Safeguarding public health

MHRA

By email only to: jan.olov.larsson@telia.com

25 October 2010

RE: FOI 10 413 – request for answer from the MHRA to the manufacturers of methylphenidate products regarding their study feasibility assessment

Dear Mr Larsson

Thank you for your Freedom of Information Act (FOIA) request of 28th September 2010 about methylphenidate products. You asked for the answer from the MHRA to the manufacturers of methylphenidate products regarding their feasibility assessment of a study of long-term effects of methylphenidate on cognition and psychiatric outcomes.

The MHRA's assessment was that:

"The market authorisation holders (MAHs) have provided a very detailed assessment of the feasibility of conducting a scientifically valid, well-designed and suitably powered long-term safety study of the effects of methylphenidate on cognition and psychiatric outcomes as requested by CHMP resulting from the Article 31 referral. Their assessment concludes that such a study is not feasible, mainly due to reasons of severity of ADHD (i.e. potential for confounding by indication), difficulties with selection of a suitable comparator group and obtaining a suitable sample size.

We consider this to be an overly negative conclusion and contend that such a study is achievable. It is recognised that randomisation in the context of a clinical trial or an observational setting, is not possible, but it is still possible to design a prospective cohort study that would lead to interpretable data. Incorporating the element of propensity score adjustment to address the confounding by indication problem, and a multivariate analysis of data contrasting exposed and unexposed ADHD subjects could still lead to meaningful conclusions.

Although the MAHs point to the difficulty of ensuring in the long term that the unexposed patients are truly unexposed, it is still possible to explore from a range

of sources suitable groups that would render the multivariate adjustment for confounding factors between exposed and unexposed groups entirely feasible. The MAHs have been unduly pessimistic in their projection of 60% drop out in their sample size calculations and we would suggest 25% to 30% is more likely.

Subject to the outcome measures examined, and the assumptions regarding drop outs, odds ratios in the region of 1.5 noted in the MAHs' table are feasible to examine against a background of 20% in the unexposed group."

The MHRA's overall conclusion and recommendation to the MAHs for methylphenidate products authorised in the EU on this issue was as follows:

"The MAH assessment of the feasibility of conducting a long-term safety study concludes that such a study is not feasible, mainly due to reasons of severity of ADHD (i.e. potential for confounding by indication), difficulties with selection of a suitable comparator group and obtaining a suitable sample size. We consider this to be an overly negative conclusion and contend that such a study is achievable. The MAH should propose how a suitable study could be performed, taking into consideration the comments in this report on how many of the suggested limitations could be overcome."

I hope this information is of use to you.

Yours sincerely

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Vigilance and Risk Management of Medicines Division