Executive Summary

The active component of Avandia is rosiglitazone maleate a thiazolidinedione that is approved in the treatment of type 2 diabetes.

This submission is a part of the Agency's Written Request dated December 10, 2003 requesting a submission of pediatric information for Avandia tablets. A population pharmacokinetic approach was used to determine the pharmacokinetics of rosiglitazone maleate in pediatric population. The population pharmacokinetic study was a subset of the clinical study (Study BRL-49653/207) "A 24-week randomized, double-blind, active-controlled, multi-center study to evaluate the safety and efficacy of rosiglitazone when administered to pediatric patients (age 10-17) with type-2 diabetes." In adults, the usual starting dose of Avandia is 4 mg administered either as a single dose QD or in divided doses BID for monotherapy as well as in combination therapy. The maximum recommended dose is 8 mg daily.

Rosiglitazone was initiated at 2 mg BID and then increased to 4 mg BID in pediatric patients with fasting plasma glucose > 126 mg/dl after 8 weeks post randomization. Blood samples were withdrawn from each subject at pre-dose and post dose at 15-30 min (Week 4), 45-60 min (Week 4), 3-5 h (Week 16), 6-10 h (Week 24).

The population PK of rosiglitazone was described by a one-compartment model with the first order absorption. Following oral administration of a single dose of rosiglitazone 2 or 4 mg in pediatric population, rosiglitazone was rapidly absorbed with Tmax of 1.5 h. Typical population PK parameters (95% CI) were 3.15 (2.1, 4.87) L/hr, 13.5 (9.11, 22.8) L and 2.05 (1.54, 3.04) hr^{-1} for CL/F, V/F and ka, respectively. These points and interval estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis (CL/F=2.4 L/hr and V/F=17.6 L). Modest negative correlations of CL with age and weight were observed. However, this does not warrant any dosage adjustments in pediatric patients. For pediatric patients, predicted average steady-state exposures over a 24-h interval were 1520 ng*hr/ml and 3040 ng*hr/ml for dosing regimens of 2 mg BID and 4 mg BID respectively. These exposures were similar to exposure estimates reported for adults at equivalent doses.

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