Attention-deficit–Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed behavioural disorders during childhood, occurring in about 4% of all school-age children. Fortunately, in recent years ADHD management has improved considerably. For treatment, several novel second-generation, once-daily methylphenidate formulations are currently available, aiming at easing symptom control, especially during school hours, and enhancing compliance by lower dosing intervals. These new formulations are as efficient as immediate-release (IR) methylphenidate drugs, which have to be administered at least twice a day.\(^1\) The outstanding feature of these novel formulations is their combination of an IR and an extended-release (ER) compound. In the case of Equasym XL, 30% of the total dose guarantees fast relief in the morning and 70% provides a long-lasting effect until the afternoon. The efficacy of this new product, which was especially developed for the daily routine of elementary-school children and high-school students, has been confirmed in various studies.

**Compliance and Its Impact – No Need for Drugs That Are Not Taken**

When psychosocial measures alone are insufficient, methylphenidate is one of the drugs of first choice for symptomatic treatment of patients with ADHD. As with all drugs, however, compliance increases with fewer administrations. In addition, children in particular often feel embarrassed to take prescription drugs in the presence of other children; therefore, they prefer to skip their medication rather than being teased. Thus, a once-daily drug administration before going to school is considered a great advantage by the afflicted and their parents. Without endangering immediate symptom control, this goal was achieved by combining IR with ER methylphenidate in one drug. While the IR compound of the drug is responsible for a fast effect – which, however, is of only short duration – the ER ingredient leads to a lasting effect throughout the afternoon for sustained relief of symptoms. Today, several second-generation methylphenidate formulations given only once a day are available either as capsules, such as Equasym XL, or as tablets, aiming at easing symptom control, especially during school hours, and enhancing compliance by lower dosing intervals. However, these once-daily formulations use different delivery systems, resulting in different pharmacokinetic profiles.\(^2\)

**Optimal Immediate-/Extended-release Ratio for a Quick and Lasting Effect**

Before Equasym XL was put on the market, the optimal dose ratio for a controlled-delivery formulation of methylphenidate was investigated. Studies were performed in healthy adults as well as in children with ADHD, investigating 20:80, 30:70 and 40:60 IR/ER prototype formulations. Efficacy measures included the Swanson, Kotkin, Atkins, M/Flavyn, Pelham (SKAMP) scale and the 10-minute permanent products measure of performance (PERMP) test.\(^3\) Pharmacokinetic analyses in the healthy volunteers revealed that all three formulations led to biphasic methylphenidate plasma concentrations with initial peaks approximately 1.5 hours after drug intake and another peak five to eight hours thereafter; however, the magnitude differed for the various agents. Since the 30:70 and 40:60 formulations were more comparable to twice-daily IR methylphenidate (Ritalin\(^\text{®}\)), these agents were further investigated in children with ADHD. Both formulations given once a day in the mornings were effective in controlling ADHD symptoms and were superior to placebo treatment in the primary efficacy measures. They both had promising profiles, yet the 30:70 formulation was preferred and chosen for commercial development due to its more consistent treatment effect over the entire study observation period\(^4\) and its superiority during morning hours, a time particularly important to children, who have to give their best in school.

**Non-inferiority**

When the clinical efficacy of once-daily modified-release (MR) methylphenidate capsules (Equasym XL) was compared with that of twice-daily IR methylphenidate (Ritalin\(^\text{®}\)) in a randomised, placebo-controlled, multicentre trial in 318 children with ADHD aged six to 12 years, non-inferiority was demonstrated.\(^1\) After a study period of three weeks it was also confirmed that children treated with either one of the drugs were better off than those receiving placebo (p<0.001 for both treatment arms). Both therapeutic options were well tolerated and superior to placebo in reducing ADHD symptoms, as assessed by clinicians, teachers and parents. Thus, two essential properties of this novel formulation – i.e. tolerability and efficacy similar to those of their short-acting counterparts – were confirmed.

**Pharmacodynamic Differences**

The various products on the market also differ with regard to their IR and ER methylphenidate ratios. For MR methylphenidate capsules (Equasym XL, also marketed as Metadate\(^\text{®}\) CD: 30/70), which is licensed in most European countries as part of comprehensive treatment programmes for children over six years of age and adolescents, 30% of its total dose is provided for IR, whereas 70% of the capsule’s ingredients are delivered by polymer-coated beads for ER to maintain efficacy for a prolonged period of time. In this way, fast and reliable symptom control in the morning hours and long-lasting effects until late afternoon are guaranteed. In MR methylphenidate tablets (Concerta\(^\text{®}\) 22/78), 22% of the total daily dose is

---


immediately set free and 78% is continuously delivered by osmotic release, leading to lower initial methylphenidate plasma concentrations.

**Adjusting Plasma Concentrations to Times of High Demand at School**

As mentioned above, galenic differences among the various products do exist, and the distinct IR/ER methylphenidate ratios of Concerta and Equasym XL are responsible for different pharmacodynamic effects on surrogate measures of behaviour and performance in children with ADHD. This considerable heterogeneity in pharmacodynamics was recently demonstrated by the randomised, double-blind, placebo-controlled, cross-over Comparison of Once-daily Methylphenidate in an Analogue Classroom Setting (COMACS) trial, a well-planned and well-designed comparison study that succeeded in recreating a classroom setting with trained instructors responsible for evaluation of outcome. In this study, Equasym XL and Concerta – two different orally administered, once-daily methylphenidate formulations, both consisting of a mixture of IR and ER methylphenidate – were investigated and compared with placebo in 184 children with confirmed ADHD aged between six and 12 years.

Evaluation was based on the results of the SKAMP rating scales (total scores reflecting both deportment and attention items) immediately after drug intake and at 1.5-hour intervals thereafter until a total of 7.5 hours had passed. The last assessment took place 12 hours after drug administration. In addition, academic productivity (maths tasks) using PERMP served for evaluation.

In the laboratory school setting, both Equasym XL and Concerta produced visible and significantly different pharmacodynamic effects in terms of behaviour, attention and performance in elementary-school children with ADHD. Different efficacy patterns were observed throughout the day. In the morning hours, Equasym XL revealed the highest efficacy (Equasym XL superiority), while in the afternoons Equasym XL and Concerta showed similar efficacy. As expected, superiority at any point was achieved by the formulation with the highest methylphenidate plasma concentration: the higher the methylphenidate plasma concentration, the better the clinical outcome. These results were reflected in SKAMP total scores: the lower the SKAMP score, the better the clinical outcome. Figure 1 shows that obeying rules was more difficult for children with ADHD receiving only placebo. Once-daily MR capsule and tablets led to significantly better results than placebo (p<0.016); however, Equasym XL achieved the best results 1.5–4.5 hours after drug administration, while Concerta was superior 12 hours after ingestion. Moreover, attention and performance were considerably improved. The number of maths tests solved at each assessment was also higher among those children receiving once-daily MR methylphenidate capsules or tablets instead of placebo (p<0.016) (see Figure 2). Again, Equasym XL showed superiority early on after ingestion.

**Consequences for Clinical Routine**

According to these results, Equasym XL is considered a real alternative with great benefits, particularly during morning sessions in school and lasting effects until the afternoon. This is in line with the fact that the MR methylphenidate capsules were especially developed for the daily routine at school. Thus, a new and promising therapeutic option has emerged for school children with ADHD symptoms that allows for an individually tailored and adaptive treatment, as recommended by the European guidelines for the assessment and treatment of children with ADHD.

The data also showed that the total daily exposure to methylphenidate may be limited to the times that are most important to school children, thus targeting a specific period of the day for maximum efficacy.

**Gender Counts**

In paediatric patients with ADHD, significant gender differences in response to once-daily methylphenidate formulations throughout the day were reported. New study results (data derived from a secondary analysis of the COMACS study) included a total of 184 children, among them 48 females) revealed that females show a more pronounced initial effect in the mornings yet a faster decline in the evenings than males when receiving either one of the novel once-daily methylphenidate formulations. In comparison with boys, girls had a statistically superior response 1.5 hours after drug intake, but an inferior response 12 hours afterwards. The authors concluded that physicians need to be aware of these sex-related differences in paediatric ADHD patients, particularly in the latter part of the day. The response of female patients may thus require additional assessments later in the day to determine the optimal dose.

---