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Human Medicines Research and Development Support Division

Report of the expert meeting on paediatric development of fixed-dose combinations (FDCs) for the treatment of human immunodeficiency virus (HIV) infection

European Medicines Agency, London, 10 November 2015

Introduction

The European Medicines Agency (EMA) held an expert meeting on 10 November 2015 to review key areas in the development of fixed-dose combinations (FDCs) for the treatment of HIV infection in children.

Purpose and objectives of the expert meeting

The purpose of the workshop was to advise the EMA and its Paediatric Committee (PDCO) on how to best set out detailed requirements for formulation development and clinical paediatric studies in order to agree with applicants high-quality and feasible Paediatric Investigation Plans (PIPs) for antiretroviral FDCs that will ensure rapid access of children to innovative and convenient new therapies.

The objectives were to learn from the invited experts about their experience with clinical trials and clinical practice in children with HIV infection, and to collect their opinions on how paediatric development should be conducted in this condition, with particular focus on FDCs. No confidential information was presented or discussed.

Programme

EMA/PDCO participants briefly introduced the Paediatric Regulation, which came into force in the European Union on 26 January 2007. Its objective is to improve the health of children in the Europe by facilitating the development and availability of medicines for children aged 0 to 17 years, ensuring that medicines for use in children are of high quality, ethically researched and authorised appropriately and improving the availability of information on the use of medicines for children. It aims to achieve this without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults.

As a requirement of the Paediatric Regulation, all new medicines developed for the treatment of HIV infection in adults, must have an agreed PIP in place, ensuring the necessary data are obtained

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through studies in children (and/or adults) to support the marketing authorisation for use in children (note, if a product is not of interest in children, the PDCO can alternatively grant a product-specific waiver). The PDCO is responsible for agreeing these PIPs.

An outline was then presented of the current regulatory requirements in adult and paediatric antiretroviral medicine development, as well as an overview of currently agreed PIPs for FDCs for the treatment of paediatric HIV infection. It was highlighted that some new active substances are only developed in FDCs, and that the PDCO cannot enforce the development of new active substances as the corresponding stand-alone products, if the applicant is not planning a marketing authorisation for the single-agent product in adults.

In addition, prior to the meeting, a questionnaire on the topics for discussion was sent to the experts and written responses were summarised and presented to the experts during the meeting.

Finally, it is acknowledged, that even though the objective of the Paediatric Legislation is to improve the health of children in the European Union, most of the medical need in paediatric HIV infection is outside the European Union, and the needs of these children are being kept in mind when agreeing PIPs.

Topics for discussion

1. Criteria for drug prioritisation for development in children

Experts discussed whether it could prove useful to prioritise some regimens for paediatric development, and, if so, based on which criteria this prioritisation could take place.

The experts agreed that, it could be useful that some regimens were prioritised for paediatric development. In principle, experts stated that they would be satisfied with development of the best compound in each drug class, also considering that the paediatric HIV market is very small. However, EMA/PDCO participants clarified that the obligation to develop a product (that is expected to be safe and effective in children) can only be waived if there is lack of significant benefit over an *existing* (i.e. authorised) product, and not because a likely better product exists in the developmental pipeline. The PDCO in consultation with companies when deciding on timelines for the PIP in particular for the deferral takes these public health aspects into consideration. It should be noted however that a waiver may be granted subsequently if an authorised medicinal product fulfils the paediatric need.

This prioritisation is most likely to address the paediatric medical need and could also help shorten the timelines of developments for antiretroviral FDCs, which in some instances extend as far as the early 2020's. Although, it was acknowledged that results of the adult development could inform paediatric development justifying some lag, in principle, it was considered that any delay should be minimised in order to ensure timely access to these new therapies for children.

Regarding **criteria for prioritisation**, *tolerability* and an acceptable *safety profile* based on non-clinical and adult clinical data was considered critical. *Once-daily dosing without special dietary requirements* was considered highly desirable.

A high *barrier to resistance* was also considered highly relevant, although not absolutely critical. Indeed, while it is generally assumed that compliance is lower in adolescents, which would increase the risk of resistance for products with a low barrier, experts reported that in their clinical practice this was a case-by-case decision and that some adolescent patients were highly compliant and successfully treated with drugs with low barrier to resistance (e.g. NNRTIs).

The need for *suitable age-appropriate formulations* was stressed by the experts as highly important with palatability, tablet size, suitable formulations for young children not able to swallow tablets being of particular concerns, and, in addition, pharmaceutical stability for use in resource-limited settings (see also point 4 below). The development of a palatable, age-appropriate formulation can be requested by the PDCO as a measure of the PIP.

Experts also highlighted work on prioritisation of paediatric antiretroviral drug development done by PADO (Paediatric ARV Drug Optimization). EMA/PDCO participants clarified that PDCO does take PADO recommendations into account; however, as PDCO reviews products at a very early stage in development, this often occurs before these products have been considered by PADO.

The experts were also questioned on the **lower age range** for which FDCs could be of interest. While this was considered in principle a case-by-case decision, experts were of the view that antiretroviral FDCs may in fact be useful from birth, with potentially the greatest need in the youngest children. Historically, the lowest waiver cut-off age agreed for antiretroviral FDCs has been 4 weeks of age. The same drugs may also be of interest for the prevention of mother to child transmission (PMTCT).

In addition, in resource-limited settings the availability of FDCs for all paediatric age groups would also facilitate prescribing, which may increase particularly the youngest children's access to care.

However, it was acknowledged that for some FDCs the development of age-appropriate formulations suitable for use in neonates and infants may take long and be technically very challenging.

Finally, for products to be used in 2nd or 3rd line, an age cut-off of 2 years could be appropriate.

2. Appropriate dosing for young children

Generally it was considered that weight, rather than age, should be considered in the development of antiretroviral FDCs, at least down to approximately 6 weeks of age.

For this, experts strongly supported the use of WHO weight bands in the development of FDCs, if possible, but also for the development of single compounds, as this would facilitate their combination in FDCs in the future.

Experts were of the view that erring on the side overexposure, without undue toxicity, could be more acceptable than underexposure (risk of resistance) and that the active substance with the narrowest therapeutic index should be the one driving the dosing of the FDC. However, regulators stressed that in the paediatric development of antiretrovirals, efficacy is extrapolated from adults based on *matching* exposure, and that hence any deviation from the adult exposure would have to be justified clinically, such as with paediatric efficacy data for underexposure, and paediatric safety data for overexposure.

In cases, where the single agents are already approved in children, but the dosing in the FDC differs from the dose authorised for the individual active substances, an early discussion with regulators is encouraged in order to restrict the number of strengths required for younger children.

Finally, it was considered that staggering of age groups (i.e. the enrolment of younger age subsets only after data has been collected in older age subsets) should be done by default but only if there is a specific safety concern. Experts considered that there is scant evidence that staggering protects younger age groups, but in contrast may expose these age groups to long periods to unauthorised use by delaying data availability. Modern modelling and simulation methods can be used to predict from the outset starting doses at least down to 2 years of age, which could then be evaluated (and adjusted, if necessary) in prospective clinical trials simultaneously in all age groups at least above 2 years of age. This approach also necessitates a much earlier initiation of formulation development.

3. Development of fixed-dose combinations in adolescents

Regarding adolescents, the experts shared the view that an inclusion of this age group in adult trials should be considered given that adolescents generally use the adult formulation and dose, and no major differences in safety and efficacy are generally expected between adults and adolescents.

However, organisational challenges of a combined adult-adolescent study were acknowledged, such as the need for parental consent, the fact that adolescents may be treated at different centres than adults, and the fact that the control arm would have to have an adolescent indication.

Therefore as an alternative, separate but simultaneously conducted studies in adults and adolescents were proposed, which would also provide the necessary data to include adolescents in the initial adult marketing authorisation. Importantly, such adolescent studies should not be deferred.

Simultaneous product development for adults and adolescents should not be envisaged, if safety issues potentially relevant only in adolescence have been seen in preclinical or early clinical data, such as adverse effects on growth or sexual maturation.

4. Formulation development in children

Formulation development was considered the probably most complicated aspect of paediatric development of FDCs.

Some HIV-infected children may be able to swallow tablets already below 6 years of age, but this does not apply to all of these young children. Therefore the development of suitable age-appropriate formulations (e.g. dispersible tablets) is key to paediatric development.

In principle, solid age-appropriate formulations (such as multiparticulate formulations [granules, pellets, minitablets] or dispersible tablets) were strongly preferred by the experts over liquid formulations. The inclusion of score lines was considered of high interest to increase flexibility with a limited number of paediatric formulations. Particularly in resource-limited settings, only ˜1-2 different paediatric strength(s) were considered workable. However, ideally not more than ˜3 tablets should have to be taken at a time, as the convenience advantage of a FDC is lost if too many tablets have to be taken at any one time.

In cases where a FDC only includes substances already authorised in children, the PIP may only include studies in healthy adults, in addition to the measures to develop an age-appropriate formulation. Acceptability/palatability data, as well as an evaluation of the ease of preparation by the caregiver if appropriate, would be needed. Palatability is important for chronic treatments where adherence is a key factor. Discussion on this requirement should be discussed based on the merits of each case, e.g. whether a pure acceptability trial in children could be requested, how such a trial should be designed, and how informative it could be requires much further discussion. Experts particularly noted that data in a small number of children for a limited duration would not be informative on the acceptability/palatability in long-term use, which could only be evaluated post-marketing.

In addition, experts highlighted a case were bioequivalence of an age-appropriate formulation with the adult formulation was confirmed in adults, but not in children, possibly due to interaction with an excipient in other liquid medicines given together in children. It was further discussed that the predictive capacity of bioequivalence data in adults for paediatric formulations should be carefully considered in particular when a different formulation technology/composition is used in the paediatric

formulation for a poorly soluble and/or permeable drug or where the dose mg/kg is higher in children (or a particular age-subset) than in adults due to higher clearance in children.

Further steps

- The Expert's opinion will be taken as a basis for discussions at PDCO on the most appropriate approach for the development of antiretroviral FDCs. In this respect, the PDCO will give specific consideration to certain issues:
  - Some FDCs for the treatment of paediatric HIV infection should be prioritised down to the youngest age according to the criteria mentioned in section 1. The inclusion of the single antiretroviral agent or the FDC in the PADO list of priorities mandates that the specific need identified by the PADO group is addressed in the PIP, as well.
  - The age cut-off for the waiver request would be defined as low as possible, paying special attention to whether the single antiretroviral agent or FDC is intended to be developed also for prevention of HIV (e.g., PMTCT).
  - The clinical development in the paediatric age range should take place as early as possible relative to the adult development unless there are specific safety concerns from the preclinical data or clinical data that may justify delaying the paediatric development. If no particular concerns were present, the development for adolescents and adults as well as for children down to the age of 2 years should not be delayed.
  - The development of an age-appropriate paediatric formulation should be started as early as possible taking into account the final age cut-off.
  - Dosing recommendations should be based on body weight rather than on age. For both single agents and FDC the use of WHO weight bands is encouraged.

  To allow an appropriate discussion by the PDCO, Applicants are encouraged to specifically address the above issues in their PIPs.
- Applicants of PIP are reminded that they should discuss the PIP by the means of a modification of the agreed PIP in case of in case of justified revision of the development approach , in particular to take into account the growing knowledge and improved pharmaceutical developments in this field,.

Acknowledgments

We thank all participants for their many contributions and in particular Dr Mentzer for his valuable input in the preparation of the meeting and for chairing the meeting.

Annex 1: list of participants

Role	Name (in alphabetical order)
Chair	Dirk Mentzer (PDCO)
External experts	Elaine Abrams (International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network, US) Abdel G Babiker (Medical Research Council, UK) Edmund Capparelli (University of California San Diego, US) Polly Clayden (HIV i-Base, UK) Albert Faye (Hôpital Robert Debré, Paris, FR) Carlo Giaquinto (Paediatric European Network for the treatment of AIDS, IT) Diana M Gibb (Institute of Clinical Trials and Methodology, UK) Devasena Gnanashanmugam (National Institute of Health, US) Rohan Hazra (National Institute of Health, US) Marc Lallemant (Drugs for Neglected Diseases, CH) Tim Niehues (Zentrum für Kinderheilkunde und Jugendmedizin Helios Klinikum Krefeld, DE; *questions answered in writing*) Antoni Noguera (Sant Joan de Déu Hospital, Esplugues, ES; *questions answered in writing*) Anthony Nunn (Alder Hey Children's Hospital, Liverpool, UK) Fernando Pascual (Medicines Patent Pool, CH) Martina Penazzato (World Health Organisation, CH) Pablo Rojo Conejo (Hospital Universitario 12 de Octubre, Madrid, ES) Catherine Tuleu (The School of Pharmacy, University of London, UK)
Participants from National Competent Authorities	Regine Magdalene Lehnert (DE) Nathalie Morgensztejn (FR) Mair Powell (UK)
PDCO members	Sylvie Benchetrit (FR) Maria Jesús Fernández Cortizo (ES) Ann Marie Kaukonen (FI) Dana Gabriela Marin (RO)

Role	Name (in alphabetical order)
	Francesca Rocchi (IT) Paolo Rossi (IT) Siri Wang (NO)
CHMP members	Filip Josephson (SE)
EMA scientific staff	Andrea Ecker Thorsten Olski Agnes Saint-Raymond Sabrina Spinosa-Guzman Paolo Tomasi
Food and Drug Administration (via TC)	Yodit Belew Linda Lewis Prabha Viswanathan