the medicinal product /active substance, its known safety profile and its use in children (free text, please use verso of the form if needed) *Captopril is widely used off-label in extemporaneous formulations for paediatric cardiology. The applicant is now developing an age-appropriate oral liquid formulation for paediatric use but requests a waiver for the youngest subsets on the grounds of safety concerns.* *Given the unquestionable clinical need for ACE-inhibitors in paediatrics including neonates, renal and*

MedDRA Medical Dictionary for Regulatory Activities



General Standard EV paediatric query



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 January 2014
EMA/10452/2014
Pharmacovigilance Department

Standard EudraVigilance Paediatric (SEVP) Query

Captopril: potential risk of renal and cardiotoxicity in children

7 Westferry Circus ▪ Canary Wharf ▪ London E14 4HB ▪ United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8501
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

1. Introduction

1. Description of the safety concern

2. Query results

2.1 General paediatric ADR profile for the product/active substance
2.2 Analysis of the specific issue in the paediatric population

2.3 analysis of the specific paediatric issue per age group

3. Summary and conclusions

Confirmation whether the risk is reflected or not in EV

4. Annexes

Standard Paediatric Query since 2010

7 out of 9 reports reflected the risk in EV

1. Captopril & **nephrotoxicity – reflected in EV**
2. Cisplatin & **Ototoxicity - reflected in EV**

Pilot phase 2009-2010

3. Gadobutrol & **Nephrogenic Systemic Fibrosis - not reflected**

2011

4. Metoclopramide & **Neurotoxicity - reflected in EV**
5. Fenofibrate & **Rhabdomyolysis** - not reflected

2012

6. Terbinafine & **haematopoietic cytopenias – reflected in EV**
7. Previgen & haemolytic disorders - **reflected in EV**
8. Enalapril & Renal and Cardiotoxicity - **reflected in EV**
9. Captopril & **Renal Cardiotoxicity – reflected in EV**

2013

Captopril and Renal Toxicity as an example

Introduction

1. Basic information

Captopril is an ACE inhibitor used for the treatment of hypertension and some types of congestive heart failure. Nephrotoxicity is an adverse reaction already recognized in adults for Captopril.

2. Information on the known safety profile

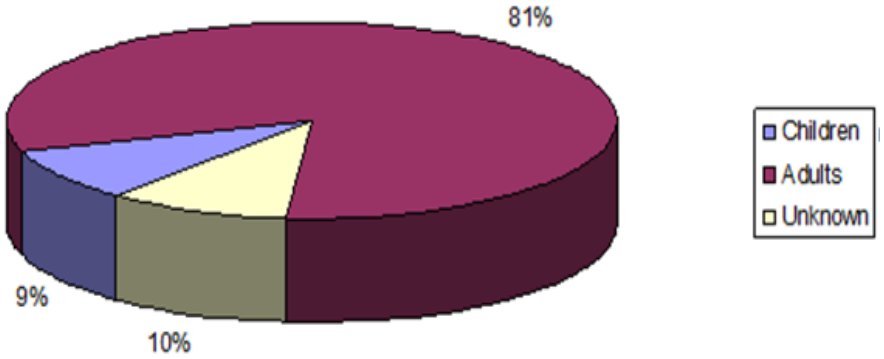
Adverse effects of Captopril include cough, angioedema, agranulocystosis, proteinuria, hyperkalemia, taste alteration, teratogenicity, postural hypotension, ***acute renal failure*** *and leukopenia*

3. Uses in children

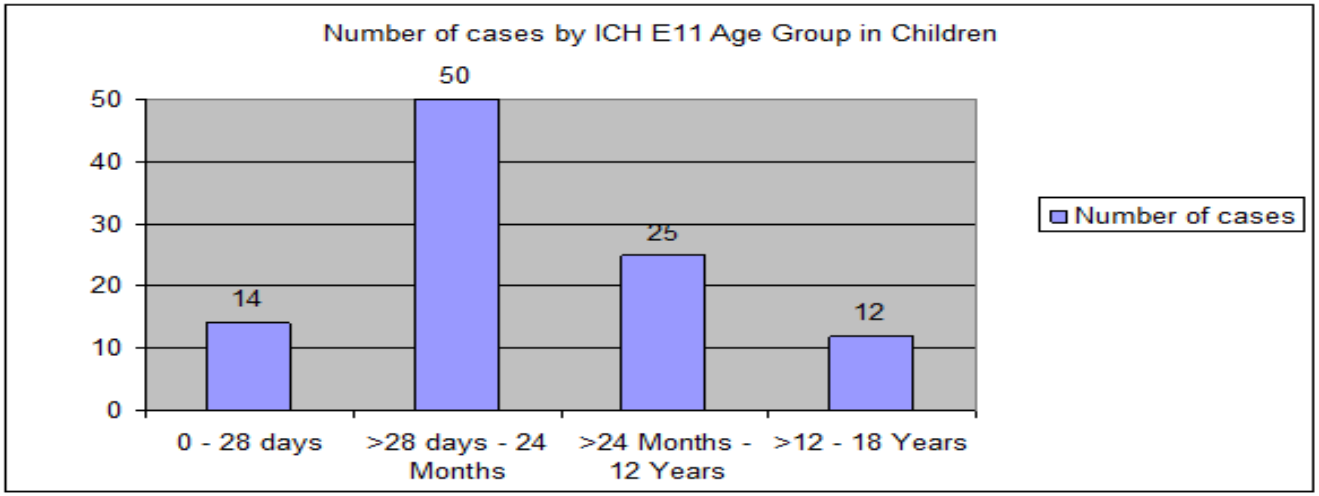
Experience with Captopril in children is limited. The BNFC refers to the use of captopril in hypertension, heart failure, ***proteinuria in nephritis****, or diabetic nephropathy.*

Captopril and Renal Toxicity as an example

1. **Graph comparing the number of paediatric and non-paediatric cases:**

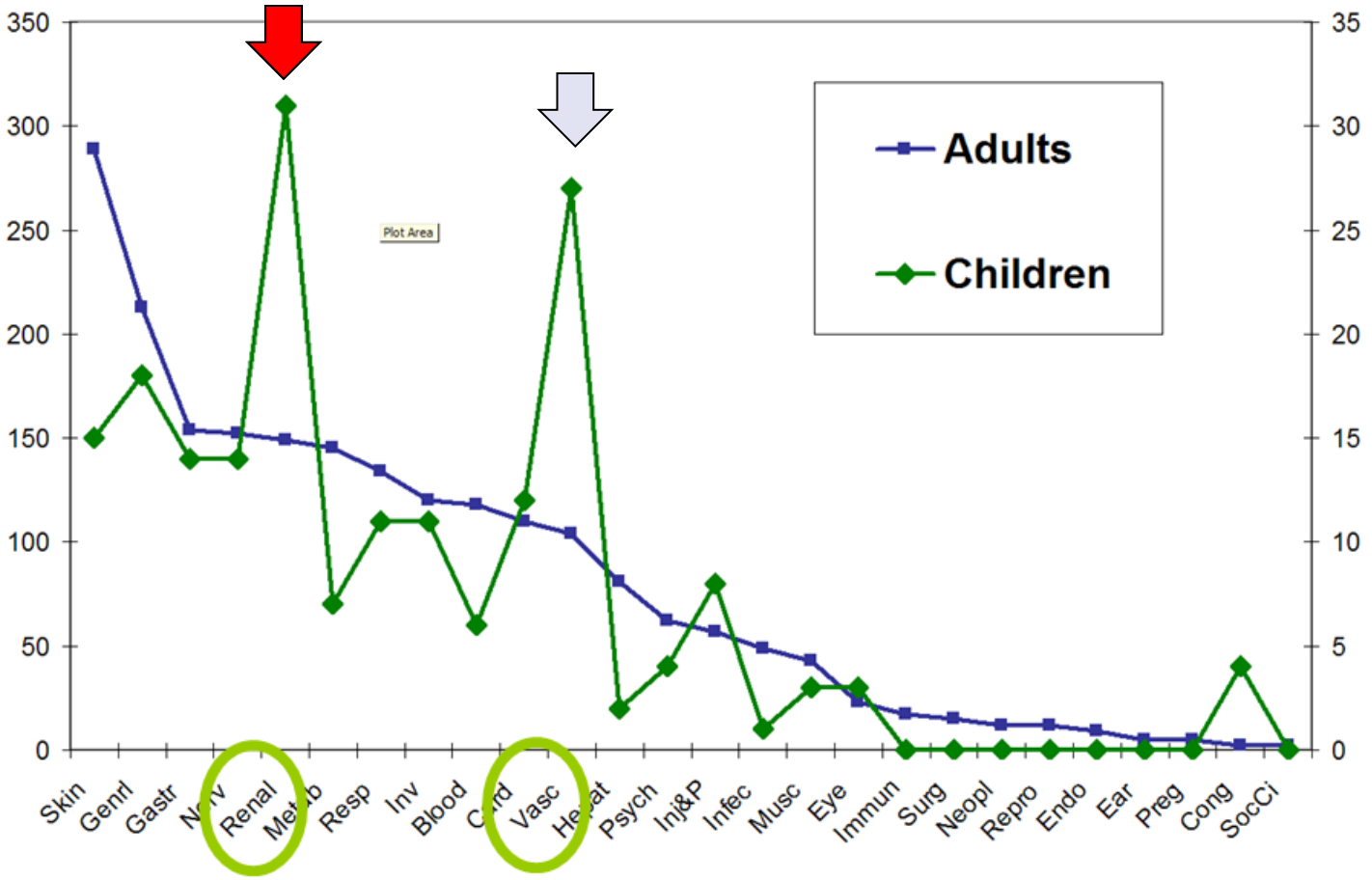


2. **Number of Paediatric ADRs by ICH E11 age group categories**



Captopril and Renal Toxicity as an example

3. General paediatric profile per SOC versus Adult ADRs:



Captopril and Renal Toxicity as an example

4. Statistical analysis : Paediatric PRR ratios at SOC level ' Renal and Urinary Disorders'

PRR-ratio statistic 1 : children vs. adult based on all cases reported **for Captopril**

Captopril cases for SOC 'Renal and urinary disorders' in children **31**
/Captopril cases in children **101**

Captopril cases for SOC 'Renal and urinary disorders' in adult **122**
/Captopril cases in adult **936**

Ratio= 2.35 CI 1.68- 3.30

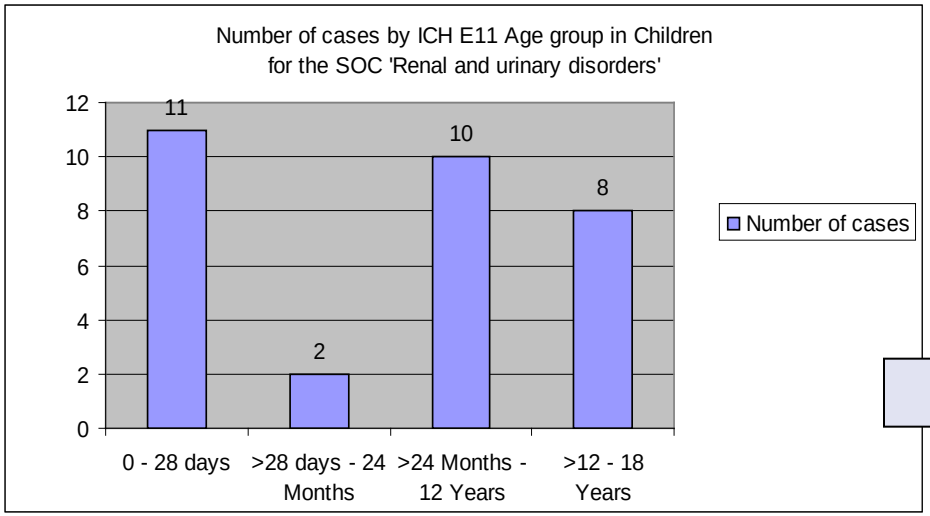
PRR-Ratio statistic 2 : Captopril vs. all other products based on **paediatric cases only**

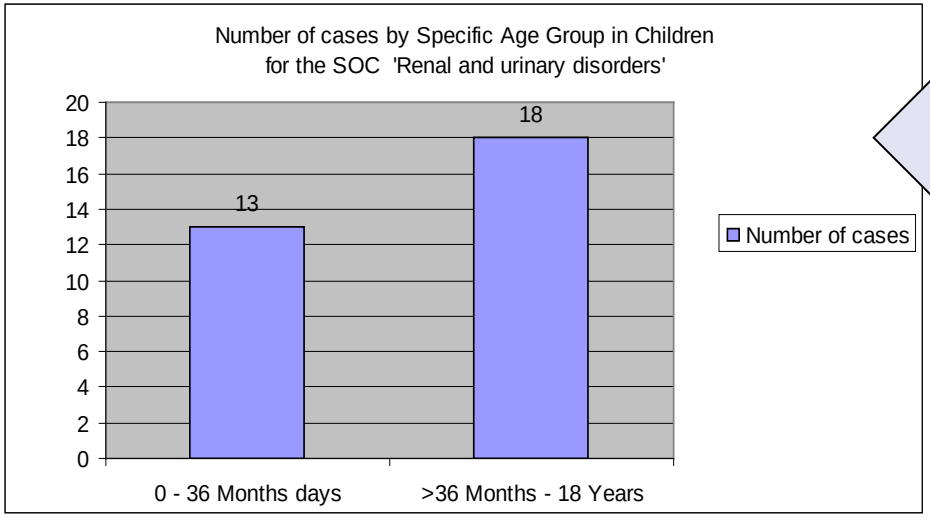
Captopril paediatric cases for the SOC 'Renal and urinary disorders' **31**
All Captopril paediatric cases **101**

All other drugs paediatric cases for the SOC 'Renal and urinary disorders' **7141**
/All other drugs paediatric cases **217 998**

Ratio = 9.37 CI 6.98 – 12.57

Stratification by Age according to the organ maturation





RENAL SYSTEM MATURATION TABLE FOR PHARMACOVIGILANCE ASSESSMENT PURPOSES

Renal system Function / Age subsets	0 – 1 year	1 – 2 years	2 – 3 years	Up to 18 years
Glomerular filtration rate (GFR)	Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area increases more slowly to reach adult levels **between 1 to 2 years of age.**			
Tubular secretion	The renal tubular secretion capacity increases over the first months of life and then declines to reach the adult level (per unit of body area) at **~ 7 months to 1 year of age.** The organic anion pathway matures faster than the organic pathway.			
Tubular reabsorbtion	The development and maturation of the glomerular permeability functions and the renal tubular reabsorbtion are gradual and continuous processes from **birth** to **adolescence**. The key stage of their maturation is at **~ 1 and 3 years of age.**			

General Standard EV paediatric query

4. Summary and conclusions

Nephrotoxicity of captopril as an example

- The nephrotoxicity of Captopril **is considered reflected** in the paediatric data available in EV.
- In terms of proportion, cases of nephrotoxicity have been reported **in children more than in adults** for the SOC 'Renal and Urinary disorders'.
- **Further evaluation is recommended.**

Limitations

*The limitations of spontaneous reporting should always be taken in account in the interpretation of the results. The **query does not evaluate the causality or the incidence** of the reaction in the paediatric population.*

The absence of evidence for the paediatric population considered in EudraVigilance **does not prove the absence of the safety issue**. The low number of reports may be due to a limitation in exposure or to underreporting.

*It should be noted that there is currently no '**gold standard**' method or threshold for significance established and that further studies are necessary.*

Future Steps

1. **PDCO adoption of the pre-defined age groups for other target organs:** liver, brain, skin etc.

2. **Review usefulness of the Paediatric queries** … outcome of the workshop

3. **Implication of the PRAC**

Brighter future: based on safety data identify the patient who most benefit from treatment

- Special population may require **ad-hoc analyses** focusing on post-marketing data
- Monitor efficacy of the **PhV system**, improve quality of reporting (age, co-morbidities, co-medications)
- **Use SEVP Query to trigger**:

1. **Signal** leading to Risk minimisation (e.g. labelling)
2. **Risk communication** – emphasise aspects relevant to paed.
3. **Post-authorization safety studies** (PASS) – target paed. ADRs
4. **Long term follow up studies** – detect drug-induced and development disorders

Thank you