Extrapolation of the Efficacy of a Dextroamphetamine Transdermal System Investigated in Pediatric Populations to Adults Using Pharmacokinetic Modeling

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INTRODUCTION

- Similitudes in pharmacokinetic, disease characteristics, and treatment outcomes between pediatric and adult populations with attention-deficit/hyperactivity disorder (ADHD) have been demonstrated1 and are acknowledged by the US FDA in its guidance on developing ADHD treatments.
- Given that postmarketing experience and published evidence support a high level of therapeutic similarity of amphetamines and their prodrugs (d-ATS) in adults, the approach of extrapolating efficacy data from children is plausible.
- The dextroamphetamine transdermal system (d-ATS) was developed as an alternative to the currently available oral amphetamine formulations for treatment of ADHD in children, adolescents, and adults.
- Although a transdermal formulation of methylphenidate is available in the US, there remains an unmet need for a transdermal amphetamine formulation for treatment of ADHD in children and adolescents.
- In a pivotal efficacy and safety study, d-ATS met its primary and secondary efficacy endpoints for treatment of ADHD in children and adolescents1.

METHODS

- A PopPK dataset was developed from data pooled across six PK studies and used to develop a PopPK model in order to characterize amphetamine disposition following 4-mg/doses administered to children and adolescents in the pivotal study (5 mg, 10 mg, 15 mg and 20 mg).
- The model was evaluated via 1) goodness-of-fit diagnostics and 2) simulation-based predictive checks, including visual predictive checks.
- To construct and validate a population PK (PopPK) model to characterize transdermal amphetamine disposition across populations of patients with ADHD.
- To extrapolate efficacy data in children (6-12 years) and adolescents (12-18 years) to an adult population (18-65 years) by simulating exposures at the doses evaluated in the pivotal pediatric study for the purpose of comparing and deriving an adult dose that yields exposures matching the efficacious pediatric doses

RESULTS

- A one-compartment model with sequential zero- and first-order absorption based on diagnostic plots and predictive checks adequately described amphetamine concentrations, as evidenced by diagnostic plots and predictive checks.
- The model was evaluated via 1) goodness-of-fit diagnostics and 2) simulation-based predictive checks, including visual predictive checks.
- For all parameter models, absorption parameters were based on diagnostic plots and predictive checks, including visual predictive checks.
- Following model validation, simulations were performed to extrapolate (i.e., exposure matching) amphetamine PK at the doses administered in the pivotal study dosages to adults by simulating 15 mg and 20 mg at post-dose time points.
- Body weights for 1050 individual adult age group bariatric, adolescents, and adults were selected from the National Health and Nutrition Examination Survey 2013-2014 database to simulate exposures for multipopulation d-ATS exposures.
- Exposure metrics across a one-compartment curve model concentration (C) and maximum concentration (Cmax) were compared among children, adolescents, and adults across dose levels.

CONCLUSIONS

- The PopPK model provided an adequate description of the amphetamine concentrations, as evidenced by diagnostic plots and simulation-based predictive checks. Simulations were observed to be in overall agreement with observed data.
- Exposures to the model predictions were primarily due to the difference in body weight among the age groups.
- Results demonstrated overall agreement between observed and simulated data when stratified to different ages and dose groups at both single doses and the steady state.
- Treatment with 10 mg d-ATS in adults produced exposures comparable to 15 mg in pediatric patients. The 15-mg dose was demonstrated as efficacious and desired within the pivotal study in pediatric patients.
- In multiethnic, controlled, single-arm 15 mg and 20 mg dose trials, exposure was comparable for adults and children, and the shape of PK profiles for d-ATS in adults was generally found to be similar to that in children.
- The results of the PopPK modeling and simulation analyses demonstrated that the 15-mg dose was effective for children, adolescents, and adults.
- Adults administered 20 mg d-ATS achieve comparable exposures to the established efficacious dose (15 mg) for children and adolescents.
- These results support extrapolation of efficacy findings from children and adolescents to adults.

REFERENCES


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