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EMA 2010 Priorities for Drug Safety Research

Long-term effects in children and in young adults of methylphenidate in the treatment of attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is defined as “a disorder of childhood and adolescence manifested at home, in school, and in social situations by developmentally inappropriate degrees of inattention, impulsiveness and hyperactivity.” Conduct, learning and psychiatric disorders may occur alongside ADHD.

Methylphenidate is indicated as part of a comprehensive treatment programme for ADHD in children aged six and over when remedial measures alone prove insufficient. Treatment in some children continues until or after puberty and so covers an important time in growth, physical, sexual and cognitive development. The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Although methylphenidate is not licensed in adults, there is evidence of off-label use and concerns over cardiovascular safety.

In 2007, the European Commission requested a referral to the Committee for Medicinal Products for Human Use (CHMP) under Article 31 of Directive 2001/83/EC, as amended, for all methylphenidate containing products because of safety concerns. During the procedure, the main potential safety areas evaluated concerned cardiovascular risks, cerebrovascular risks, psychiatric disorders, carcinogenicity, effect on growth and effects of long term treatment.

The CHMP concluded in January 2009 that the benefit risk of methylphenidate in the authorised indication remains favourable but that more data were needed on long term effects in children and young adults.

http://www.emea.europa.eu/pdfs/human/referral/methylphenidate/MethylphenidateQ&A_65828508en.pdf

Research is needed on long term effects, and this should focus in particular on:

- Design of appropriate tools to study developmental effects.
- Study of long term developmental effects including growth
- Study of long term neurological effects including cognitive function
- Study of long term psychiatric outcomes (including mood disorders, hostility and psychotic disorders)
- Study of long term effects on sexual development and fertility
- Cardiovascular effects in adults who are either currently taking methylphenidate or who have a history of use in childhood.

Specific research outputs will be the generation of data that will allow for the comparison of exposed children with suitable control groups bearing in mind that ADHD covers a broad spectrum of inappropriate behaviour and may be associated with other disorders. Pre-clinical data shows that methylphenidate causes behavioural changes in animal models manifesting as hyperactivity and stereotyped behaviour so control of confounding will be an important issue in study design.