Lurasidone Exposure-Response in Pediatric Bipolar Depression: Simulation and Comparison to Adults

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Objectives: To evaluate the consistency of the exposure-response (E-R) relationship of lurasidone between children/adolescent and adult patients with bipolar depression.

Methods: An external posterior predictive check was conducted to evaluate the utility of an adult E-R model [1] in predicting efficacy for child and adolescent patients with bipolar depression (N=343) who were randomized in a double-blind, placebo-controlled, 6-week study of flexibly dosed lurasidone (20-80 mg/d). In the event the external PPC demonstrated differences in the efficacy between pediatric and adult patients, further model development was planned with appropriate covariates to help explain the discrepancy. The updated model was then to be used to determine pediatric doses that produce similar efficacy to the adults. In the pediatric study, the Children's Depression Rating Scale, Revised (CDRS-R) was administered weekly over the course of the treatment period and converted to the adult efficacy measure, the Montgomery-Åsberg Depression Rating Scale (MADRS) total score [2] to compare with the adult model.

Results: The adult population E-R model was not able to adequately predict the mean MADRS change from baseline or the placebo-corrected mean MADRS change from baseline for the pediatric patients. However, a revised model based on combined adult and pediatric data that included a separate baseline MADRS for pediatric and adult patients, and that did not include the effect of age on maximum placebo effect, adequately described the dose-response relationship for a fixed dose study design in pediatric populations. Using the revised model, the simulated dose-response relationship in pediatric patients was shown to be similar to that in adult patients.

Conclusions: This modeling and simulation analysis indicated that, as in adults, higher doses of lurasidone are likely to result in greater drug-related improvements in MADRS for pediatric patients with bipolar depression.