Part IC 3

Clinical Expert Report

Ritalin® (methylphenidate)

10 mg tablets

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The results of physical examinations are normal, and so the evaluation is essentially clinical and based on the following criteria: an interview with the parents and with the child, completed by information provided by teachers; the standardised observation of the child, as much as possible in the presence of the parents; psychometric tests, such as behavioural evaluation scales (Conners' scale, Barkley's questionnaire), the evaluation of intellectual efficiency, and the evaluation of cognitive functions (particularly language and the search for learning difficulties).

The estimated prevalence of the disease in the United States is about 3% of the pre-pubertal population (Goldman,1998), with a clear predominance among males and a greater frequency in some families (DSM III-R).
The epidemiological data in Italy is very limited, but the observations made at school level indicate that it is very frequent.

The aim of this report is therefore to provide a critical review of the therapeutic indications and safety of methylphenidate by analysing the documentation available in the international literature.

With reference to the AIC application, the requested indication is the treatment of attention disorders with or without hyperactivity (ADHD).

The bibliographical references, cited by author, are listed at the end of the report in alphabetical order by author.

It is important to stress that the active ingredient described in this report has been widely used as a reference drug in many clinical trials carried out over the last few decades.
This report will therefore summarise the most representative data for evaluating the rationale for admistering the product.

2. CLINICAL PHARMACOLOGY OF METHYLPHENIDATE

2.1 Pharmacodynamics

We shall here describe the mechanism of action, its correlations with therapeutic and side effects, and the correlations between the therapeutic and dose and plasma levels.
Ritalin® is a stimulant of the central nervous system (CNS). It is well known that CNS stimulants improve pathological hyperactivity in children (Elia,1999; Losier,1996), which is why Ritalin® has been proposed for the therapy of ADHD.
Like the other CNS stimulants, Ritalin® is presumed to act at the level of the central monoaminergic system by increasing monoamine release, inhibiting their

psychotherapy, behavioural therapy, educational and pedagogical interventions, and interventions relating to social and environmental factors (Vallée,1991)
Other drugs have been used in the case of intolerance or comorbidity.
It has been shown that tricyclic antidepressants have some efficacy in the treatment of behavioural disturbances and are more useful in the case of a concomitant depressive syndrome or anxiety disorders. They can also be prescribed for children at risk of toxicomania or with a personal or family history of tics. Their side effects are more frequent and more severe than those of psychostimulants and they must therefore be considered second-choice treatments.
Some physicians in the United States also use MAOI as first-choice therapy, particularly because of their rapidity of action; however, the considerable risk of pharmacological or dietary interactions greatly limits their interest.

Clonidine is not efficacious in the treatment of attention disorders without hyperactivity. It is useful in children who do not respond to or cannot tolerate psychostimulants, and in those with growth alterations or associated tics. Some authors have pointed out the greater interest of clonidine in cases involving prevalently aggressive behaviour (Mervyn Fox,1993; Hunt, 1987).

6. CONCLUSIONS/RISK-BENEFIT RATIO

Attention deficit hyperactivity disorder is a serious disease because it leads to both short-term (scholastic failure and the rejection of the child by his/her environment) and long-term-risks, including the development of an antisocial personality with or without alcohol or drug abuse.

In conclusion, a large number of controlled studies of well-defined doses of Ritalin® have shown that it is efficacious in improving the symptoms of ADHD syndrome and the educational and social difficulties arising from it.
Its tolerability profile is particularly well known because it has been used in clinical practice for 40 years. The observed effects are mainly benign and transient (reduced appetite, sleep disorders, headache, gastralgia and irritability; more rarely, the appearance or exacerbation of tics).

The manifestation of growth disturbances is now much more limited provided that the proposed treatment-free intervals are respected. In the same way, acquired experience does not confirm the risk of drug abuse in children treated with psychostimulants.
The proposed therapeutic regimen also foresees beginning treatment at a dose of 0.3 mg/kg, with progressive increases up to a limit of 1 mg/kg/die given in 2-3 daily administrations and the use of treatment-free intervals during periods requiring less commitment, such as school holidays. Periodic individual controls during the course of