EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Report on the survey of all paediatric uses of medicinal products in Europe

established according to article 42 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use

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Regulation (EC) No 1901/2006 on medicinal products for paediatric use - the "Paediatric Regulation"

Article 42

Member States shall collect available data on all existing uses of medicinal products in the paediatric population and shall communicate these data to the Agency by 26 January 2009.

The Paediatric Committee shall provide guidance on the content and the format of the data to be collected by 26 October 2007.

PDCO guidance for data collection (I)

Information collected:

- Member State
- Source of information
- Name of medicinal product
- Authorisation status of the product in the MS
- Condition/disease
- Treatment/prevention/diagnosis
- Formulation
- Setting
- Age group
- Route of administration

PDCO guidance for data collection (II)

- Dose/dose range
- Treatment duration
- Estimate of the extent of use
- Actual use authorised
- Actual use off-label
- Authorised indications
- Information on safety

Expectations

- to provide general statistics on the frequency and extent of use of medicinal products in children.

- supplied data would have:
  - some degree of heterogeneity
  - a different level of detail and completeness.

Results (I)

- The most frequent medicines used off-label / unauthorised:
  - antiarrhythmics,
  - antihypertensives (rennin-angiotensin inhibitors and beta-blockers),
  - proton pump inhibitors and H2-receptor antagonists,
  - antiasthmatics, and
  - antidepressants (mainly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants).
- High rate of off-label use of oral contraceptives in adolescents
  - mainly in Scandinavia.

Results (II)

- Extensive off-label use of antimicrobials in very young children.
  - macrolides
  - betalactamines plus betalactamase inhibitors
  - carbapenems

- Corticosteroids (dexamethasone) used off-label in the systemic treatment of very young children.
  - Some for systemic use (e.g. dexamethasone) are not even authorised in some countries (Norway).

Results (III)

- Analysis of the pharmaceutical forms:
  - both oral and parenteral formulations are being used unauthorised or off-label,
  - common reason: lack of appropriate dosages and strengths for the treated age groups.
- off-label use of
  - multivitamins
  - many antiasthmatics.

Limitations of the analysis (I)

- Some Member States did not submit any data
  - Some large states did not submit/collect data
- Data not fully representative (more than 50% of the EU paediatric population not covered).
- Submitted data did not overlap with the guidance issued by the Paediatric Committee
- Data heterogeneity was present (exercise was based on **existing data**)
- A prospective survey would have required extensive resources including funding.

Limitations of the analysis (II)

- Some datasets did not distinguish between authorised, unauthorised and off-label use of medicines.
- The definitions of the 'uses' of medicinal products (authorised, unauthorised, off-label) were subject to different interpretations
  - e.g. extemporaneous medicinal products are either considered unauthorised or off-label in the Member States.
- The status of a medicinal product does differ between countries, i.e. a product that is authorised in one MS is not in another.
- Reports on the OTC medicine use are subject to recall bias.

Limitations of the analysis (III)

- Absence of quantitative measurement of the extent of use ⇨ "number of appearances" of a product or product class in each dataset.

- Every method used to quantify the paediatric extent of use is subject to individual limitations

- DDD is defined in adults, so this may be inaccurate in children.

- Not all medicines have a WHO-assigned DDD.

Limitations of the analysis (IV)

- Paediatric safety, which was one of the objectives of the survey, has not been addressed by the data received (with just one exception).

Discussion(I)

- Prescriptions of off-label/unauthorised medicines for children is widespread throughout the European Union:
  - between 45-60% of the total number of prescriptions from this survey
- Both hospitalised children and out-patients are frequently treated with medicines used outside the terms of their marketing authorisation.
  - Higher rates in the premature (up to 90% of prescribed medication) and term neonates and in infants, as well as in patients having serious conditions and being admitted in the intensive care units (both neonates and paediatric).

Discussion(II)

- Medicines are mainly used "unapproved" for the treatment of children, with lower figures for prevention.

- main areas of needs:
  - oral contraceptives in adolescents,
  - gastro-enterology (reflux),
  - cardiovascular (hypertension),
  - respiratory (asthma).

Discussion(III)

- data submitted confirm that the neonates, in particular preterm neonates, have high unmet needs.

- The future will have to address those needs through dedicated trials despite the feasibility issues.

Regulatory actions (I)

a. The medicinal product is authorised in some, but not all the Member States and is therefore used as unauthorised in some countries.

Regulatory action at Member States level, in particular through the CMDh to make those products available in all the Member States.

Regulatory actions (II)

b. The medicinal product is authorised, but used off-label in the respective age groups / indication / route of administration/dose/formulation.

Art 45: widening indications, doses and information if the data submitted are of sufficient quality. Otherwise, it is hoped that the PUMA may answer some of the needs.

Conclusions

- Unmet needs are in some major therapeutic areas;
- Not sufficient information to safety;
- Generalisability of data not certain;
- A tool for the PDCO to establish the inventory of paediatric needs (art 43 of the Regulation).