Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: MD, PhD, MSc paediatric medicine Helle Holst on behalf of Department of Clinical Pharmacology, Bispebjerg Hospital, University of Copenhagen
Transparency Register ID number (for organisations): _____

Country: Denmark

E-mail address: helle.holst.01@regionh.dk

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Please indicate whether you are replying as:

- o A citizen
- o A business
- o A non-governmental organisation (NGO)
- o An industry association
- o A patient group
- x A healthcare professional organisation
- o A Academia or a research or educational institute
- o A public authority
- o Other (please specify)

If you are a business, please indicate the size of your business

- o Self-employed
- o Micro-enterprise (under 10 employees)
- o Small enterprise (under 50 employees)
- o Medium-sized enterprise (under 250 employees)
- o Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- X Local
- o National
- o Across several countries
- o EU
- o Global

2. PART II – CONSULTATION ITEMS

(You may choose not to reply to every consultation items)

2.1. More medicines for children

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

The Paediatric regulation has unquestionably led to development of many evidence-based paediatric medicines as demonstrated by the number of agreed paediatrics investigation plans (PIPs), and in particularly the number of children enrolled in clinical trials embracing all age groups.
However, we have addressed some areas bellow where the regulation might impede more evidence based medicine for children in our point of view:

First. The link between adult indication and a paediatric investigation plan (PIP)

Since the number of required children enrolled in paediatric trials now exceed almost 1 % of the European paediatric population (page 42, Table 19), and the regulation links the adult indication to the obligation to have a paediatric investigation plan; it might be even more difficult to foster new trials in areas of unmet medical needs in children with high disease burden (Table 11 page 27). This is very well illustrated in the report with lack of PIPs in very common disease such as neonatal gastrointestinal injury (e.g. NEC) and neonatal abstinence syndrome (NAS), page 36 or neurological conditions, such as chemotherapy-induced peripheral neuropathy in paediatric cancer patients (Moor, Groninger, Cureus. 2013). This issue is also partly addressed by the Paediatric committee in the 10 year report page 87-88.

Second. Adoption of PIPs for several medicines for the same condition

The competition for several medicines for the same condition in a limited paediatric patient pool is a well-recognized challenge, page 23 and 87-88. To overcome the limited number of available participants it might be feasible to use data from completed PIP´s and elaborate on data e.g. by modelling and make them available in a non-competitive platform for ongoing trials. Accordingly, each company might contribute but also benefit from data. One example is the completed PIP for Bosentan as adjunctive therapy for persistent pulmonary hypertension (PPHN) in neonates. The main primary outcome was treatment failure, defined as the need for extracorporeal membrane oxygenation (ECMO) or initiation of an alternative pulmonary vasodilator. Recruitment was slower than anticipated, and was below the study goal, (Steinhorn et al, Journal of Pediatrics 2016). The authors considered several reasons for the lower-than-expected recruitment, e.g. the short time frame and between birth, enrollment, and exclusion of infants with congenital diaphragmatic hernia, which has become the most common indication for ECMO support. Even if the recruitment goals had been met (20 bosentan, 10 placebo), a benefit to bosentan would not have been detected for any of the primary outcomes, as the incidence of ECMO cannulation is much lower than first anticipated. Based on these findings, they estimate that enrollment of hundreds of patients would have been required to detect a difference in ECMO utilization. They concluded that these results and recruiting challenges provide important information for the design of future interventional trials for infants with PPHN (Steinhorn et al, Journal of Pediatrics 2016). Two other PIP´s are planned for PPHN both Macitentan (PIP from 1 month of age) and Ambrisentan (PIP from 1 year of age) to be finished 2022. These PIPs are suggested to include neonates as well and might be improved by the experience gained from Bosentan trials.

Third. Modification of agreed PIPs

An applicant may propose changes or request deferral or waivers as stated in article 22 in the paediatric regulation. It isproposed that Paediatric committee (PDCO) may likewise be able to suggest a modification when the PIP has been adopted if e.g. efficacy or safety data has been generated from an academic trial, which might be adopted in in the PIP, in order to avoid duplication of trials. In the newest SmPC for paracetamol i.v. from 2016, it is stated that there are no safety data for premature children. The PIP for paracetamol in children from preterm to 28 days of age (EMEA-000130-PIP01-07) was scheduled to be completed in September 2011 but this PIPs was not completed by the agreed date, and there are no further obligation to complete it (for details see Annex 9, in the Annual report on benefits

and infringements under the Paediatric Regulation dated the13.05.2016.
https://ec.europa.eu/health/sites/health/files/files/paediatrics/2015_annual_report.pdf)
However, the data of i.v. paracetamol are already available in the PARANEO study, which includes 60 neonates and preterm children. The study concluded that the effective compartment concentrations for neonates are similar to children (Allegaert et al, Paediatr Anaesth 2013). These data were supported by pooled data from three related studies (Allegaert et al, Arch Dis Child 2011)

Fourth. Revision of product specific waivers in the current framework
For details please see section 2.8

2.2. Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

There are many new treatment options. In particular we like to highlight:

Extension of indications of TNF-α inhibitors, abatacept (selective T-cell co-stimulator modulator) and tocilizumab (IL-6 monoclonal antibody) to include treatment of various juvenile idiopathic arthritis subtypes in patients from 2 years and above.

Extension of indications of deloratidin to urticarial in addition to a new pharmaceutical form of orodipersible tablets

Extension of indication of levetiracetam to include the treatment of partial onset seizures with or without secondary generalization in adolescents, children, and infants from 1 month of age with epilepsy. Including a user friendly oral solution for use in the youngest population.

Ref For details see, Annex 10 year report to the European commission, page 3-18.

2.3. Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

A significant country-to-country difference continue to exist with the lowest availability of new paediatric medicines in the small countries. This is also confirmed in a recent published paper by Bajcetic et al Curr Pharm Des. 2015, We have collected similar data from Denmark (paper in review). Existing extemporaneously preparations and unlicensed drugs is not always replaced be licensed treatments despite the overall intention of the paediatric regulation. This problem arise as some pharmaceutical companies choose to sell a specific formulation to a subset of the member states even if the product is authorized in all member states. Examples are losartan liquid formulation (10 year report p. 14 and the PIP for losartan potassium) which is not available in the Danish market.

2.4. Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

We recognize that there are substantial costs when developing medicine. However, it seems to be a trend that new medicines is priced very high. We acknowledge that this is a matter for the membership countries, but maybe it should have a place in the general evaluation of a marketing approval. At least for very old drugs of which a lot of evidence on both efficacy and safety data is available.

Recent examples are Peyona® (caffeine citrate) used to treat apnea since the 1970s in premature newborns where the prices has increased 4000 per cent after Chiesi got patent protection of the drug from the European Union and began marketing it throughout the 28 Member States (ref. Danish EU politicians push for legislation reforms on pharmaceutical drug pricing | Reporting the EU – Fall 2016. http://eu2016.mediajungle.dk/2016/10/05/danish-eu-politicians-push-for-legislation-reforms-on-pharmaceutical-drug-pricing/ accessed 28 Dec2016).
Other examples are Hemangiol® 3.75mg/ml, 120 ml (PUMA), versus propranolol extemporaneous preparation oral solution 4 mg/ml ,100 ml approximately 300 per cent as expensive and Revatio(sildenafil) ® 10mg/ml, 60ml, versus sindafanil extemporaneous preparation being 1285 per cent as expensive.

2.5. Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

No comments

2.6. The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

No comments

2.7. Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

There are still some information gaps which need to be considered. Herein, the SmPC is not always updated, e.g. according to the ten year report page 30, captopril is licensed for children between 0 and 18 years of age, whereas according to the SmPC "The efficacy and safety of captopril have not been fully established". Similarly, for Enalapril page 30

2.8. Waivers and the 'mechanism of action' principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

The PDCO has adopted a review of the class waiver list on 23 July 2015. in the 10 year report which resulted in revocation of 8 condition waivers (including 2 cancers), Table 29, page 61. However, a revision of product specific waivers in the existing framework is warranted.
Currently, it is not possible to omit a granted waiver albeit the product is widely used for other conditions in children than original developed for in adults. Cancers that affects children are biologically different from those that affect adults, as also addressed in the 10 year report page 57. Therefore any medicine's mechanism of action needs to be used to guide investigating treatments of the paediatric malignancies and to address the unmet therapeutic needs in paediatric oncology instead of adult indications.
Further, if a waiver granted on the grounds that a condition does not occur in a specific subset e.g for the subset bellow 2 years of age, this incentive should continuously be validated. Current diagnostic criteria might lack sensitivity in certain population such as infants, and new reaches of pathogenesis etc. provide new insight and knowledge of unmet medical needs in the youngest population. E.g. we did a chart review of 383 patients with the diagnosis JIA, of which 182 patients met the inclusion criteria of minimum of 1 biologic drug during a 4-year observation period. The mean age of the population was 12.3 years, however age range was between 1 and 18 years. All Biologic drugs administered to children with JIA holds a waiver for the youngest subset on the ground that the condition does not occur. In addition, infliximab a (TNF) inhibitor holds a waiver covering children from 2 to 18 years granted due to no real advantage over existing treatment. However, it has been shown in several studies that infliximab seems to improve the outcome of childhood uveitis in patients with JIA (ref Tynjälä et al Ann Rheum Dis 2007, Foeldvari et al J Rheumatol 2007) and is widely used for this indication, despite the waiver being granted. Similarlly ,two full waivers have been granted covering the entire population for testosterone on the following grounds: "no benefit over existing treatment" and "the condition does not occur in the paediatric subset", although testosterone is required in replacement treatment for hypogonadism in adolescent boys.

The use in paediatric subset of which the product has been waived should be therefor be monitored, and If the product is used in large scale off label it should then be possible to reevaluate the waiver granted (Haslund-Krog et al, Eur J Clin Pharmacol 2014).

2.9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?

In some cases, studies can be deferred until after the studies in adults have been conducted. This ensures that research in children is done only when it is safe and ethical to do so. On the other hand deferrals can lead to unnecessary delays. Important to note is the fact that dosing regimens, used off-label by clinicians before licensing, might be inappropriate, as previously shown in cases where underdosing of HIV patients was observed (ref Kemper et al Paediatr Anaesth 2011).

This issue has also been raised in a comprehensive review of new antibiotics, which pointed out the need for faster studies on potential paediatric drug use, run in parallel with adult trials, without which between 3 and 5 years might pass before prescribing information becomes available (Garazzino et al Int J Antimicrob Agents 2013)

2.10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?

No comment

2.11. Biosimilars

Consultation item No 11: Do you have any comments on the above?

2.12. PUMA — Paediatric-use marketing authorisation

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

2.13. Scientifically valid and ethically sound — Clinical trials with children

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

What happens if the PIP is made for 1-18 years, the studies in the age range 1-5 years did not provide robust proof of efficacy and therefore no indication is obtained. How can there be a follow up, since the need is still there. E.g. Diovan (PIP for valsartan). During the assessment process, the CHMP consulted the PDCO on the following issues (ref http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diovan_1219_29_Paediatrics/WC500093237.pdf) :

The lack of understanding of the reasons behind the results of the studies in children aged 1 to 5 years, and the possible need for a further study in this age group

If a further study in this age group was to be considered as needed, input on main principles of the design and methodology

The PDCO's response indicated that the reasons behind the inconsistent results seen in the two clinical trials involving patient from 1 to 5 years old are not entirely understood, and it should be noted that no clear and well-established approach exists as to how to design clinical trials for antihypertensive agents in the paediatric population. However, the Assessment report for DIOVAN concluded the clinical need in this age group exists and therefore it would be relevant to conduct a new study as valsartan has shown efficacy in the older age group and there is a pharmacological rationale for its use in secondary hypertension. Further, a post-approval study of long-term effects in CKD and non-CKD patients' needs to be carried out and the efficacy of valsartan in younger age group (having potential impact also to the older children with secondary hypertension) has to be clarified in an additional randomised trial. This Assessment report was dated 19 April 2010, EMA/296504/2010.
Currently, Diovan is still not recommended for use in children below the age of 6 years due to a lack of data on safety and efficacy.

2.14. The question of financial sustainability

Consultation item No 14: Do you have any views on the above and the fact that the

paediatric investigation plan process is currently exempt from the fee system?

2.15. Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

2.16. “Mirror, mirror on the wall” - Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

2.17. Other issues to be considered

Consultation item No 17: Overall, does the Regulation’s implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

When updating the guideline on excipients, it should be considered that neonates are often poly-medicated. Hence, the accumulative amount of e.g ethathol and propylenglycol becomes important. Two examples of relatively new drugs, nationally approved for children: Oramorph contains 0,105 ml/ml of ethanol and Alprostadil contains 1g/100 ml of ethanol (According to SmPC). The suggested limit for ethanol for children below 6 years of age is 6 mg/kg/day. (Questions and Answers on Ethanol in the context of the revision of the guideline on ‘Excipients in the label and package leaflet of medicinal products for human use’ (CPMP/463/00) EMA/CHMP/507988/2013)
We recognize that the PIP in its early stages cannot account for the excipients. However, the content of excipients can be emphasized when the PIP contains an agreement of development of age appropriate oral solutions taking the above consideration into account.