EMA workshop on Extrapolation of Efficacy and Safety in medicine development across age groups

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European Medicines Agency

Paediatric
Pulmonary arterial hypertension

Regulatory Perspective

Presented by

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Disclaimer: Any viewpoints represented in this talk are not necessarily those of EMA or the Dutch MEB.

Presented data are available on public websites.

Pulmonary Arterial Hypertension

Orphan disease with active development (Companies and regulators)

Definition:

An increase in mean pulmonary arterial pressure
≥25 mmHg, assessed by **right heart catheterization**.

Paediatric addendum to CHMP guideline for PAH

- 5 June 2012

- Allows extrapolation of adult to paediatric population for medicinal products where the benefit-risk profile is known in adult PAH

Vasodilators*: prostanoids, endothelin receptor blockers and phosphodiesterdase-5-inhibitors*.

- An extensive paediatric development is not foreseen
- Main issue is defining the therapeutic dose, short and long term safety
- Considering their MoA, the primary endpoint for the dose-finding study should be **haemodynamic parameters** measured at 12 weeks.

10 drugs developed for adults

1 drug with Paediatric indication

1 drug with paediatric formulation and "some' paediatric dosing guidance.

Off label use…..

Revatio (Sildenafil)

Single clinical study

- 5 years
- 250 patients
- PEP: change in exercise capacity (CPET) in children able to exercise, and on haemodynamic parameters in younger children at week 16.
- Three dose levels were investigated.

Section 4.1:

Paediatric population

Treatment of paediatric patients aged 1 year to 17 years old with PAH.

Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown

…(see section 5.1).

Tracleer (bosentan)

Paediatric studies did not result in an actual indication

Section 4.2:
Paediatric population
Paediatric pharmacokinetic data have shown that bosentan plasma concentrations in children with PAH aged from 1 year to 15 years were on average lower than in adult patients and were not increased by increasing the dose of Tracleer …(dose or frequency) (see section 5.2). Increasing the dose or the dosing frequency will likely not result in additional clinical benefit.

Based on these pharmacokinetic results, when used in children with PAH 1 year and older, the recommended starting and maintenance dose is 2 mg/kg morning and evening.

Section 5.2:

Based on the findings in studies BREATHE-3, FUTURE 1, and FUTURE-3, it appears that the exposure to bosentan reaches a plateau at lower doses in paediatric patients than in adults, and that doses higher than 2 mg/kg twice daily (4 mg/kg twice daily or 2 mg/kg three times daily) will not result in greater exposure to bosentan in paediatric patients.

How to proceed?

- Choice of the endpoint….
  - catheterisation: ethical? Risks? regulators?
  - Exercise capacity: younger patients?
  - **Outside current scope of workshop**

- One proposed way:

  Perform a mortality and morbidity study in children.


C B G
M E B