CONCERTA® (methylphenidate HCl ER)
Abuse Liability of CONCERTA

SUMMARY

- **CONCERTA (methylphenidate HCL) Extended-Release CII** has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including CONCERTA, can result in overdose and death.[1]
  - Before prescribing CONCERTA, assess each patient's risk for abuse, misuse, and addiction.
  - Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.
  - Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.
- Two studies compared the relative abusability of CONCERTA to immediate-release (IR) methylphenidate (MPH).[2,3]
- One study utilized positron emission tomography (PET) imaging to evaluate various abuse liability-related endpoints for subjects taking IR MPH versus CONCERTA which utilizes the osmotic-controlled release delivery system.[4]

PRODUCT LABELING

- Please refer to the following sections of the enclosed Full Prescribing Information that are relevant to your inquiry: **BOXED WARNING**: ABUSE, MISUSE, AND ADDICTION; **CONTRAINDICATION**, Abuse, Misuse, Addiction; **ADVERSE REACTIONS**; **DRUG ABUSE AND DEPENDENCE**, Controlled Substance, Abuse, Dependence; **PATIENT COUNSELING INFORMATION**, Abuse, Misuse, and Addiction; **MEDICATION GUIDE**.

CLINICAL DATA

Randomized, placebo-controlled studies

In 2 placebo-controlled abuse-potential studies in subjects with a history of recreational stimulant use, CONCERTA was associated with a relatively lower response on subjective measures of abuse potential compared to IR MPH.[2,3]

Parasrampuria et al (2007)[2] evaluated the abuse-related subjective effects of CONCERTA compared to IR MPH and placebo in healthy adults with a history of light (1-25 occasions of stimulant use in the previous year) recreational stimulant use (N=49).

Study Design/Methods

- Randomized, placebo-controlled, double-blind, 5-period crossover study.
- Each subject (18-45 years of age) received a single oral dose of placebo, CONCERTA 54 mg and 108 mg, and IR MPH 50 mg and 90 mg during 5 different drug administration periods separated by 48 hours each. Subjects remained housed at an inpatient facility for the duration of the study.
- The primary dependent measures were positive effects (visual analog scales [VAS] Drug Liking and Overall Drug Liking, and Morphine Benzedrine Group [MBG] scales).
- The secondary dependent measures were stimulatory effects (Addiction Research Center Inventory [ARCI] Amphetamine and Cole/ARCI Stimulation-Motor scales) and other positive effects (Cole/ARCI Stimulation-Euphoria and VAS Good Effects, High, Take Drug Again scales).
- Plasma samples were also collected at various intervals over a 24-hour period after study drug or placebo was administered.

Results

- Pharmacokinetic results revealed that IR MPH peaked at approximately 2 hours postdose while CONCERTA peaked at approximately 7 hours postdose.
- At comparable doses, IR MPH produced higher early (within 3 hours) exposure (partial area under the curves) and peak plasma concentrations (Cmax) compared to CONCERTA.
- Pharmacodynamic results showed that both doses of IR MPH (50 mg and 90 mg) produced significantly greater subjective effects than placebo on all primary and secondary dependent measures ($P<0.05$).
- CONCERTA 108 mg produced significantly greater subjective effects for most measures ($P<0.05$), while CONCERTA 54 mg was associated with numerically higher (but many not statistically significant) subjective response scores compared with placebo.
- When comparing IR MPH and CONCERTA, the low doses (IR MPH 50 mg vs CONCERTA 54 mg) resulted in statistically significant differences between the 2 formulations on all primary and secondary subjective measures except for the Cole/ARCI Stimulation-Motor (area under the effect curve [AUE] from 0 to 1 hour postdose [$AUE^{0\text{-}1\ hr}$]).
- At high doses (IR MPH 90 mg vs CONCERTA 108 mg), comparisons between all primary and secondary measures were statistically significant except VAS Drug Liking (AUE0-1 hr and AUE from 0 to 2 hours postdose), Overall Drug Liking, and Take Drug Again.
- Overall, the subjective responses were highly consistent across all primary and secondary measures with the following rank order of magnitude (highest to lowest): IR MPH 90 mg > IR MPH 50 mg > CONCERTA 108 mg > CONCERTA 54 mg > placebo.

Parasrampuria et al (2007)[3] evaluated the abuse liability of single doses of CONCERTA and IR formulations of MPH (N=49).

Study Design/Methods

- Randomized, placebo-controlled, double-blind, single-center, crossover study.
- All subjects (primarily white, male subjects with a mean age 28.3±7.55 years) included in the study had a history of recreational stimulant use.
- Subjects were given single oral doses of CONCERTA 108 mg, IR MPH 60 mg, or placebo.
- MPH plasma concentrations were taken from blood samples collected predose and at multiple intervals over a 24-hour time period for pharmacokinetic analysis.
- Subjects were also evaluated for subjective drug effects.

Results

- Pharmacokinetic results revealed that Cmax were lower for CONCERTA than IR MPH (CONCERTA C_{max} was approximately 69% of IR MPH C_{max}).
- The mean time to Cmax of CONCERTA occurred around 8 hours postdose, compared to IR MPH, which occurred at about 2 hours postdose.
- The subjective liking effects of CONCERTA were statistically significantly lower than IR MPH for the Cole/ARCI Stimulation-Euphoria scale (P-values of 0.023 and 0.006 for peak effect and Partial AUE respectively) and ARCI Amphetamine scale ($P=0.049$ for Partial AUE) but not for VAS Drug Liking or Cole/ARCI Abuse Potential scale.
- Stimulation-Motor scores were significantly higher ($P=0.028$) in IR MPH compared to CONCERTA at 2 hours postdose.

Winhusen et al (2011)[5] analyzed datasets from 2 randomized, placebo-controlled trials of CONCERTA for the treatment of attention-deficit/hyperactivity disorder (ADHD).

Study Design/Methods

- One study included 303 adolescents (aged 13-18 years) with ADHD and at least 1 non-tobacco substance use disorder (SUD).
- The other study included 255 adult smokers (aged 18-55 years) with ADHD.

- The subjective effects, misuse/diversion, and adverse effects of CONCERTA were evaluated and compared with placebo in adolescents with ADHD and an SUD as a function of treatment group and baseline substance use severity.
- Adolescent ratings on the subjective effects of CONCERTA, as measured by the Massachusetts General Hospital (MGH) Liking Scale, were compared with ratings provided in the adult study.

Results

- At baseline, adolescents reported greater use of cannabis and tobacco relative to alcohol or other illicit drugs.
- Adolescents in the CONCERTA group reported higher ratings for 3 of the 6 items on the MGH Liking Scale: effectiveness in treating ADHD ($P<0.0001$), feeling high ($P<0.001$), and feeling depressed ($P<0.01$). No significant treatment effects were reported for: liking how the medication makes you feel, craving the medication, and craving substances.
- None of the MGH Liking Scales were significantly affected by substance use severity.
- For the misuse/diversion measures, there were no significant treatment or substance use severity effects in adolescents treated with CONCERTA versus those who received placebo.
- When comparing subjective effects (MGH Liking Scale) in the adolescent and adult studies, adults rated CONCERTA as more effective than placebo in treating ADHD, while adolescents in the CONCERTA group reported a greater rating of depressed mood.
- On measures of misuse/diversion, there were no significant treatment differences between adolescents and adults. However, adolescents reported a greater incidence of lost pills compared with adults, regardless of whether they were in the CONCERTA or placebo groups, indicating that this effect was not specific to CONCERTA.

Randomized, active-controlled studies

Spencer et al (2006)[4] conducted a study comparing single-dosed CONCERTA and IR formulations of MPH to assess whether differences in the oral delivery system would affect the abuse potential of MPH (N=12).

Study Design/Methods

- Randomized, active-controlled, double-blind, single-center study.
- All subjects (Caucasian adults, mean age 25 years) were healthy and had no current or past drug/alcohol abuse.
- Subjects were randomized to receive 40 mg of IR MPH or 90 mg of CONCERTA.
- Subjects underwent a total of 5 PET imaging sessions after drug administration on 3 different days to observe the dopamine transporter receptor occupancy.
- MPH levels were obtained hourly for 10 hours after MPH administration to measure and compare Cmax values in each patient.
- Subjects also completed a subjective Drug Rating Questionnaire to assess drug liking and abuse potential.

Results

- The dopamine transporter occupancy was observed to be higher for the IR MPH compared to the CONCERTA at hours 1-3, similar occupancies at hour 4, and lower occupancy than CONCERTA at hours 5-7.
- Cmax values were slightly higher with CONCERTA (17.7 ng/mL vs 14.1 ng/mL; $P=0.05$); however, time to reach peak plasma concentration was 3.5 times longer with CONCERTA compared to IR MPH (7.5 hours vs 2.2 hours; $P<0.0001$).
- Subjects who received IR MPH reported greater subjective response on all 3 scales of the Drug Rating Questionnaire across all 10 hours after MPH treatment ($P<0.05$).

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 02 November 2023.

REFERENCES

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