ABSTRACT

Dasotraline is a novel compound in clinical development for the treatment of ADHD. Pharmacokinetic and pharmacodynamic analyses were conducted using data from an open-label, Phase 2 study. Dasotraline was characterized by a mean apparent half-life of 2.84 hours. This study used Model building and simulations successfully related dasotraline PK to pharmacological activity via DHPG and ADHD RS. The following parameter estimates were found to be highly correlated (r² ≥ 0.810): (power of weight on CLind and Vmax: Maximum Elimination Rate (mg/h)). The nonlinear CL/F represented a saturable elimination pathway operating at approximately 50% of its capacity based on the estimate of the Michaelis-Menten constant (Km). Linear apparent clearance was found to be time dependent following the inclusion Phase 2 data. This allowed the linear portion of CL/F to increase over time. The exposure response model for DHPG concentration was a power function of the time matched, model predicted dasotraline concentrations. The pcVPC results indicated that the final DHPG model adequately characterized the data. The observed values for DHPG in Study SEP360 201 matched well with predicted values. This study used a one compartment model with sequential zero order followed by first order absorption and dual (nonlinear and linear) elimination described dasotraline kinetics. The rates of elimination were dependent on dose and body weight.

RESULTS

Dasotraline was characterized by a mean apparent half-life of 2.84 hours. The exposure response model for DHPG concentration was a power function of the time matched, model predicted dasotraline concentrations. The pcVPC results indicated that the final DHPG model adequately characterized the data. The observed values for DHPG in Study SEP360 201 matched well with predicted values. This study used a one compartment model with sequential zero order followed by first order absorption and dual (nonlinear and linear) elimination described dasotraline kinetics. The rates of elimination were dependent on dose and body weight.

PHARMACOKINETICS AND EXPOSURE-RESPONSE RELATIONSHIPS OF DASOTRALINE IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS

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BACKGROUND

Dasotraline is a novel compound in clinical development for the treatment of ADHD. Pharmacokinetic and pharmacodynamic analyses were conducted using data from an open-label, Phase 2 study. Dasotraline was characterized by a mean apparent half-life of 2.84 hours. This study used Model building and simulations successfully related dasotraline PK to pharmacological activity via DHPG and ADHD RS. The following parameter estimates were found to be highly correlated (r² ≥ 0.810): (power of weight on CLind and Vmax: Maximum Elimination Rate (mg/h)). The nonlinear CL/F represented a saturable elimination pathway operating at approximately 50% of its capacity based on the estimate of the Michaelis-Menten constant (Km). Linear apparent clearance was found to be time dependent following the inclusion Phase 2 data. This allowed the linear portion of CL/F to increase over time. The exposure response model for DHPG concentration was a power function of the time matched, model predicted dasotraline concentrations. The pcVPC results indicated that the final DHPG model adequately characterized the data. The observed values for DHPG in Study SEP360 201 matched well with predicted values. This study used a one compartment model with sequential zero order followed by first order absorption and dual (nonlinear and linear) elimination described dasotraline kinetics. The rates of elimination were dependent on dose and body weight.

METHODS

Dasotraline was characterized by a mean apparent half-life of 2.84 hours. This study used Model building and simulations successfully related dasotraline PK to pharmacological activity via DHPG and ADHD RS. The following parameter estimates were found to be highly correlated (r² ≥ 0.810): (power of weight on CLind and Vmax: Maximum Elimination Rate (mg/h)). The nonlinear CL/F represented a saturable elimination pathway operating at approximately 50% of its capacity based on the estimate of the Michaelis-Menten constant (Km). Linear apparent clearance was found to be time dependent following the inclusion Phase 2 data. This allowed the linear portion of CL/F to increase over time. The exposure response model for DHPG concentration was a power function of the time matched, model predicted dasotraline concentrations. The pcVPC results indicated that the final DHPG model adequately characterized the data. The observed values for DHPG in Study SEP360 201 matched well with predicted values. This study used a one compartment model with sequential zero order followed by first order absorption and dual (nonlinear and linear) elimination described dasotraline kinetics. The rates of elimination were dependent on dose and body weight.