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Human Medicines Development and Evaluation

Minutes of the paediatric anticoagulation therapy expert meeting

European Medicines Agency, London, 06 November 2012

Introduction

The European Medicines Agency (EMA) held an expert meeting on 06-Nov-2012, to review key areas for the development of anticoagulation medicinal products to treat children, with or at risk for, arterial or venous thromboembolism.

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 non-clinical and clinical paediatric studies,
- to compose high-quality Paediatric investigation plans (PIPs) for anticoagulation therapy.

The objectives were to learn from the invited experts about their experience with clinical trials in patients with or at risk for thromboembolism, and to collect to their opinions on how non-clinical, and paediatric clinical studies should be conducted. Information on demographics, biology and treatments as well as on the relationship between paediatric and adult population subsets, and between different disease conditions was discussed, to define which data need to be collected and evaluated in order to establish the safe and efficacious use of new medicinal products in this paediatric setting. No confidential information was presented or discussed.

Introduction to anticoagulation therapy in children

The aim of this meeting, i.e. the identification of the best possible development approaches for new anticoagulation medicines in childhood and adolescence for Paediatric Investigation Plans, was emphasised. An outline of the current situation was given.

The EMA briefly introduced the European Paediatric Regulation and its requirements for paediatric medicine development for the authorisation of medicinal products in children. Companies are required to propose paediatric investigation plans (PIPs) that are evaluated by the PDCO. As soon as

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pharmacokinetic data from adults have been obtained, details of the pharmaceutical, non-clinical and paediatric clinical studies are to be defined.

Questionnaire

Summarised responses to the items of the questionnaire (see annex) were presented and commented upon by participants. In total 7 responses (from 7 countries) had been received.

Priorities for new products / for clinical investigations

- The following questions were sent to the experts, ahead of the meeting:

1. Where do you see the highest unmet medical need for new products, and the highest need for additional information for anticoagulation therapy for existing products?
2. In view of the currently developed compounds, which ones do you consider to have the highest therapeutic benefit in the paediatric population and why?
3. Which characteristics (pharmacological, biological targets & clinical experience) would prioritise a medicinal product for study in children?

1-3)

The panel agreed that additional investigations into the **currently used anticoagulants (unfractionated and low molecular heparin, vitamin K antagonists**, with their requirement for frequent monitoring and dose adjustment) could be of benefit, as well as investigation into short-term treatment itself. Despite their use for many years and accumulated practical experience in paediatric patients, there have only been a few, small prospective, and mostly uncontrolled trials designed to characterise mainly pharmacokinetic and pharmacodynamic activity, thus providing limited information for clinical practice.

With regard to novel therapeutic agents, most experts in the panel agreed that **new products would be of potential benefit** with improved PK and clinical characteristics over current therapies, even if short-term anticoagulation is currently reasonably covered by available low molecular weight heparins. In particular, very ill paediatric subsets could benefit from the products currently in development. The novel oral direct anti-Xa inhibitors and thrombin inhibitors would warrant further investigation. However, particularly for antiplatelet agents, most experts believed that the benefit would be rather limited in venous thromboembolism. There is a high incidence of off-label use, and treatment mainly based on individual experience. The challenges with the therapeutic range and dosing-control in currently used anticoagulants was acknowledged. The need for further data on PK-PD clinical correlation to monitor the novel direct oral anticoagulants was stressed.

The PDCO has requested applicants to conduct specific **paediatric investigations** for new therapeutic agents also **in clinical settings that differ from the ones targeted with the adult programme**. The arguments brought forward in favour of this approach are the different physiological circumstances and responses to the therapeutic agents in children. Also, previous results have indicated that benefit for children may occur in clinical settings where such a benefit would not have been expected based solely based on adult data. There was agreement that more differentiation was warranted between various clinical settings. Paediatric differences to adults in therapeutic practice were seen in dosing recommendations, duration of treatment and treatment intensity. Evaluations of prognostic subgroups and outcomes in patient subgroups were considered to be of interest. It was underscored that arterial and venous thromboembolism need to be addressed separately. The neonatal and newborn population have the most pressing need for further clinical data and medicines.

The **characteristics of a desirable product** were discussed. Currently available formulations are often not appropriate. Studies of newer formulations are warranted. There was agreement that, in general, intravenous formulations are needed. Ideally, however, a medicine would be available also in age-appropriate oral pharmaceutical forms needed for patients on maintenance therapy who can be fed orally. The least possible interactions with food or other drugs should be aimed for. A rapid onset of action, an extended duration of action, and a wide therapeutic range would be desirable. Ideally, the medicine should require little monitoring and dose titration. An important feature of any newly developed anticoagulant should be the availability of an antagonist allowing rapid reversal of the anticoagulant effect. Short-acting anticoagulants would be used in a setting with high risk for bleeding, owing to easier control or better titration.. Products with long half-lives would be reserved for chronic treatment settings. In this context, the potential need for life-long treatment starting in the paediatric setting was brought forward.

Choosing the study population

The experts stressed the heterogeneity of paediatric populations with or at risk of thromboembolism. This complicates the assessment of anticoagulants, aggravated by the low number of children affected. In most cases, thrombosis is not the child's primary medical problem but a secondary complication of underlying diseases such as cancer, sepsis, surgery, congenital heart disease, use of total parenteral nutrition, or inflammatory conditions.

The experts agreed that the population with the **most pressing need for data** were neonates and young infants; these should be prioritised. The types and location of thrombotic events that occur in neonates differ from those in older children; there is not much experience in studying this age subset. Preterm and term infants should be studied separately.

In terms of choosing the **disease condition** for an initial study population, there was no clear agreement in the panel, whether to start with a high-risk or low-risk population. The inclusion criteria should be chosen sufficiently broadly to avoid exclusion of too many patients and maintain the feasibility of studies. This should be done in conjunction with exploratory subgroup analysis. As a suitable population to be investigated initially, children with central venous lines or children with Fontan shunts were suggested because of their relatively high rates of thrombotic events and their unmet clinical need, particularly for Fontan. For patients with Fontan shunts, it was underscored that no standard of care had been established so far, and thus, any clinical trial would have to deal with varying treatment/management approaches for the prevention of thromboembolic events.

As for the issue **of treatment vs. prevention indication**, participants stated that the issue should be defined as high-intensity versus low-intensity therapy. It was considered of high importance for the long-term perspective for the development of medicines to establish **better correlation between PK, PD and clinical efficacy**.

Extrapolation

An overview of the overall concept and methodologies for the PDCO's approach to extrapolation was presented by Dr Christoph Male. For the scientific review by the PDCO, the term extrapolation is used as follows: The use of a medicinal product in the paediatric population will be informed at least in part by adult data. Based on efficacy data from adult populations, it may therefore be possible to draw conclusions for paediatric age groups based on reduced paediatric study data (pharmacokinetics, pharmacodynamics, safety, toxicity, and efficacy data with limited patient numbers). The degree to which paediatric data requirements may be reduced will depend on the similarity of disease and

pharmacological response between adult and paediatric populations. Extrapolation may also be possible across disease conditions or across pharmacological substances of the same class.

- Other questions sent to the experts ahead of the meeting:

4. How necessary do you consider separate dosing investigations for treatment and primary prevention? Could a paediatric trial in primary prevention patients inform a trial with treatment (or secondary prevention)? Do you see a need to investigate sinus venous thrombosis and would you differentiate the need for dosing information with regard to low/medium/high-risk patients?
5. What biological/molecular rationale would support extrapolation from one group (age, ..) to another? How precise would PK-PD-data have to be? Especially, when adult PK-PD data has already been generated.
6. What data would allow extrapolation between different products of the same class?
7. How, and from which subsets could efficacy be extrapolated from older children to very young children? (i.e., birth to less than 3 to 5 years) Which age cut-off, do you consider appropriate for a staggered approach?

4–7)

There was consensus that **extrapolation** was not acceptable for safety **data from adults to children**. In addition, the group stated that data on dosing, efficacy and PK from the adult population would only be extrapolable to children to a limited extent. In most cases, separate studies in children were needed and a staggered approach of paediatric trials could be useful. Important differences for the paediatric population were expected for the therapeutic range, and PK-PD weight correlation. The neonatal age group was acknowledged to deserve separate investigations.

It was stressed that the possibility for extrapolation would depend on the condition having been investigated in adults. Any extrapolation of dose/efficacy from acute coronary syndrome and any extrapolation of dose/efficacy to sinus venous thrombosis were seen as very difficult and the high variability of results for adults in certain conditions was stressed.

Even with the availability of adult results, the time points of efficacy assessment used in the adult trials could prove not fully compatible to address clinical questions relevant for paediatrics. It may not be necessary to await the results from adults before starting studies in children. Long-term safety should be studied and whenever feasible registries should be used.

As a strong **supportive factor** for extrapolation, the linearity of PK and PK-PD was cited. Supportive in-vitro data could prove helpful in this context. However, it was stressed that a difference in dose-response would not necessarily preclude extrapolation.

Juvenile animal studies as well as PK and safety studies are needed, in general, as early as possible The potential to use animal data was supported in particular, if no proof-of-concept was available, with a characterisation of the mode of action as a prerequisite.

In addition to extrapolation across age groups, the possibilities to inform paediatric studies using **information from other conditions** or from **other products of the same class** were discussed. With regard to new classes of products, the group agreed that confirmatory data would be needed. As a strategic approach across several development plans, it was stated that at this point in time with the knowledge available, extrapolation would have to be very limited. Any progress for extrapolation would have to start with high quality data in adults and with support within one product development for one specific product only without extrapolation within the product class. A disadvantage in this context was brought forward in that the development plans in adults are not decided by the EMA and may not provide the information necessary to inform extrapolation. For future developments, a dynamic

adaptive approach was suggested, modifying and adapting features of the clinical development as more data/information become available in the course of investigating older age groups, or other conditions. With more evidence available from performed studies, the ideal final approach would be to divide the different indications across developments for different anticoagulants. The triage as to which conditions to investigate would be based on the adult trial results.

Lessons learned from experience and optimal study design

- To discuss feasible and optimal study designs comprising control arms, choice of comparator, active or placebo the following questions were sent to the experts:

8. Judging from your experience with/knowledge of already completed/published trials, which mistakes would you say should be avoided in future developments? (Lessons learned until now?)
9. Which definitions and diagnostic measure of VTE, ATE (clinical and laboratory) do you consider most appropriate to be used as an endpoint? What do you consider the best endpoint for Prevention of VTE, Treatment of VTE, Prevention of ATE, Treatment of ATE and time interval for regression or reoccurrence of thrombi?
10. Do you consider an adequately powered dose comparison possible? What would you consider a minimal requirement for a formal superioirity/non-inferioirity analysis?
11. By which criteria would you select an active comparator?

8-11)

Ethics committees have raised the question of acceptability of pure PK studies given that their benefit was not direct for participating children. This issue could be addressed by inclusion of these investigations in larger clinical efficacy studies. The risk of dosing errors as a consequence of **lack of adequate PK data** was stressed; also the risk of choosing a too low dose and risking failure to demonstrate efficacy. The inclusion of interim analyses to avoid negative findings at a later stage was suggested. Dose-comparison should be considered before starting respective phase 3 trials in children. Ideally, this should be performed with the final formulation available.

Randomised active controlled studies were scientifically most preferable, but also possibly difficult to carry out. **Recruitment problems** were stated in particular in the acute therapeutic setting. Placebo-controlled studies in children would raise ethical questions in serious conditions. If a comparator were to be included, current standard of care at the respective centre would be used. It was pointed out in this context that different therapies are currently accepted and also reflected in the American College of Chest Physicians guidelines. The use of vitamin-K antagonists, unfractionated heparin, or low molecular weight heparin would be different according to patient age, accompanying conditions and thrombus location.

The optimal **choice of endpoints** for paediatric studies was discussed. The considerations of the Perinatal and Paediatric Haemostasis Subcommittee of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) were endorsed in principle (Mitchell at el. J Thromb Haemost 2011; 9:1856-9).

For studies of **treatment of venous thromboembolism**, a composite primary endpoint was recommended comprising (1) all recurrent venous thromboembolism defined as either contiguous progression or non-contiguous new thrombus and including deep venous thrombosis, pulmonary embolism and paradoxical embolism and (2) venous thromboembolism-related mortality. The secondary endpoint would comprise (1) Each individual component of primary outcome; (2) all-cause mortality; (3) new symptomatic DVT (including DVT progression); (4) new symptomatic PE; (5) new

paradoxical embolism; (6) new asymptomatic DVT (including DVT progression); and (7) post thrombotic syndrome.

For investigations into **prophylaxis of venous thromboembolism**, the suggested composite primary endpoint was endorsed comprising (1) all incident venous thromboembolisms including deep venous thrombosis, pulmonary embolisms and paradoxical embolism and (2) venous thromboembolism-related mortality. Secondary endpoints would be (1) each individual component of primary outcome and (2) all-cause mortality.

The **safety endp**oint would be major bleeding as a composite of: (1) fatal bleeding; (2) clinically overt bleeding associated with a decrease in Haemoglobin of at least 20 g/L) in a 24-h period; (3) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (iv) bleeding that requires surgical intervention in an operating suite. Furthermore, clinically relevant non-major bleeding would have to be tracked as a secondary endpoint as a composite of: (1) overt bleeding for which a blood product is administered and which is not directly attributable to the patients underlying medical condition and (2) bleeding that requires medical or surgical intervention to restore haemostasis, other than in an operating suite. Minor bleeding not covered by either of the above definitions would also have to be tracked.

It was supported that asymptomatic thromboembolisms would have to be included. CNS-located TE-events would have to be considered separately from non-CNS-related TE-events. An assessment with both, ultrasound and MRV, was considered to be necessary for the clinical trial setting. For investigations in the treatment-of-TE setting, the resolution of the treated thrombus was considered to be a sufficient measure to be assessed. However, the advantage of tracking also the reoccurrence of thrombi was stressed. The benefit of tracking asymptomatic thrombi in the treatment setting was questioned. The usefulness of the generation of clinical data in a **post-marketing** setting was questioned.

Further steps

- EMA will consider holding a follow-up meeting with experts in order to facilitate practical aspects for paediatric investigation plans (PIPs).The results of the discussion as presented above will be taken into account.
- The EMA / PDCO will continue to involve external experts in medicinal product-specific PIP evaluations for this setting. As foreseen by the European legislation for paediatric medicines (Regulation (EC) 1901/2006), clinical trials for authorised medicines can and should be submitted for regulatory assessment.
- The EMA offers scientific advice, and advice to support the qualification of novel methodologies and biomarkers.

Acknowledgments

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Annex 1: list of participants

Role	Name
Chair Vice-Chair	Dirk Mentzer (PDCO) Thorsten Olski (EMA)
External experts:	Manuela Albisetti (CH), Anthony Chan (CA) *via TC*, Paola Giordano (IT), Kristin Jochmans (BE), Angela Thomas (UK), Christoph Unkrig (DE) *via TC*, Cornelia H van Ommen (NL)
PDCO members:	Christoph Male (AT), Sylvie Benchetrit (FR), Jan Taminiau (NL), Adriana Ceci (health care representative)