Appendix Development of the Pharmacokinetic and MOAA/S Pharmacodynamic Models of Remimazolam

Comparison of Performance of Some Physiologically-based Pharmacokinetic Models of Remimazolam (Figure 2)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Run | Clearance Compartment | Arterial Compartment (V3) | IIVa | Degrees of Freedom | Covariates {Factor / Exponent (θ2)}cd | OFVb | ΔOFVb |
| Rem-R01 | Pulmonary (V2) | Fixede | 4 | 13 |  | 5125.0 | --- |
| Rem-R02 | Central (V1) | Fixede | 4 | 13 |  | 5151.3 | +26.3 |
| Rem-R03 | Hepatic | Fixede | 4 | 13 |  | 5161.0 | +36.0 |
| Rem-R07 | Peripheral (V4) | Fixede | 4 | 13 |  | 4879.5 | -245.5 |
| Rem-R12 | Peripheral (V4) | Unfixed | 4 | 14 |  | 4822.6 | -302.4 |
| Rem-R13 | Peripheral (V4) | Unfixed | 5 | 15 |  | 4750.3 | -374.7 |
| Rem-R18 | Peripheral (V4) | Unfixed | 5 | 16 | Sexc / Qf (-0.074) | 4728.0 | -22.3 |
| Rem-R19 | Peripheral (V4) | Unfixed | 5 | 16 | Weightd / Qf (0.309) | 4729.1 | -21.2 |
| Rem-R22 | Peripheral (V4) | Unfixed | 5 | 16 | Weight / Clf (0.487) | 4745.3 | -4.9 |
| Rem-R40 | Peripheral (V4) | Unfixed | 6 | 16 |  | 4740.1 | -10.2 |
| Rem-R55 g | Peripheral (V4) | Unfixed | 5 | 16 |  | 4721.1 | -29.2g |
| Rem-R56g | Peripheral (V4) | Unfixed | 5 | 16 |  | 4721.1 | -29.2g |

a Inter-individual variability: included for Clf, V1f, V4f, V5 and V3f (R13 – R55), V2f (R56), Qf (R40) (see Figure 2)

b OFV, ΔOFV = objective function value and change in OFV, respectively. ΔOFV relative to Rem-R01 for Rem-R02 to Rem-R13 and relative to Rem-R13 for Rem-R18 to Rem-R56.

c Categorical Covariate -  (Category = 1 in males and 0 in females, θ1 = population mean parameter value)

d Continuous Covariate -  (θ1 = population mean parameter value)

e Arterial volume (V3) = Weight x 0.65 liter /70 kg

f Cl = elimination clearance, Q = cardiac output, V1= venous volume, V2 = cardiac / pulmonary volume, V3 = arterial volume, V4, V5 = Volumes of Compartments 4 and 5, respectively (see Figure 2).

g V2 unfixed. Identical objective functions obtained when IIV included for either V3 (Run R55) or V2 (R56). In both cases coefficient of variation of this volume equaled 181% and population mean volumes were mirror images (Run 55, V3 and V2 = 0.28 and 1.84 litres, respectively; Run 56, V3 and V2 = 1.84 and 0.28 litres, respectively).

Comparison of Performance of Some MOAA/S Pharmacodynamic Models of Remimazolam

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| PK Model | PD Run | IIVa | Error | OFVb |
| Rem-R13 | 01 | IC50, ke0, IMAX, γ, Effect | Sc | 1240.6 |
|  | 02 | IC50, ke0, IMAX, γ | --- | 1244.8 |
|  | 03 | IC50, ke0, IMAX, Effect | --- | 1279.6 |
|  | 04 | IC50, ke0, γ | --- | 1251.6 |
|  | 17 | IC50, ke0, γ, Effect | IIV (Effect) ⭢ 0 | 1251.6 |
|  | 18 | IC50, IMAX, γ, Effect | Sb | 1247.9 |
|  | 19 | ke0, IMAX, γ, Effect | --- | 1263.2 |

a Inter-individual variability, included where shown for the pharmacodynamic parameters and the overall effect

b Objectiuve Function Value

c “S” matrix algorithmically singular