



## **I. Calculation of predicted *in vivo* plasma concentration profiles**

The predicted plasma concentration time curve for zolpidem from modified release formulations can be estimated using the *in vitro/in vivo* correlation (IVIVC) model developed and submitted in the NDA for AMBIEN CR (Study POH0037). This model was established using data from 24 fasted male subjects treated with modified-release formulations in Study GAR4624 and was validated for internal and external reliability in Study POH0037 to accurately predict measured plasma zolpidem concentrations from formulations of zolpidem with the release characteristics of AMBIEN CR.

The IVIVC model derived for AMBIEN CR and described in report POH0037, uses the equation given below to predict plasma concentrations (y) from *in vitro* dissolution data:

Hill model:  $y = (a * x^b) / (c^b + x^b)$ .

## **II. Convolution of absorption profile for formulation G**

Using the equation described above, it was possible to calculate the expected bioavailability characteristics (plasma concentrations) of zolpidem from formulation G (the slow releasing formulation) at various time points based on dissolution data at those time points (convolution method).

Numerical convolution calculations were performed using Kinetica 4.0 (Innaphase, Philadelphia, PA, USA).

## **III. Calculation of relative bioequivalence**

Evaluation of the relative bioequivalence of the slow-releasing formulation with the intermediate releasing formulation that was developed as AMBIEN CR, required the comparison of specific pharmacokinetic parameters for these formulations ( $C_{max}$ , AUC, partial  $AUC_{0-3h}$ ,  $AUC_{3-6h}$  and  $AUC_{6-\infty}$ ). For the slow releasing formulation these parameters were calculated using the point estimates of the plasma concentration curve data developed for formulation G. The non-compartmental analysis of these parameters was performed using WinNonlin 4.1.

In order to evaluate the relative bioequivalence of the G formulation with the intermediate-releasing formulation that was developed as AMBIEN CR, comparisons were made between the estimates for the pharmacokinetic values from formulation G and the geometric mean values obtained for these parameters in clinical study GAR4624, a pharmacokinetic study of the formulation developed as AMBIEN CR.

The data used to obtain ratios in the above comparison did not allow calculations of 90% confidence intervals because of the nature of the plasma concentration curve data (existing only as point estimates) for formulation G. 90% confidence intervals for the ratios of the calculated pharmacokinetic parameters were estimated for each parameter using intra-individual coefficients of variation obtained in a 72-subject study (Study BDR5478; see Table 1). This study evaluated the bioequivalence between the Phase III 1A1 formulation and the marketed formulation (2C3) in 72 healthy young male and female subjects using a two-way cross-over

design. The statistical analysis of these data with PROC MIXED allowed an estimation of the intra-individual coefficient of variation of each parameter as the residuals.

**Table 1. Intra-individual coefficients of variation, point estimates and 90% confidence intervals estimated for formulation 2C3 compared to 1A1 in study BDR5478 (n=72 subjects).**

Parameter	From BDR5478 - All Subjects			
	CV intra(%)	PE	90%CI lower	90%CI upper
Cmax	24.6	1.02	0.96	1.10
AUC	25.3	0.99	0.92	1.06
AUC0-3h	33.6	1.08	0.99	1.19
AUC3-6h	29.0	0.97	0.90	1.05
AUC(6-inf)	42.8	0.94	0.83	1.06