Ritalin, 10 mg, tablets and Ritalin LA, 20, 30 and 40 mg modified-release capsules

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PART I - OVERALL CONCLUSION ON THE MEDICINAL PRODUCT

1 EXECUTIVE SUMMARY

This is a complete national bibliographic application concerning Ritalin tablets 10 mg, and Ritalin LA capsules 20, 30 and 40 mg formulated as modified release. Ritalin contains *d,l*-methylphenidate hydrochloride (*d,l*-MPH HCl). The application is based on well-established use of MPH, which has been used for the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy for 50 years.

Ritalin is intended for treatment of ADHD in children 6 years and older. The starting dose is 5 mg 1-2 daily, and the maximum dose is 60 mg daily (for a 6 year-old weighing 20 kg, this gives at maximum 3 mg/kg).

Concerta® was approved in 2002 following a MR procedure. Concerta® is a prolonged-release formulation of *d,l*-MPH and intended for children (6 years and older) and adolescents with an ADHD diagnosis. The recommended dosage is between 20 and 60 mg daily.

MPH has two chiral centres and can exist as four stereoisomers, two *erythro*- and two *threo*-enantiomer pairs. The therapeutic activity resides predominantly in the *d-threo*-enantiomer (*d*-MPH).

1.1 CHEMICAL/PHARMACEUTICAL ISSUES

The AR on the product Ritalin 10 mg tablets is communicated at this stage and the AR on the product Ritalin LA 20, 30 and 40 mg modified-release capsules will be communicated at a later stage, i.e. on reception of a clarification requested by the Authority in an e-mail communication with the Applicant on the 15th of December 2004.

In most parts the chemical/pharmaceutical documentation confirms the quality of the product, Ritalin tablets 10 mg. There are, however, some chemical/pharmaceutical issues as specified in part II of the assessment that need to be satisfactorily addressed prior to approval of the product.

1.2 PRECLINICAL EFFICACY AND SAFETY ISSUES

The Applicant has supplemented a bibliographic dossier with new reproductive toxicity studies.

Previous reproductive toxicity studies, public and related to other applications concerning methylphenidate, have shown equivocal results. However, in study 997034 conducted by the Applicant, MPH was shown to cause spina bifida and malrotated hind limbs in rabbit, with a margin less than 20 to maximum clinical systemic exposure. It can be concluded that MPH has shown reproductive toxicity in rodents and is likely to be teratogenic in rabbits. The 4.6 text of the SPC should be the same as for already approved Concerta®, which includes a contraindication for use in pregnancy.

From published literature it has been demonstrated that *d,l*-MPH is not mutagenic in bacteria *in vitro*, but weakly positive/equivocal at cytotoxic concentrations in studies on chromosome aberrations and sister chromatid exchanges in CHO cells. It can be concluded that *d,l*-MPH has some clastogenic activity in CHO cells, but these effects have been shown at high and cytotoxic concentrations. MPH holds a low genotoxic risk.

Regarding carcinogenicity, the significance of the increased incidence of hepatoblastomas and hepatocellular adenomas seen in mice to humans is not known. However, increases in liver tumours in mice but not in rats and with no findings in other organs is not an uncommon observation. Also considering the results from the genotoxicity studies, it can be concluded that MPH does not have a carcinogenic potential in humans.

There are no preclinical objections to concerning Ritalin tablets 10 mg, and Ritalin LA capsules 20, 30 and 40 mg.

1.3 Human Efficacy and Safety Issues

Clinical efficacy in the treatment of ADHD was demonstrated by 36 double-blind placebo-controlled and 21 active-controlled published studies. In addition two placebo-controlled studies were presented (one showing superiority over placebo on teacher-rated SKAMP attention, deportment and math tests in 34 children in a classroom setting; the other showing superiority over placebo on teacher-rated and parent-rated Conner's test in 137 children with ADHD in the usual home setting). Efficacy was proven within the dose range 10-40 mg/day of the MR methylphenidate drug Ritalin LA.

Clinical safety revealed the well-known pattern of side effects: headache (11.8%), insomnia (9.3%), abdominal pain (6.8%) and appetite decreased (6.8%). Children receiving methyl-phenidate should be regularly monitored for height and weight. On the whole, methylpheni-date was well tolerated and there were no reports of drug abuse in the studies presented. The risk of drug abuse and dissemination of the drug has been reported, but did not occur during the presented studies. This rare adverse event will probably be even lower with the new formulation, which does not require a second administration during the school day.

The benefit/risk ratio is sufficiently high, when diagnostic measures to define ADHD according to DSM-IV are observed.

1.4 Summary of Product Characteristics

See the SPC.

2 Overall Benefit/Risk Assessment

The overall benefit/risk assessment can not be assessed until the questions regarding the pharmaceutical and pharmacokinetic parts have been satisfactorily resolved.

3 Recommendation

3.1 Overall conclusion on the medicinal product

The application can not be recommended for approval before complementary information has been received and judged to be acceptable.