CONCERTA® (methylphenidate HCl ER)
Dosing - Dosing of CONCERTA Over 72 mg Per Day in Adults

SUMMARY

- The maximum approved dose of CONCERTA (methylphenidate) HCl Extended-Release CII in adults is 72 mg/day. Dosing over 72 mg/day in adults is not recommended.[1]
- In a pivotal trial of CONCERTA in adults with attention deficit/hyperactivity disorder (ADHD) conducted in the United States, the maximum allowable dose was 108 mg/day.[2]
- There have been several studies in which adults were titrated up to 144 mg/day of CONCERTA.[3-12]
- The studies demonstrated efficacy of CONCERTA at higher doses in adults with ADHD. In some of the studies, CONCERTA was associated with weight reductions, as well as small but statistically significant changes in cardiovascular parameters.

PRODUCT LABELING

Please refer to the following section of the enclosed Full Prescribing Information that is relevant to your inquiry[1]: DOSAGE AND ADMINISTRATION, Dose Titration.

CLINICAL DATA: RANDOMIZED, CONTROLLED STUDIES

Adler et al (2009)[2]

Study Design/Methods

- Randomized, placebo-controlled, double-blind, dose-escalation study investigating the safety and efficacy of CONCERTA in adults with ADHD (N=229)
- Subjects were randomized to CONCERTA (n=110) beginning at 36 mg/day or placebo (n=116) for a 5-week titration period.
- Doses were increased in 18 mg increments every 7 days and continued until the primary endpoint was achieved or maximum dose of 108 mg/day was reached.
- The primary efficacy endpoint was the change in baseline ADHD Investigator Symptom Report Scale (AISRS) total score.
- The percentage of study responders as defined by a 30% decrease in AISRS score, and a Clinical Impression-Improvement (CGI-I) rate of 1 (very much improved) or 2 (much improved) from baseline to endpoint were also assessed as secondary outcome measures.

Results

Efficacy

- The mean final doses for CONCERTA and placebo were 67.7 mg/day and 86.9 mg/day, respectively.
- There was a statistically significantly greater improvement in baseline AISRS total score in subjects treated with CONCERTA (-10.6) compared with placebo (-6.8) at study endpoint (p=0.012).
- Similar results were observed for improvements in CGI-I in subjects taking CONCERTA compared to placebo (3.02 vs. 3.43, respectively; p=0.008).
- Additionally, 36.9% of subjects in the CONCERTA group were considered responders based on their AISRS and CGI-I scores compared to 20.9% in the placebo group (p=0.009).

Safety

- In the CONCERTA group, 84.5% of subjects reported an adverse event compared to 63.8% of subjects in the placebo group.

- Adverse events reported by at least 10% of CONCERTA subjects compared to the placebo group included: decreased appetite (25.5% for CONCERTA vs 6.0% for placebo), headache (25.5% vs 13.8%), dry mouth (20% vs 5.2%), anxiety (16.4% vs 3.4%), nausea (12.7% vs 2.6%) and increased blood pressure (10% vs 5.2%).
- Adverse events leading to discontinuation of therapy were reported in 14.5% of subjects in the CONCERTA group compared to 5.2% of subjects in the placebo group.
- In the CONCERTA group, mean changes (mm Hg) in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse were -1.2, +1.1, and +3.6 bpm, respectively. These changes for placebo were -0.5, +0.4, and -1.6 bpm, respectively.

Biederman et al (2006)[3]

Study Design/Methods

- Randomized, double-blind, 6-week, placebo-controlled study evaluating the safety and efficacy of once-daily CONCERTA in the treatment of adults with ADHD (N=141)
- CONCERTA was initiated at 36 mg/day and titrated to optimal response up to 1.3 mg/kg/day (maximum of 144 mg/day).

Results

Efficacy

- The mean daily dose of CONCERTA at week 6 was 80.9±31.8 mg (0.99±0.32 mg/kg).
- Clinically and statistically significant reductions in symptoms of inattention and hyperactivity/impulsivity were observed in subjects treated with CONCERTA.
- Sixty-six percent of patients on CONCERTA (n=44) and 39% of patients receiving placebo (n=23) attained the response of much or very much improved on the CGI-I scale ($p=0.01$) plus a >30% reduction in AISRS score ($p<0.001$).

Safety

- CONCERTA was associated with small but statistically significant increases in SBP (3.5±11.8 mm Hg), DBP (4.0±8.5 mm Hg), and heart rate (HR) (4.5±10.5 bpm), but with statistically significant decrease of ECG QT interval.
- Adverse events associated with CONCERTA use included anorexia, dry mouth, gastrointestinal problems, tension/jitteriness, insomnia, cardiovascular complaints, depression, anxiety, and dizziness. These events were statistically significant compared to placebo.

Reimherr et al (2007)[4]

Study Design/Methods

- Double-blind, placebo-controlled, 8-week, crossover study assessing the efficacy of CONCERTA in adults with ADHD (N=41)
- CONCERTA was initiated at 18 mg/day and then increased every 2-3 days to a maximum daily dose of 90 mg. The maximum tolerated dose was then held constant for 2 weeks.
- Efficacy was assessed using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), the Adult ADHD Rating Scale (ADHD-RS), and the CGI-I scale.

Results

Efficacy

- The overall results demonstrated that there were statistically significant decreases in ADHD symptoms with regard to the mean total WRAADDS score (42% for CONCERTA vs. 13% for placebo, p<0.001).
- The mean ADHD-RS score decreased 41% on CONCERTA and 14% on placebo (p=0.003).
- In terms of improvement in CGI-I score, 54% of subjects who received CONCERTA and 22% of subjects who received placebo achieved "much" or "very much improved" scores (p=0.018).

Safety

- Treatment with CONCERTA was associated with small but statistically significant increases in both SBP and DBP (p=0.064 and p=0.042, respectively).
- There was a mean weight reduction of 2.5±3.8 lb in subjects who received CONCERTA versus an increase of 1.3±4.3 lb in subjects who received placebo.
- There was a statistically significant drug-placebo difference with regard to changes in QT interval (369±29.5 m sec for placebo vs. 387.3±33.1 m sec for CONCERTA, p=0.001); however, there was no significant difference in QTc interval.
- Adverse events which were statistically significant and deemed to be related to CONCERTA included sleep disturbance, decreased appetite, and/or anxiety.

Biederman et al (2007)[5]

Study Design/Methods

- Double-blind, randomized, placebo-controlled, 6-week study assessing the impact of psychiatric comorbidity and concomitant use of serotonergic reuptake inhibitors (SRIs) on the Efficacy of CONCERTA in adults with ADHD (N=182)
- In addition to ADHD, patients with a history of psychiatric comorbidity without active symptoms and those treated for anxiety (ANX) or depression (MDD) disorders on a stable medication regimen for at least 3 months were included in this study.
- Adults were randomized to CONCERTA 36 mg/day or placebo. The dose was then titrated in increments of 36 mg up to a maximum of 1.3 mg/kg/day.
- Patients were stratified by concomitant SRI use (n=12), ADHD comorbidity with mood or anxiety disorder (n=36), and with ADHD only (n=41).
- Efficacy measures were assessed using the CGI and the AISRS.

Results

Efficacy

- At the end of the study, CONCERTA treated subjects achieved significantly greater reduction in AISRS score compared to those in the placebo group (p=0.0006).
- There were no clinically or statistically significant differences across cohorts with regard to improvement in CGI score, a 30% change in AISRS score from baseline, and clinical response (which was defined as CGI≤2 and AISRS – 30%).

Safety

- With the exception of small changes in PR intervals, treatment with CONCERTA did not result in statistically significant changes in cardiovascular parameters.

Chronis-Tuscano et al (2008)[13]

Study Design/Methods

- Randomized, placebo-controlled, double-blind, dose-titration study investigating dose-related effects of CONCERTA on parenting behaviors in mothers with ADHD (N=23)

- The study included mother-child dyads, both with diagnosed ADHD.
- Over a 5-week period, mothers received CONCERTA which was titrated to their optimal dose (starting with placebo, then CONCERTA 36 mg/day, 54 mg/day, 72 mg/day, up to maximum 90 mg/day).
- Following the 5-week titration period, mothers were randomized to placebo or their maximally effective dose for 2 weeks.
- Primary efficacy measures included maternal ADHD symptoms as measured by Conners' Adult ADHD Rating Scale (CAARS), and parenting as measured by the Alabama Parenting Questionnaire (APQ).

Results

Efficacy

- During the titration period, 75% of subjects were titrated to CONCERTA 90 mg; the remaining 25% were titrated to 72 mg. Mean dose of CONCERTA at the end of titration was 83.7 mg/day (or 1.26±0.25 mg/kg).
- At the end of the titration period, CONCERTA was associated with a statistically significant reduction in self-reported CAARS inattention ($p<0.0001$), hyperactivity/impulsivity ($p<0.01$), and ADHD index scores ($p<0.05$).
- Inattention was significantly reduced on 54 mg ($p<0.001$), 72 mg ($p<0.0001$) and 90 mg ($p<0.005$) relative to placebo. Hyperactivity/impulsivity was significantly reduced at 72 mg ($p<0.001$) and 90 mg ($p<0.01$) compared to placebo.
- For the APQ, significant dose effects were observed for inconsistent discipline (with improvements noted at 72 mg and 90 mg; $p<0.01$) and for use of corporal punishment (with improvements noted at 54 mg [$p<0.05$], 72 mg [$p<0.01$], and 90 mg [$p<0.0001$]).

Safety

- A significant dose effect on weight was found ($p<0.0001$). A weight loss from baseline to 90 mg ranged from 0 to 6.90 kg, with a mean loss of 2.31±1.62 kg.
- There were no serious adverse events or reports of suicidality, psychotic symptoms or mania, or significant blood pressure/heart rate changes.
- However, one patient withdrew during the third week of the titration period due to increased blood pressure and heart palpitations while taking CONCERTA 36 mg (no conduction abnormalities were detected on an electrocardiogram).

Mick et al (2007)[6]

Study Design/Methods

- Single-blind, randomized, 6-week, parallel-design study examining the efficacy, tolerability, and adherence of CONCERTA substitution in adults with ADHD receiving immediate release (IR) MPH administered three times daily (N=53)
- Immediate release MPH responders were randomized to either continue IR MPH therapy (n=12) or to receive an equipotent dose of CONCERTA (n=41).
- The maximum daily dose of MPH was 1.3 mg/kg or 144 mg per day.
- Efficacy was assessed using the AISRS while tolerability was evaluated using the CGI.

Results

Efficacy

- Throughout 6 weeks of treatment, there was no clinically or statistically significant difference between the treatment groups with regard to AISRS rating scale.

- There were no differences in terms of maintenance of clinical Efficacy, tolerability, or satisfaction at the end of the study in subjects continuing IR MPH and those switched to CONCERTA.

Safety

- Analysis of changes in cardiac parameters and spontaneously reported adverse events showed no clinically or statistically significant differences between subjects switched to CONCERTA and those continuing IR MPH.

CLINICAL DATA: OPEN-LABEL STUDIES

Ginsberg et al (2012)[11] and **Ginsberg et al (2015)**[12]

Study Design/Methods

- The authors evaluated the long-term effects of CONCERTA in male prison inmates (N=30) with ADHD who were enrolled in a 52-week trial, which was followed by a 3-year naturalistic observation study.
- The first phase of the study was a 5-week, double-blind, placebo-controlled trial where inmates were randomized to CONCERTA 72 mg/day (n=15) or placebo (n=15).
  - The primary endpoint was the change from baseline in the CAARS - Observer: Screening Version (CAARS-O:SV).
  - The secondary endpoint was the frequency of patient-reported ADHD symptoms as measured by the Adult ADHD Self-Report Scale (ASRS).
- After the randomized phase, all 30 patients entered the 47-week open-label extension and were treated with CONCERTA (dose titrated up to 1.3 mg/kg/day). The median dose of CONCERTA was 108 mg/day or 1.1 mg/kg/day for the 25 patients who completed the 52-week study.
- Twenty-five patients entered the observation study which had assessments at 1 and 3 years (total time on CONCERTA was 2 and 4 years, respectively). The median dose of CONCERTA was 142 mg/day for the 20 patients still receiving treatment at the 1-year assessment. The median dose of CONCERTA was 144 mg/day for the 15 patients still receiving treatment at the 3-year assessment.

Results

Efficacy

- The mean decrease in CAARS-O:SV score from baseline to week 5 was 19.6 (95% CI 14.7-24.5; p<0.001) in the CONCERTA group and 1.9 (95% CI -0.4 to 4.2) in the placebo group. The Cohen's *d* score was 2.17.
- The mean decrease in CAARS-OV:SV score from baseline to week 52 was 29.3 (95% CI 25.6-33.0) in the CONCERTA group and 22.4 (95% CI 16.6-28.2) in the placebo/ CONCERTA group.
- The mean decrease in ASRS score from baseline to week 5 was 17.1 (95% CI 9.5-24.4; p=0.003) in the CONCERTA group and 2.1 (95% CI 0.02-4.1) in the placebo group. The Cohen's *d* score was 1.67.
- The mean decrease in ASRS score from baseline to week 52 was 30.7 (95% CI 22.0-39.3) in the CONCERTA group and 24.1 (95% CI 16.5-31.6) in the placebo/ CONCERTA group.
- Significant decreases from baseline CAARS-O:SV and ASRS scores were observed at both the 1- and 3-year assessments during the long-term observation study (p<0.001 for all comparisons). The mean CAARS:O-S decreased from a mean pretrial score of 39.8 to a score of 17.2 at 3 years (n=20).

Safety

- Mucosal dryness was reported more frequently in the CONCERTA group than the placebo group during the randomized phase of the trial. There were no serious adverse events.
- The most frequently occurring adverse events during the 52-week study were abdominal discomfort, headache, mucosal dryness, depressed mood, loss of appetite, anxiety, diarrhea, sweating, interrupted sleep, and fatigue.
- SBP increased by 21.5 mmHg (95% CI 8.9-34.0) and the DBP increased by 11.0 mmHg (95% CI 4.9-17.1) in patients treated with CONCERTA for 52 weeks. SBP increased by 6.3 mmHg (95% CI -6.7 to 19.2) and the DBP increased by 0.5 mmHg (95% CI -4.9 to 5.9) in patients treated with placebo/ CONCERTA for 52 weeks.

Adler et al (2011)[14]

Study Design/Methods

- Open-label, dose-titration, flexible dose, long-term study evaluating the long-term safety of CONCERTA in adult patients with ADHD (N=550)
- Patients were initiated on CONCERTA 36 mg once daily and titrated in 18 mg increments every 7 days until they reached a maximum dose of 108 mg daily or until a predefined treatment response of a decrease in AISRS score from baseline by >30% and a CGI-I score of 1 (very much improved) or 2 (much improved) was reached.
- Once the subjects reached the maximum dose or met predefined treatment responder criteria, they continued treatment for either 6 or 12 months.
- Efficacy measures included the AISRS scores, the Global Assessment of Effectiveness, and CGI.

Results

Efficacy

- Fifty-seven percent (n=146) of subjects in the 6-month duration and 44% (n=129) of subjects in the 12-month duration completed the study. The mean final dose of CONCERTA was 67.4 mg daily.
- The mean change in AISRS scores from baseline to final titration visit was –17.2 points, and 73.5% of subjects were classified as responders at the final titration visit. The mean change in AISRS scores from baseline to final observation visit was -18.7.

Safety

- Of the 91.6% of subjects reporting at least one treatment-emergent adverse event, 1.5% reported serious adverse events of which none were considered by the investigators to be drug-related.
- Adverse events that resulted in study withdrawal occurred in 18.2% of subjects with incidence reported in ≥2% of subjects were anxiety (3.3%) and insomnia (2.2%).
- The most commonly reported adverse events (in ≥10% of subjects) included: decreased appetite (26.7%), headache (24%), insomnia (20.7%), and dry mouth (14.7%).
- Dose reductions due to an adverse event were reported in 30.4% of subjects with the most common reasons being increased heart rate (4%), increased blood pressure (3.8%), and irritability (3.3%).
- Overall, 9.6% of the subjects experienced SBP >140 mm Hg, 12% experienced DBP >90 mm Hg, 10.2% experienced HR >100 bpm, and 11.2% experienced greater than 10% weight loss.
- No clinically significant changes in ECG measurements were observed.

Buitelaar et al (2011)[15]

Study Design/Methods

- **Buitelaar et al (2011)**[15] continued to evaluate the safety and tolerability of CONCERTA in adults with ADHD who were enrolled in the LAMDA trial conducted by **Medori et al (2008)**[16] and the 7-week open-label extension conducted by **Buitelaar et al (2009)**[17].
- 52-week, open-label extension study of the LAMDA trial
- Subjects who completed the 5-week double-blind LAMDA trial and the 7-week open-label extension were eligible to enroll in the 52-week open-label phase. At the end of the open-label study, subjects who received at least 52 weeks of treatment with CONCERTA were eligible to participate in a 4-week, randomized, double-blind, placebo-controlled withdrawal phase.
- Subjects received a flexible dose of CONCERTA 18 mg/day up to a maximum of 90 mg/day.

Results

Safety

- 155 subjects entered the open-label study, and 99 subjects completed the open-label phase.
- The mean daily dose of CONCERTA was 52.8±21.0 mg.
- During the open-label period, 126 subjects (81.3%) reported at least one treatment-emergent adverse event.
- Adverse events that resulted in study withdrawal in >1 patient included insomnia, depressed mood, and hypertension (all n=2, 1.3%).
- Mean changes from baseline in SBP, DBP, and HR were 0.3±14.0 mm Hg, 1.4±9.7 mm Hg, and 0.9±14.4 bpm, respectively. Abnormally high blood pressure values were reported in 21.7% of subjects (for SBP >140 mm Hg) and in 17.1% of subjects (for DBP >90 mm Hg) at any post-baseline visit during the open-label phase. Pulse rate >100 bpm was reported in 9.2% of subjects.

Efficacy

- In the open-label phase, the mean CAARS:O-SV total score improved from baseline to endpoint with a reduction of 1.9±7.8 ($p \leq 0.01$).
- CAARS Self-rated Short Version (CAARS:S-S), CGI-S, and Sheehan Disability Scale (SDS) scores were also significantly improved from baseline, while no significant change was observed with Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q).
- During the double-blind withdrawal phase (CONCERTA, n=23; placebo, n=22), CAARS:O-SV score increased from double-blind baseline in both treatment groups (4.0±7.6 vs. 6.5±7.8); the treatment difference was not statistically significant.

Buitelaar et al (2009)[17]

Study Design/Methods

- Seven-week, open-label extension of the LAMDA trial conducted by **Medori et al (2008)**[16].
- Subjects started on CONCERTA 18-36 mg/day, then the dose was titrated in increments of 18 mg up to 90 mg based on clinical response.

Results

- Of the 370 subjects who continued on to the open-label phase of the study, 337 completed the 7-week extension phase.
- Subjects were taking an average daily CONCERTA dose of 47.5 mg.
- A total of 253 (68%) patients reported at least one treatment-emergent adverse event; the most common adverse events included headache (16.8%), decreased appetite (12.7%), and insomnia (11.1%).

- Nine percent of patients received the 90 mg dose. At the final treatment visit (week 7), the following adverse events were reported by >2% of patients receiving the 90 mg dose: decreased appetite (n=2, 6.3%), headache, insomnia, nasopharyngitis, dry mouth, depressed mood, and disturbance in attention (each n=1, 3.1%).
- At the final treatment visit, clinically relevant increased blood pressure (SBP ≥140 mm Hg, DBP ≥90 mm Hg) or pulse (≥90 bpm) were observed at a similar rate across the lower doses (18, 36, and 54 mg), and trended toward higher percentages with the 72 mg and 90 mg doses. See Table: Patients Who Experienced Clinically Relevant Increases in Blood Pressure and Heart Rate by CONCERTA Dose.
- With regards to the efficacy assessment, patients continued to show improvement in ADHD symptoms during the open-label phase as demonstrated by decreases in CAARS total score.

Patients Who Experienced Clinically Relevant Increases in Blood Pressure and Heart Rate by CONCERTA Dose

Measurement, bn (%)	18 mg (n=21)	36 mg (n=82)	54 mg (n=110)	72 mg (n=65)	90 mg (n=32)
SBP ≥140 mm Hg	2 (9.5)	13 (15.9)	20 (18.2)	14 (21.5)	11 (34.4)
DBP ≥90 mm Hg	6 (28.6)	23 (28.0)	25 (22.7)	22 (33.8)	12 (37.5)
Pulse ≥90 bpm	7 (33.3)	29 (35.4)	37 (33.6)	32 (49.2)	16 (50.0)

SELECTED ADDITIONAL REFERENCES

Biederman et al (2006)[7] conducted a 6-week open-label study in adults with late-onset ADHD (N=36) who were treated with CONCERTA up to a maximum dose of 1.3 mg/kg/day (maximum 144 mg/day).

Liebrenz et al (2012)[18] reported the case of a 38-year-old patient with ADHD who was treated with CONCERTA 378 mg/day.

Orman et al (2008)[9] reported additional secondary efficacy Results from the previously-described study conducted by **Adler et al (2009)**[2].

Pandina et al (2008)[10] evaluated the efficacy of CONCERTA in the same study population as the study conducted by **Adler et al (2009)**[2] using patient-reported (CAARS-S:S) and clinician-rated (AISRS) improvement in ADHD symptoms.

Spencer et al (2007)[19] assessed the effectiveness of the AISRS in the evaluation of ADHD symptom improvement in adults treated with high-dose MPH (maximum dose of 1.0 mg/kg/day for IR MPH and 1.3 mg/kg/day for CONCERTA).

LITERATURE SEARCH

A literature search of MEDLINE® pertaining to this topic was conducted on 17 October 2023.

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