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Concept paper on the need for a paediatric addendum of the guideline on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease

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Introduction

A number of new EMA guidelines related to clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolism (VTE) are already available [1,2,3], but recommendations are applicable only to adults. In contrast to adults, VTE in children is a rare event, but represents a significant management dilemma that requires therapeutic intervention. *A paediatric addendum to the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of VTE* is considered necessary to discuss and make methodological recommendations adapted to children.

1. Problem statement

VTE is a rare disease in children, occurring with an incidence that is approximately 100 times lower than in adults. While the overall incidence rate for a VTE event in adults is approximately 100-200 per 100,000/year, the incidence of symptomatic thrombosis is approximately 1 case per 100,000 paediatric patients [4,5]. Immediate complications of VTE include death from extension and/or embolization into the heart or lung (PE), while long-term complications involve recurrent VTE, post-thrombotic syndrome (PTS), and bleeding associated with anticoagulation therapy.

In contrast to VTE in adults, VTE in children is rarely truly idiopathic in nature [6]. The distribution of VTE events in paediatric patients is bimodal with the majority of events occurring in neonates and infants [4,5] and in adolescents [7]. Approximately ≥90% of children with VTE have a serious underlying disorder [e.g.: cancer, congenital heart disease (CHD), nephrotic syndrome, etc.], or a precipitation factor [central venous catheter (CVC), infection, trauma or surgery], or a hereditary pro-thrombotic condition. Apart from better awareness for VTE, the widely observed increase in childhood VTE is mainly due to the medical progress in the treatment and/or interventions of critically ill children. In adolescents, VTE is generally associated to the use of hormonal contraception (HC) for contraceptive and noncontraceptive indications [7]. VTE in adolescents is broadly similar to VTE in adults, and hormonal contraception is already covered as VTE risk factor in the adult guideline [1]. Therefore, the focus of this paediatric addendum is for clinical investigation of VTE in neonates and young children. This statement does not mean that adult data may be completely extrapolated to adolescents, but that adolescents may be included in VTE studies in adults provided that it is appropriately justified from a clinical standpoint.

The typical location of VTE in neonates and infants differs from that in adults and adolescents. In neonates and young children, VTE occurs more often (60%) in the upper venous system (vs. only 2% in adults). This reflects the common placement of CVC (the most frequent precipitating factor of VTE in children) via the internal jugular or subclavian veins. The location of the clots results in fewer classic VTE symptoms (e.g., unilateral limb swelling) and also may impair the effective/precise diagnosis with standard measures [i.e. compression ultrasound (CUS) cannot be performed in this location]. Loss of catheter patency and loss of central venous access have important consequences in children with cancer and other serious medical conditions [6].

A growing body of evidence shows that preterm neonates require higher doses of LMWH to achieve anti-factor Xa levels within target ranges [8]. However, in the absence of large randomized controlled trials, and with much of our current understanding of PK extrapolated from adult studies, ideal dosing for anticoagulation in critically ill neonates remains uncertain. Current recommended therapeutic regimens for VTE in children are largely based upon case series and cohort studies, and are otherwise

extrapolated from adult VTE data. The majority of the recommendations for dosing in children are based on Grade 2 level of evidence. The current standard of care for the treatment of VTE in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for 5-7 days followed by (at least) three months of LMWH or oral anticoagulation with a vitamin K antagonist (VKA) [8,9].

Finally, primary prophylaxis of VTE is not well established in the pediatric population [8]. Proof-of-concept and appropriate dosing has to be established in dedicated studies in high risk populations.

In summary, there is a medical need for additional clinical studies that address the PK/PD, efficacy and safety of antithrombotic treatments in children, particularly in neonates and young children.

2. Discussion

The following critical aspects will need to be discussed and covered as appropriate by the paediatric addendum of the VTE guidelines:

1. Extrapolation from adults. The possibilities of extrapolation of data from adults to children should be discussed [10]. Pediatric-specific aspects should be addressed related to the occurrence of VTE in neonates and young children (e.g. natural course of the disease, VTE localization and risk factors) and related to the investigational treatment (e.g.: dose regimens, duration of therapy, monitoring requirements, possibility of establishing therapeutic ranges, factors influencing dose-response relationships, side effects, and the impact of general anesthesia and non-pharmacologic interventions).

2. Clinical trial designs (respecting the rarity of the condition in paediatrics).

3. Selection of patients (in relation to the heterogeneity of the population).

4. Diagnostic tests to detect VTE in neonates and young children (as CUS cannot be applied in many cases due to the location of the thrombus in the central venous system).

5. Primary and secondary end points suitable for neonates and young children (e.g.: symptomatic and asymptomatic VTE), including also a discussion on surrogate and composite end points.

6. Safety endpoints suitable in children (e.g.: bleeding and other endpoints).

3. Recommendation

The Cardiovascular (CVS) Working Party and the Paediatric Committee (PDCO) recommend the CHMP to consider an Addendum to the VTE Guidelines in line with the criteria stated above.

4. Proposed timetable

It is anticipated that a draft document may be released 6 months after adoption of the Concept Paper. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 3 months.

5. Resource requirements for preparation

The preparation of this guidance document will be led by the CVS Working Party of the CHMP.

6. Impact assessment (anticipated)

The document is intended to update methodological aspects when performing trials to develop drugs in the prophylaxis and treatment of VTE in children. It should also provide a clear basis for the CHMP when assessing efficacy and safety data from studies for paediatric VTE and providing advice in this field.

7. Interested parties

The interested parties in the guideline include the Industry (PhARMA, EFPIA, JPMA and others), Academia and Scientific Societies of medical specialities involved in the treatment investigation and/or recommendations about treatment of VTE in children (e.g.: The International Society of Thrombosis and Haemostasis (ISTH), European Hematology Association (EHA), European Society for Cardiology (ESC), Association for European Paediatric and Congenital Cardiology (AEPC), European Society of Pediatric Radiology (ESPR), clinical trialists in VTE and other Regulatory Agencies.

8. References

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