CONCERTA® (methylphenidate HCl ER)
Use of CONCERTA in Adolescents with ADHD

SUMMARY

- CONCERTA is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adolescents aged 13 to 17 years in doses up to 72 mg/day.[1]
- The efficacy and safety of CONCERTA (OROS methylphenidate [MPH]) in adolescents with ADHD were evaluated in a multiphase, multicenter trial[2] and in a community study.[3]

PRODUCT LABELING

Please refer to the following sections of the CONCERTA Full Prescribing Information that are relevant to your inquiry[1]: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, and CLINICAL STUDIES.

CLINICAL DATA

Multicenter, Controlled Study

Wilens et al (2006)[2] evaluated the efficacy and safety of CONCERTA 18 mg up to 72 mg in adolescents aged 13-18 years with ADHD (N=220).

Study Design/Methods

- Four phases: a one-week washout phase; an open-label dose titration phase; a randomized, placebo-controlled, double-blind phase; and an open-label follow-up phase.
- Eligible subjects underwent a one-week washout phase during which no ADHD medication was given, and at the end of which baseline measurements were made.
- In the open-label dose titration phase, subjects (n=220) were initiated with once-daily CONCERTA 18 mg for 7 days. The dose was increased weekly (±2 days) by 18 mg increments to a maximum of 72 mg daily until the criteria for improvement in ADHD symptoms, measured on the investigator-scored ADHD Rating Scale (ADHD RS), was achieved. The criteria for improvement was described as a reduction of ≥30% from baseline in ADHD symptoms and a rating of "good" or "excellent" by the Global Assessment of Effectiveness (GAE).
- 177 subjects who successfully completed the dose titration phase continued to the randomized, double-blind phase. Subjects received their individualized CONCERTA dose (18 mg, 36 mg, 54 mg, or 72 mg) or a matched placebo once daily for 2 weeks, based on their dosage from the dose titration phase.
- At the end of each week, efficacy, safety and adherence were assessed. Efficacy was assessed using the ADHD RS (investigator and parent/caregiver), Conners-Wells' Adolescent Self-Report Scale (CASS-L), Child Conflict Index (CCI) (parent/caregiver), the GAE (investigator) and the Clinical Global Impressions (CGI) Improvement subscale (investigator).
- The primary efficacy measure was the change from baseline to the end of the double-blind phase in the total investigator-rated ADHD RS score. Subjects who completed the double-blind phase or discontinued the double-blind phase prematurely because of lack of efficacy were eligible to enter the 8-week, open-label phase at their individualized CONCERTA dose.

Results

Efficacy

- CONCERTA was statistically and clinically significantly superior to placebo on the primary measure of efficacy, the mean change from baseline in investigator rating on the ADHD RS (P=0.001).

- Post hoc analysis of responder rates showed that significantly more subjects responded to treatment with CONCERTA than placebo for all efficacy measures. Similar results were reported by parents/caregivers.
- Additionally, CONCERTA demonstrated significant superiority on the Conners-Wells' Self-Report Scale for subject rated efficacy compared to placebo (*P*=0.001).
- Adolescent-parent conflict was also significantly improved with CONCERTA compared to placebo (*P*=0.005), using the Child Conflict index.
- At the end of the double-blind phase, 51% of subjects in the CONCERTA group reported treatment as good or excellent as measured by the GAE, compared to 33% of subjects receiving placebo (*P*=0.004).
- A significantly higher number of investigators considered ADHD symptoms in their study subjects to be much improved or very much improved with CONCERTA (52%) compared to placebo (31%) (*P*=0.01).

Safety

- The most frequently reported study-drug related adverse event was headache (placebo, 7%; CONCERTA, 3%). Other treatment emergent events from the double-blind phase included decreased appetite (CONCERTA, 2%; placebo, 0%), insomnia (CONCERTA, 5%; placebo, n=0), and abdominal pain (CONCERTA, 1%; placebo, 2%).
- Early discontinuations occurred in 28 subjects (31%) from the placebo group and 16 (18.4%) in the CONCERTA group. Discontinuation from the study was primarily due to lack of efficacy (placebo, 25.6%; CONCERTA, 16.1%).

Open-Label Extension of Multicenter, Controlled Study

McGough et al (2006)[4] evaluated the safety and tolerability outcomes from the open-label extension phase of the multicenter controlled study in adolescents.[2]

Study Design/Methods

- 8-week, open-label extension phase
- Subjects who continued in the extension phase received their individualized daily dose of CONCERTA, which was determined during the dose titration phase of the multicenter controlled study.
- Safety assessments were collected on a monthly basis.

Results

- A total of 171 (97%) of 177 subjects continued in the open-label extension phase, and 135 (79%) completed the extension phase.
- The individualized doses were as follows: 18 mg/day (n=12), 36 mg/day (n=48), 54 mg/day (n=49), 72 mg/day (n=62).
- A total of 96 (56%) subjects reported 189 adverse events, most of which were reported as mild or moderate in severity.
    - Eighty (42%) adverse events were considered to be treatment-related by investigators.
- There was no statistically significant difference in the percentage of subjects reporting adverse events among the CONCERTA treatment groups.
- The most frequently reported treatment-related adverse events were headache (12%), anorexia/decreased appetite (8%), insomnia (4%), and weight loss (2.3%).
- No clinically significant changes were observed with regard to blood pressure and ECG measures.
- When adverse events were evaluated according to weight-based doses, there was no trend showing that the higher weight-adjusted doses were associated with increased adverse events; CONCERTA was well tolerated up to 1.84 mg/kg/day.

Sub-Analysis of Open-Label, Dose-Titration Phase of Multicenter, Controlled Study

Newcorn et al (2010)[5] conducted a sub-analysis of the multicenter placebo-controlled trial conducted by Wilens et al[2] to assess the dose-response characteristics in adolescents aged 13-18 years (N=220) treated with CONCERTA during the 4-week, open-label, dose-escalation phase.

Study Design/Methods

- Open-label, dose-titration phase
- Dose titration was based on achievement of clinical response, which was defined as a reduction in the ADHD RS total score of ≥30% and a rating of either 'good' or 'excellent' on the GAE scale.
- Patients were initiated on CONCERTA 18 mg/day and were evaluated for one week; if clinical response was not achieved, the dose was titrated by 18 mg increments on a weekly basis for up to four weeks with a maximum dose of 72 mg/day.

Results

- At the end of the dose-titration phase, 182 (83%) of the initial 220 subjects had successfully titrated to an effective once-daily dose of CONCERTA.
- A linear dose-response relationship was observed, with more non-responders achieving pre-defined threshold response with each escalated dose level.
- 49 (27%) subjects achieved criterion improvement with 54 mg/day, and 70 (38%) achieved criterion improvement with 72 mg/day.
- There were no significant relationships between absolute dose and subject weight, height, or age.
- However, baseline symptom severity (specifically hyperactive-impulsive symptoms) was identified as a predictor of higher CONCERTA dose; when evaluating this relationship, a weight-based approach was slightly more sensitive than an absolute dosing strategy.
- The incidence or severity of adverse events did not correlate with increases in absolute dose.

Community Setting Study

Schnipper and McDaniel (2001)[3] studied the effectiveness of once-daily CONCERTA in adolescents aged 13 to 17 years with ADHD (n=256) in a community setting.

Study Design/Methods

- Adolescents receiving methylphenidate (MPH) prior to study initiation were assigned a daily CONCERTA dose of 18, 36 or 54 mg based on previous MPH dose and clinical judgment.
- Treatment naïve subjects were initiated with a CONCERTA dose of 18 mg, which was subsequently titrated in 18 mg increments to a safe and effective dose to not exceed 54 mg.
- Doses were adjustable over the 9-month study at weekly intervals up or down between 18, 36, and 54 mg based on investigator discretion. Treatment effectiveness was assessed at baseline and at the end of months 3, 6 and 9. Safety assessments were performed at baseline and after 1, 2, 3, 6, and 9 months of treatment. Ninety-one percent of adolescents enrolled (n=256) were receiving stimulant medication at enrollment.

Results

- At the time of the interim analysis, 219 (83.2%) adolescents had received at least 3 months of CONCERTA therapy.
- At month 3, 84.4% of parents/caregivers rated CONCERTA treatment as good or excellent using Global Assessments of treatment effectiveness.

- At month 6, 96.8% of parent/caregivers rated CONCERTA therapy as good/excellent. The Investigator's Global Assessments of effectiveness showed similar results.
- At month 3 or at final assessment (if treatment was discontinued earlier) parent/caregiver satisfaction was examined. Of this group, 87.5% of parents reported being satisfied, very satisfied, or extremely satisfied with CONCERTA therapy. CONCERTA therapy was preferred to prior medication to control ADHD symptoms by 75% of parents/caregivers. The reasons cited were as follows: increased convenience (84.1%), longer duration of effect (72.5%), and improved consistency and smoothness of effect (67.6%).
- Once-daily CONCERTA therapy was well tolerated with 155 adolescents (60.6%) experiencing no adverse events. The most frequently reported adverse events included: headache, upper respiratory tract infection pharyngitis, accidental injury, and anorexia.

SELECTED ADDITIONAL REFERENCES

Additional studies have been conducted with CONCERTA in adolescents with ADHD and the citations are included for your reference.[6-25]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 12 March 2024. Please note that the topic pertains specifically to the use of CONCERTA (OROS MPH) for the treatment of ADHD in adolescents.

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