CONCERTA® (methylphenidate HCl ER)
Pharmacokinetics of CONCERTA

SUMMARY

- CONCERTA (methylphenidate HCl extended-release [MPH ER]) is an osmotic controlled-release delivery system that allows once-daily dosing of methylphenidate (MPH).[1]
- Plasma MPH concentrations increase rapidly, reaching an initial peak concentration at approximately 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after taking CONCERTA. Peak plasma concentrations were observed between 6 to 10 hours.[1]
- The mean terminal half-life ($t_{1/2}$) of MPH in adults and adolescents was approximately 3.6 hours. There were no differences in pharmacokinetics of CONCERTA following single and repeated dosing, indicating no significant drug accumulation.[1]
- CONCERTA exhibited linear and dose-proportional increases in maximum concentration (C_{max}) and area under the concentration-time curve to infinite time (AUC_{inf}) following single and repeated administration of total daily doses up to 144 mg/day.[1]
- MPH is metabolized primarily by de-esterification to α-phenyl-piperidine acetic acid (PPA or PPAA), which has little or no pharmacological activity.[1] The primary location of presystemic metabolism of MPH is in the intestinal and/or gut wall.[2]
- No difference in the pharmacokinetic or pharmacodynamic performance of CONCERTA was observed with regard to food. There was no evidence of dose dumping in the presence or absence of food.[1]
- Increase in age resulted in increased apparent oral clearance. The pharmacokinetics of CONCERTA in children younger than 6 years of age have not been evaluated.[1]
- There is no experience with the use of CONCERTA in patients with renal or hepatic insufficiency.[1]
- A coadministration study of guanfacine extended-release and CONCERTA did not result in significant pharmacokinetic drug-drug interactions.[3]

PRODUCT LABELING

Please refer to the following section of the enclosed Full Prescribing Information that is relevant to your inquiry[1]: CLINICAL PHARMACOLOGY, Pharmacokinetics.

CLINICAL DATA

Modi et al (2000)[4] studied the single-and multiple-dose pharmacokinetics of CONCERTA once daily in 36 healthy adults.

Two separate studies describe the pharmacokinetics and bioavailability of CONCERTA relative to immediate-release (IR) and sustained-release (SR) formulations of MPH, and to evaluate the single-dose and repeated-dose pharmacokinetics of CONCERTA. The most commonly reported adverse events (AEs) in both studies were headache, nausea, and dizziness.

Study 1

Study Design/Methods

- Open-label, randomized, 3-treatment, 3-period, 6-sequence crossover study in 36 healthy adults (mean age, 27.4 years).
- Rate and extent of absorption of CONCERTA were compared to that of IR and SR MPH.
- On 3 separate occasions, subjects received a single dose of CONCERTA 18 mg, a single dose of SR MPH 20 mg, and 3 doses of IR MPH 5 mg in random order.
- Blood samples for measuring plasma MPH and PPA/PPAA concentrations for CONCERTA and SR MPH were obtained predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, and 30 hours postdose.

- Blood samples for measuring plasma MPH concentration for IR MPH were obtained predose and at 0.25, 0.5, 1, 1.5, 2, 4, 4.25, 4.5, 5, 5.5, 6, 8, 8.25, 8.5, 9, 9.5, 10, 12, 14, 17, 20, 24, and 30 hours postdose.

Results

- Thirty-six subjects were assigned to receive CONCERTA and SR MPH; 35 subjects were assigned to receive IR MPH 3 times a day.
- Following oral administration of CONCERTA, plasma MPH concentrations increased rapidly over the first 1 to 2 hours, followed by gradually ascending concentrations over the next 3 to 4 hours.
  - Mean time to reach peak plasma MPH concentration (T_{max}) was observed at approximately 6.7 hours.
- In contrast, following IR MPH administration, plasma MPH concentrations fluctuated with peak concentrations reached approximately 1 to 2 hours after each dose; T_{max} was observed 6.5 hours after dosing.
- Following SR MPH administration, plasma MPH concentrations increased rapidly with T_{max} occurring at 3.7 hours, after which plasma concentrations rapidly declined.
- Compared with IR MPH and SR MPH, C_{max} of MPH for CONCERTA was lower and T_{max} occurred later.
- The terminal half-lives for MPH for all 3 formulations were comparable (~3–4 hours).
- The relative bioavailability of MPH from CONCERTA relative to IR MPH was 91.4% and to SR MPH was 101%.
- Similar observations were made for the pharmacokinetic parameters of PPA.
  - C_{max} of PPA for CONCERTA was also lower and occurred later compared with that of IR MPH and SR MPH; $t_{1/2}$ of PPA for all 3 formulations was approximately 8 hours.

Study 2

Study Design/Methods

- Open-label study conducted to assess single- and repeated-dose pharmacokinetics of CONCERTA 18 mg.
- Thirty-two healthy adults (mean age, 29.7 years) were given a single oral dose of CONCERTA 18 mg on day 1, followed by a multiple-dose regimen on days 3–6.
- Blood samples for measuring plasma MPH concentrations were obtained predose and at predefined times for 36 hours following the single dose on day 1 and following multiple doses on day 6, in addition to predose on days 3–5.

Results

- Following single and repeated dosing of CONCERTA 18 mg, mean C_{max}, AUC_{inf} and $t_{1/2}$ of MPH for the 2 regimens were similar (C_{max}: 2.81±0.96 ng/mL vs 3.0±1.1 ng/mL, respectively; AUC_{inf}: 32.9±12 ng•h/mL vs 35.2±12 ng•h/mL, respectively; $t_{1/2}$: 3.9±0.73 hrs vs 3.9+0.76 hrs, respectively).
- Similarly, following repeated dosing, mean C_{max}, AUC_{inf}, and $t_{1/2}$ of PPA were comparable to the values after a single dose.
- Accumulation after repeated dosing was 13.7% for MPH and 17.5% for PPA, indicating the lack of clinically significant drug accumulation after repeated dosing.

Dose Proportionality

Modi et al (2000)[2] assessed the pharmacokinetics of d- and l-MPH and d- and l-PPA of CONCERTA 18, 36, and 54 mg in a randomized, open-label, 3-way crossover study.

Study Design/Methods

- Thirty-five healthy adults (22 men, 13 women), ages 18 to 45 years, were assigned to 1 of 6 treatment sequences to receive CONCERTA 18, 36, or 54 mg daily.
- Blood samples were collected over a 30-hour period to measure plasma MPH and PPA concentrations.

Results

- Following oral administration of CONCERTA, d- and l-MPH plasma levels increased rapidly for the first 1 to 2 hours, followed by gradual ascending concentrations over the next 3 to 4 hours.
- Peak plasma concentrations of d- and l-MPH were observed 6 to 8 hours postdose.
  - Plasma concentrations of l-MPH were only detected at certain time points and were lower than those of d-MPH.
- Plasma concentrations of d- and l-PPA were similar to one another and were higher than concentrations of d- and l-MPH.
- There was a linear, dose proportional increase in both C_{max} and AUC_{inf} of d- and l-MPH and of d- and l-PPA.
- The estimated $t_{1/2}$ for d-MPH was approximately 4 hours, but the estimated $t_{1/2}$ for l-MPH was not calculated due to the lack of detectable concentrations.
- The estimated $t_{1/2}$ for d-PPA and l-PPA were 9 and 7 hours, respectively.
- Following CONCERTA administration, plasma concentrations of l-MPH were approximately 40-fold lower than the plasma concentrations of d-MPH.

Safety

- The most commonly reported AEs were headache, nausea, and nervousness.

Food Effects

Wigal et al (2011)[5] conducted a single-center, double-blind, double-dummy, randomized, crossover study to compare the pharmacokinetics and pharmacodynamics of CONCERTA with IR MPH after fasting state and different breakfast conditions in children with attention-deficit/hyperactivity disorder.

Study Design/Methods

- Thirty-one children (mean age, 10.1 years) were divided into 2 groups and then randomized into 1 of 3 treatment regimens in a 3-period crossover design with a minimum of 5 days in between treatments.
  - The 3 treatment regimens administered in group 1 included CONCERTA after a high-fat breakfast, CONCERTA in a fasted state, and IR MPH TID in a fasted state.
  - The 3 treatment regimens administered in group 2 included CONCERTA after a high-fat breakfast, CONCERTA after a normal breakfast, and IR MPH TID with first dose given after a normal breakfast.
- The normal breakfast had about 4 g of fat and the high-fat breakfast had about 34 g of fat.
- Patients were assigned to 1 of 3 dosage levels (CONCERTA 18, 36, and 54 mg once daily, and an assumed equivalent regimen of IR MPH 5, 10, and 15 mg given 3 times a day) based on their prestudy established clinical dose of IR MPH.
- Serial blood samples were collected at 0 (predose), 1.5, 2.5, 4, 5.5, 6.5, 8, 9.5, and 11.5 hours after the morning dose to measure the plasma concentrations of MPH and PPAA.
- Pharmacokinetic parameters were evaluated using noncompartmental analyses and a change in means by 20% was used as a criterion to evaluate food effect.

Results

- The pharmacokinetic values for MPH and PPAA after administration of CONCERTA under high-fat breakfast and fasting conditions were similar to those observed after administration of IR MPH under fasting conditions (group 1).
- The pharmacokinetic values for MPH and PPAA after administration of CONCERTA under high-fat and normal breakfast conditions were similar to those observed after administration of IR MPH after a normal breakfast (group 2).
- The drug-to-metabolite ratios for all CONCERTA and IR MPH treatments were similar.

Safety

- The most commonly reported AEs included headache, accidental injury, twitching, and anorexia.

Auiler et al (2002)[6] conducted a single dose, open-label, randomized, crossover study to compare the effect of a high-fat breakfast on early drug exposure from a morning dose of CONCERTA and Adderall XR (mixed amphetamine salts [MAS]).

Study Design/Methods

- Thirty-six healthy subjects (mean age, 29 years) received either CONCERTA 36 mg or MAS 20 mg in the morning after an overnight fast (fasted) or 15 minutes after consuming a high-fat breakfast (fed).
- A high-fat breakfast included 2 eggs fried in butter, 2 slices of buttered toast, 2 bacon strips, 4 ounces of hash brown potatoes, and 8 ounces of whole milk.
- Blood samples were collected by venipuncture predose and at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 12, 15, 24, and 28 hours after the stimulant dose.
- The effect of food on each stimulant medication was assessed using AUC_{inf} and C_{max}.
  - Changes in either of these parameters within ±20% after consuming a high-fat breakfast indicated no food effect.
- The effects of early drug exposure using partial areas under the concentration-time curve from 0 up to 4, 6, and 8 hours (AUC_{p4h}, AUC_{p6h}, and AUC_{p8h}) was also assessed.

Results

- Results revealed that 32 out of 36 study subjects had a significant decrease (20% to 80%) in amphetamine plasma levels over the first 8 hours post-MAS dose after a high-fat breakfast ($P<0.0001$).
- Mean decreases of 55.5%, 42.5%, and 35% for MAS exposure over 4, 6, and 8 hours were significant compared to the mean increases of 3%, 9.2%, and 10% for CONCERTA exposure over the same time period ($P<0.0001$).
- Plasma levels of CONCERTA were unaffected by food over the first 8 hours of exposure.

Modi et al (2000)[7] conducted 2 randomized, open-label, crossover studies to assess the effect of food on the pharmacokinetics of CONCERTA in healthy volunteers.

Study Design/Methods

- The first study involved 24 healthy males (aged 21 to 49 years), who received a single dose of CONCERTA 18 mg while the second study enrolled 36 healthy subjects (17 women, 19 men), between the ages of 18 and 45 years, who received a single dose of CONCERTA 36 mg.
- Subjects in both studies were administered CONCERTA in either a fasted state or in a fed state, within 30 minutes of consuming a high-fat breakfast containing 900-1000 calories.
- Blood samples were collected from each subject for up to 30 hours after dosing.

Results

Study 1: 18 mg

- All 24 subjects completed both the fasted and fed treatments.
- Following the administration of CONCERTA 18 mg in the fasted state, mean plasma MPH concentrations increased rapidly with an initial peak concentration observed at 1 hour postdose, followed by gradually ascending concentrations.
- T_{max} was observed at approximately 6.1 hours postdose.
- In the presence of food, the initial peak concentration of MPH was not observed; however, mean peak plasma concentrations were somewhat higher and T_{max} occurred later (at 7.2 hours) compared to the fasted state.

Study 2: 36 mg

- 31 subjects completed both the fasted and fed treatments.
- Following the administration of CONCERTA 36 mg, the initial peak concentration was not evident in either the fasting or fed dosing condition. T_{max} in the fasted state was noted at approximately 6.5 hours postdose.
- As in the 18-mg dose group, peak MPH plasma concentrations were higher and T_{max} occurred later (at 7.4 hours) in the fed state.

Comparison of Fasted and Fed States

- When administered in the fed state, mean peak MPH concentrations were approximately 30% higher in the 18-mg dose group and 12% higher in the 36-mg dose group compared with administration in the fasted state.
- There was no evidence of dose dumping in the presence of food as the differences in initial MPH plasma concentrations between the fasted and the fed state were not significant.
- T_{max} was also noted approximately 1 hour later in the fed state compared to the fasted state.
- The plasma AUC was 20% higher in the fed state for both the 18- and 36-mg dose groups.
- The ratio of MPH AUC_{inf} to PPA AUC_{inf} was similar between the fasted state and the fed state (0.021 and 0.025, respectively), indicating that food does not affect the metabolism of MPH.

Safety

- The most commonly reported AEs were headache, dizziness, somnolence, and nausea.

Coadministration Study

Roesch et al (2013)[3] conducted a single-center, open-label, randomized, 3-period crossover, drug-drug interaction study to assess the pharmacokinetics of guanfacine extended release (GXR) 4 mg and CONCERTA 36 mg, alone and in combination in healthy volunteers.

Study Design/Methods

- Thirty-eight adults (mean age, 30.8 years) were randomly assigned to 1 of 6 different administration sequences; each sequence consisted of 3 treatment periods separated by a washout period of at least 7 days.
- Blood samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 48, and 72 hours postdose for each treatment period to measure plasma levels of guanfacine, d-MPH, and l-MPH.

Results

- Analyses of the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of the C_{max} and AUC_{inf} values for guanfacine following administration of GXR alone or in combination with CONCERTA met bioequivalence criteria (defined as 90% CIs within the interval of 0.80–1.25).
- Similarly, the analyses of 90% CIs for GMRs of the C_{max} and AUC_{inf} values for d-MPH following administration of CONCERTA alone or in combination with GXR met bioequivalence criteria.
- No significant differences in concentration of l-MPH were observed following administration of CONCERTA alone or in combination with GXR.
- The combination of GXR and MPH did not alter the pharmacokinetic parameters of either medication.

Safety

- The most common treatment-emergent AEs reported were headache, dizziness, and postural dizziness.

SELECTED ADDITIONAL REFERENCES

Data from animal studies suggest that the primary location of presystemic metabolism is in the intestinal and/or gut wall and not in the liver or lungs.[2] Additional comparative studies evaluating pharmacokinetics and/or bioavailability of MPH from CONCERTA relative to other MPH formulations are available.[8-11]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 03 February 2025.

REFERENCES

1. CONCERTA (methylphenidate HCl) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-edb60a5a-a794-4ed6-b7ab-758d0aa94194.

2. Modi NB, Wang B, Noveck RJ, et al. Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system. *J Clin Pharmacol*. 2000;40(10):1141-1149.

3. Roesch B, Corcoran M, Haffey M, et al. Pharmacokinetics of co-administration of guanfacine extended release and methylphenidate extended release. *Drugs R D*. 2013;13(1):53-61.

4. Modi NB, Lindemulder B, Gupta SK. Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol*. 2000;40(4):379-388.

5. Wigal SB, Gupta S, Heverin E, et al. Pharmacokinetics and therapeutic effect of OROS methylphenidate under different breakfast conditions in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2011;21(3):255-263.

6. Auiler JF, Liu K, Lynch JM, et al. Effect of food on early drug exposure from extended-release stimulants: results from the CONCERTA, Adderall XR Food Evaluation (CAFÉ) study. *Curr Med Res Opin*. 2002;18(5):311-316.

7. Modi NB, Wang B, Hu WT, et al. Effect of food on the pharmacokinetics of osmotic controlled-release methylphenidate HCl in healthy subjects. *Biopharm Drug Dispos*. 2000;21(1):23-31.

8. Pierce D, Katic A, Buckwalter M, et al. Single- and multiple-dose pharmacokinetics of methylphenidate administered as methylphenidate transdermal system or osmotic-release oral system methylphenidate to children and adolescents with attention deficit hyperactivity disorder. *J Clin Psychopharmacol*. 2010;30(5):554-564.

9. Reiz JL, Donnelly GA, Michalko K. Comparative bioavailability of single-dose methylphenidate from a multilayer-release bead formulation and an osmotic system: a two-way crossover study in healthy young adults. *Clin Ther*. 2008;30(1):59-69.

10. Markowitz JS, Straughn AB, Patrick KS, et al. Pharmacokinetics of methylphenidate after oral administration of two modified release formulations in healthy adults. *Clin Pharmacokinet*. 2003;42(4):393-401.

11. González MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Int J Clin Pharmacol Ther*. 2002;40(4):175–184.