Population Pharmacokinetic Analysis of Bupropion XL and Its Three Metabolites in Chinese Subjects

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Objectives: A pharmacokinetic (PK) study (NCT02698553) of bupropion XL was conducted in Chinese healthy subjects. For safety considerations, dose was titrated from 150 mg to 300 mg till reaching steady state. The objectives of the population modeling were to characterize the PK of bupropion and its active metabolites and to predict their exposures.

Methods: A total of 16 healthy Chinese subjects took bupropion XL 150 mg QD from Day 1 to Day 5 and then 300 mg QD from Day 6 to Day 14. Population PK modeling was performed using NONMEM (Version 7.3). To consider the first-pass effect, a dose apportionment independent of the rate constants ($k_{ap}$, $k_{am1}$, $k_{am2}$, and $k_{am3}$) with fractions of the dose (F1, F2, F3, and F4) leading to the parent and 3 metabolites as hypothetical absorption compartments prior to reaching plasma was assumed (Figure 1). To avoid non-identifiability, the dose apportionment fractions were fixed to the proportions determined from the observed peak molar concentrations ($C_{max}$) of the parent and metabolites. Moreover, the proportions of parent to metabolite transformation were assumed to be a scale of F2, F3, and F4. All the parameters were estimated simultaneously using ADVAN5 for general linear models. Simulations were performed to estimate AUC(0-inf) following single dose and accumulation ratios at steady state.

Results: A sequential approach was adopted as the initial step for model building, but the final model estimates came from simultaneous model-fitting. The joint parent-metabolite model consists of a two-compartment model for bupropion and one-compartment model for all three active metabolites. The goodness-of-fit plots showed good agreement between the observed, and population- and individual-predicted concentrations. Conclusions: A population PK model was developed for bupropion and its three active metabolites from the PK study conducted in Chinese healthy volunteers for bupropion XL. For a typical 61-kg Chinese subject, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydro-bupropion have apparent CL/F of 219.6, 14.3, 27.1, and 152.7 L/h, respectively, under the current assumptions.

Figure 1. Model Diagram