Mechanistic Population Pharmacokinetics of Oseltamivir in neonates to young adult patients with normal renal function

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Objectives: To develop a predictive mechanistic population pharmacokinetics (PK) model for oseltamivir (OP) and its active metabolite, oseltamivir carboxylate (OC) in term neonates and young adults (≤40 years) with normal renal function accounting for the developmental physiological changes taking place in the first 2 years after birth. Additionally, to evaluate various dosing regimens in term neonates and infants providing exposures established in adults.

Methods: The analysis included 3100 OP and 3560 OC concentrations from 436 subjects (13 trials; ages 2 weeks-40 years; post-menstrual age, PMA>38.6 weeks; weight 2.9-128 kg) following oral (346 subjects) or intravenous (90 subjects) OP. A more mechanistic PK model was developed based on previous models [1, 2] for oseltamivir by including effects such as renal maturation with post-menstrual age (PMA) on the systemic exposure of OC. Extensive model evaluations across all ages and simulations for PK bridging to adults were performed.

Results: The estimates (RSE%) of clearance for OP and OC for a typical subject (with WT ≥ 43 kg) were 197 L/hr (4.6%) and 27.4 L/hr (3.6%), respectively. Maturation of renal OC clearance \( CL_{M,AGE} \) was described by the Hill function of post-menstrual age (PMA) [3]:

\[
CL_{M,AGE} = \frac{PMA}{50} ^\gamma + \frac{(PMA)}{\gamma + (PMA)}
\]

with \( PMA_{50} = 45.6 \) weeks (4.5%) and sigmoidicity parameters \( \gamma = 2.35 \) (14.9%). Incorporation of hepatic maturation did not improve the model. Posthoc estimates indicated that variability of exposure in term neonates and infants administered 3 mg/kg doses was higher than in adults administered 75 mg doses, median exposure was higher, but the lowest percentiles of exposure distributions were comparable.

Conclusions: The developed model supported a dose of 3 mg/kg BID in children 0-1 years.

References: