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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE IMPACT OF LIVER IMMATURITY WHEN INVESTIGATING MEDICINAL PRODUCTS INTENDED FOR NEONATAL USE

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Comments should be provided to: peg@emea.eu.int or by fax +44 20 7523 7040.

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel: (44-20) 74 18 84 00, Fax: (44-20) 75 23 70 40
E-mail: mail@emea.eu.int http://www.emea.eu.int

1 INTRODUCTION

This paper is considered part of a series of documents highlighting the uniqueness of neonates, including preterm neonates, when exposed to medicines. It specifically describes the issues relating to the immature capacity of neonates for metabolising and eliminating drugs by the liver. This concept paper is the initial step for developing a guideline on the impact of liver immaturity and development on how to study medicinal products in the neonatal population, to be followed by a global guideline on clinical investigation of medicinal products in neonates. The philosophy of this paper is similar to that of the discussion paper on the impact of renal immaturity on drug elimination in neonates (CPMP/PEG/35132/03).

Among the paediatric population, the neonate and in particular the preterm neonate remains the most neglected "therapeutic orphan" with an unacceptably high percentage of unauthorised and/or off-label medicines use. In addition, there is a paucity of knowledge regarding the quantitative and qualitative development of the neonatal hepatic drug-metabolising enzyme systems. Especially, the *in vivo* ontogeny of these systems remains poorly understood even though recent *in vitro* studies have substantially contributed to the understanding of enzymatic systems expression and activity in the immature liver. The neonates hospitalised in intensive care units are often exposed to multiple medicines requiring intravenous administration. Several of these medicines may affect the metabolism of others. An increase in both immediate or delayed morbidity and even mortality may result from the use of medicines that have impaired metabolism by the neonatal liver, especially when prescribed in combination.

2 PROBLEM STATEMENT

The dramatic physiologic changes, which arise during pregnancy and after birth, influence the capacity of the neonate to metabolise medicines. This counts for both phase I (e.g., cytochrome P450) and II (e.g., conjugation) reactions of the drug biotransformation process, although to different degrees. The normal development (ontogeny) of metabolic pathways may partly be changed by antenatal/perinatal use of medicines, and may also show a different pattern depending on genetic polymorphisms (e.g., CYP2C9). Genetic polymorphisms can influence the qualitative or quantitative contribution of the enzymes involved in the clearance of the drug. For example, the neonatal hepatic expression of CYP450 isoenzymes 1A2, 2C, 2D6, 2E1 and 3A4 is very low at birth; most of these enzymes will be increasingly expressed during the first weeks of life, reaching 50-80 % of the adult level by 1 year of age. CYP3A7 has been considered as the foetal expression of the CYP3A4 enzyme, but its catalytic activity may not necessarily be used for the metabolism of the CYP3A4 xenobiotics. On the other hand, glucuronidation in the human neonatal liver is largely immature and does not reach adult levels before a few years of life. Other conjugation reactions are not so immature in the neonatal liver and partly compensate the immature metabolic pathways; this is the case for sulphation and conjugation with glycine, which are therefore major pathways. Due to the differences in enzyme expression, the contribution of a specific enzyme is also likely to differ between adults and neonates. Drug metabolising pathways may be absent, or unique, in the neonate as compared to the more mature human being. In addition, other immature systems – themselves with considerable individual variability – are involved in bioavailability of drugs (e.g., gut absorption) and this may affect drug disposition and metabolism.

3 DISCUSSION

Some data on the neonatal hepatic biotransformation process have become available but most are still missing. While the development of this process has to be regarded as a continuous developmental status (not represented by ICH E11 age classes), the following issues remain to be addressed and studies in neonates may be necessary whilst recognising that this is a highly vulnerable population:

- The value of *in vitro* immature microsomal preparations (from human foetal and neonatal origin) for the assessment of neonatal liver metabolism should be discussed. This technique

provides protein activity cDNA expressed cytochrome tool and mRNA measurement in order to assess how a specific product is metabolised by the neonatal liver;

- In neonates of various gestational (term and preterm) and postnatal (1-28 days of life) ages differences in pharmacokinetics and pharmacodynamics need to be discussed, with emphasis on the potential formation of metabolites that might result in age-specific adverse drug reactions;
- The use of population PK and PK/PD modelling techniques;
- Acceptability of existing adult data (PK/PD, clinical trials) to bridge with neonatal age data should be discussed;
- The use of surrogate endpoints in the assessment of efficacy;
- IV administration of medicines as there is normally poor bioavailability of medicines given to hemodynamically unstable neonates;
- Oral administration in more stable patients. The factors that might influence bioavailability as it affects liver metabolism should be identified, e.g. absorption by the gastrointestinal tract (including intestinal CYP3A4 activity), first pass effect, enterohepatic circulation, effect of persistent ductus arteriosus and venosus.
- The use and predictability of juvenile animals studies or data gathered from pre/post natal reproduction toxicity studies;
- The effect of medicines administered to pregnant women with regard to maturation of metabolic pathways in the neonatal liver
- Liver synthesis of albumin (or other binding proteins) with consequences on drug binding and free bilirubin.
- Drug-drug interactions (on the liver) for combinations likely to be used in this population.

4 RECOMMENDATION

It is proposed to prepare a guideline on the impact of liver immaturity when investigating medicinal products intended for neonatal use.

5 TIMETABLE

The guideline on the impact of liver immaturity when investigating medicinal products in neonates could be ready by the end of 2005. It could be anticipated that the full 'neonate' guideline will be ready by the end of 2006.

6 RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will involve the PEG and other relevant CHMP Working Parties.

7 IMPACT ASSESSMENT

The development of this Guideline will help industry and other parties to study medicinal products in the neonates in view of the upcoming Paediatric Regulation and this is likely to increase the interest for applying for MA in this neglected population.

8 INTERESTED PARTIES

Interested parties with specific interest in this topic will also be consulted during the preparation of this guideline.