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*Evaluation of Medicines for Human Use*

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

# CONCEPT PAPER ON THE IMPACT OF BRAIN 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)
E-mail: mail@emea.eu.int http://www.emea.eu.int

## 1. INTRODUCTION

This concept paper forms part of a series of documents addressing different aspects of organ immaturity to be considered during studies into medicinal products intended for neonatal use. It represents a further preparatory step for the development of a general guideline on the investigation of medicinal products in neonates. Following previously released concept papers on the impact of renal, liver and heart & lung immaturity, this paper specifically addresses the impact of the immaturity of the human brain. It aims to describe the potential effects and interactions between the use of medicinal products and the immature brain of the neonate.

## 2. BACKGROUND

Knowledge about the developing brain is largely derived from animal models and anatomo-pathological studies using human brain tissue. Various critical steps between the second month of gestation and adult age in the development of the human brain have been identified. These steps consist of neuronal proliferation, migration, organization and myelination. Two main phases are distinguished: The first occurs between the 2nd and 4th month of gestation and mainly involves neuronal proliferation and generation of radial glia. The second phase between 5 months and 1 year primarily implies glial multiplication. Brain plasticity derives from a subtle balance between neuronal proliferation and physiological apoptosis, with glutamic acid, an excitatory amino acid, likely to represent the key mediator in this process. By acting on the *N*-methyl-D-aspartate (NMDA) receptors, it provides trophic functions in the developing brain, influences synaptic construction, and promotes proliferation and migration of neuronal progenitors. Neurotransmitter represent another important role in the control and modulation of brain maturation, with e.g. neurons with gamma-aminobutyric acid (GABA) being involved in migrational events following radial glial guides.
Major underlying causes for brain immaturity therefore derive from immature barriers, incomplete myelination and receptor-maturation as well as a lack of endogenous protectors especially in the preterm neonate. The vulnerability of the immature brain may be further aggravated through pre- and postnatal events (maternal diseases, medicines used by the mother, iatrogenic stress, infection, haemorrhage etc.) adversely affecting the susceptible system of brain maturation.

## 3. PROBLEM STATEMENT

Beyond the influences resulting from environmental factors and the clinical condition of the neonate, the complex process of brain maturation may further be affected through the administration of medicinal products to the neonate. Especially in preterm neonates, frequently requiring mono- or multimodal treatment, this may have adverse effects on the neurological and cognitive development of the neonate. In the same way, pharmacokinetic characteristics may be substantially different in the neonate due to the immature brain, with botha potential impact on clinical efficacy and safety, including a higher risk of severe adverse drug reactions. The lack of data on short- and long-term effects of medicinal products on the developing brain and the fact that adverse effects are often diagnosed or become apparent only later in the development increases the risk of unexpected effects for neonates. Investigations of medicinal products for neonatal use should therefore take account and aim to identify the various potential mechanisms of interactions. This need becomes even more evident with an increased number of highly immature preterm infants surviving through recent and ongoing improvements in neonatal care.

## 4. DISCUSSION

Prior to the investigation of a medicinal product for neonatal use, the following aspects should be addressed:

### *I. General considerations:*

- Wherever appropriate, available in-vitro or in-vivo models should be used to study the potential effect of a medicinal product on the immature brain.

- Measuring plasma concentrations in the neonate might be ineffective to monitor medicinal products acting on the human brain. Even if cerebrospinal fluid and plasma concentrations have been shown to be correlated in adults or older children, these correlations may be altered in neonates.

- Where appropriate, new methods to study effects of medicinal products on the immature brain should be used and further be investigated (e.g. posittron emission tomography, PET).

***II. Physiological and pathophysiological aspects:***

*Blood Brain Barrier*
Transport across the blood brain barrier by both passive diffusion and by active transporters is age-related and may therefore be substantially different in neonates. This may contribute to a significantly altered distribution of active substances or metabolites into the CNS with a potential impact on both clinical efficacy and adverse effects.
Where appropriate, the free level of the active substance or its metabolites which is sufficiently safe in the neonate has to be determined taking into account the differences in pharmacokinetics in this population.*Transporters*
In this context developmental aspects of transporters (e.g. P-glycoprotein (PGP)) in the brain may have an impact on the degree of distribution of drugs into the CNS. As PGP contributes to a decreased CNS distribution of active substances by expelling hydrophobic drugs from the cell and as the level of PGP expression seems to be lower in neonates compared to adults, special concern has to be put on medicinal substances known or expected to be PGP substrates.

*Neurotransmitter*
Neurotransmitters such as glutamate, GABA, dopamine, serotonin, acetylcholine, opiates and adenosine are involved in the control and modulation of pre- and postnatal brain development while also acting as targets for many neuroactive drugs. Therefore any potential adverse effect on the developing brain has to be considered during the investigation of medicinal products acting on the release or substituting neurotransmitters in the neonate.
In this context it has been shown that dopamine infusion in the neonate consistently suppresses prolactin, growth hormone and thyrotropin secretion and may induce or aggravate partial hypopituitarism. This is of special concern in preterm infants who show an increased risk of transitory hypothyroidism.
Additionally, medicinal products acting via an enhancement of GABA activity and/or a blockade of glutamergic excitatory neurotransmission may – via a mechanism of suppression of synaptic neurotransmission - trigger apoptotic neurodegeneration in the immature brain.
Investigations into medicinal product known or suspected to affect neurotransmitter levels have to take account of the potential effect on human brain maturation.

*Glucose metabolism*
Hypoglycemia is an important risk factor for perinatal brain injury, particularly in depressed infants who require resuscitation and have severe fetal acidemia. Due to the high metabolic rate and the dependence on glucose as unique source of energy, any medicinal product affecting glucose metabolism in the neonate may therefore have an effect on the developing brain.

*Bilirubin encephalopathy*
Increased intracerebral bilirubin concentrations may lead to bilirubin encephalopathy and subsequently to severe brain damage (kernicterus). The pathogenesis of bilirubin encephalopathy is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding capacity, blood brain barrier development and neuronal susceptibility to injury. Medicinal products with a known or presumed effect on these factors should take account of a potentially increased risk of the neonate to develop bilirubin encephalopathy (e.g. active substances competing with bilirubin binding to albumin).

*Cerebral blood flow*
Autoregulation of cerebral blood flow (CBF) is limited in the immature brain. Hyperoxemia and hypocapnia (especially when being associated) as well as vasoactive substances may have a dramatic impact on CBF in the neonate during the first days of life. The potential impact of medicinal products on CBF has to be considered, as it may be associated with severe neuropathological consequences.

*Hypoxic ischemic encephalopathy*
Post ischemic encephalopathy is one of the major causes of brain damage in the neonatal period. Investigations into medicinal products should take account of any potential effect on the course and outcome after hypoxic-ischemic events, in order to potentially identify pharmacologic preventive or adverse effects.

*Exposure to pain*
Excessive exposure to repetitive pain may trigger both an altered hypothalamic-pituitary-adrenal-axis reactivity and an increase in NMDA/excitatory amino acid activation resulting in damage to developing neurons. As shown in cultured neurons, excessive stimulation of opiate receptors can also induce cellular and molecular alterations. Both aspects should be considered during the investigation of medicinal products in the neonate.

***III. Long-term follow-up***

As adverse reactions originating in the neonatal period may have a lifelong impact and frequently become apparent or are diagnosed only later in the development, any evaluation of a medicinal product potentially affecting the developing brain should include measures to ensure long-term follow-up. This implies repeated and age-appropriate cognitive and neurological assessment according to validated methods.

***IV. Potentially new approaches:***

For example, promising possibilities of pharmaceutical neuroprotection are derived from animal experiments. These may be further developed in relation to brain maturation.

## 5. RECOMMENDATION

Due to the lack of established guidelines while investigating a medicinal product in the neonate, a guideline is in preparation summarising the aspects to consider in studies of medicinal products for use in the neonate is currently under preparation.

## 6. PROPOSED TIMETABLE

It can be anticipated that the document outlining the Guidelines for the investigation of medicines in the neonate will be ready by the end of 2006.

## *7. RESOURCE REQUIREMENTS FOR PREPARATION*

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

## *8. IMPACT ASSESSMENT*

The development of this Guideline aims to help industry to study medicinal products in the neonates also with a view on the upcoming Paediatric Regulation. It aims to facilitate and encourage the development of medicinal products in this subpopulation.

## *9. INTERESTED PARTIES*

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