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| [**WorldWide Antimalarial Resistance Network**](https://www.wwarn.org/impact-outcomes/publications/population-pharmacokinetic-properties-piperaquine-falciparum-malaria)  [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups)  Version 1. Created 10 April 2019. |
| WWARN is committed to supporting efficient and quality data collection and analysis for antimalarial drug research. As such we are sharing the NONMEM code used for this publication. NONMEM is a computer program, NONlinear Mixed Effects Modeling, used by WWARN’s [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups).  For further information, please contact [info@wwarn.org](mailto:info@wwarn.org) |
| **Please use the following reference:**  WWARN NONMEM code file used to develop: [Population Pharmacokinetic Properties of Piperaquine in Falciparum Malaria: an Individual Participant Data-level Meta-analysis.](https://www.wwarn.org/impact-outcomes/publications/population-pharmacokinetic-properties-piperaquine-falciparum-malaria)  R.M. Hoglund, L. Workman, M.D. Edstein, I. Zongo, J.B. Ouedraogo, S. Borrmann, L. Mwai, C. Nsanzabana, R.N. Price, P. Dahal, N.C. Sambol, S. Parikh, F. Nosten, E.A. Ashley, A.P. Phyo, K.M. Lwin, R. McGready, N.P.J. Day, P.J. Guerin, N.J. White, K.I. Barnes, J. Tarning.  *PLoS Medicine*. 2017 Jan 10;14(1):e1002212  Read the full summary of the [Piperaquine PK / PD Study Group](https://www.wwarn.org/working-together/study-groups/piperaquine-pkpd-study-group) |
| **NONMEM code:**  $INPUT  ID ; Patient ID  TIME ; Time of sample  DV ; Dependent variable (natural logarithm of observed concentration, ng/mL)  WT ; Body weight (covariate)  EVID ; Event ID record  MDV ; Missing dependent variable (1 = missing)  AMT ; Dose amount (mg)  CMT ; Compartment  AGE ; Age (covariate, years)  MAT ; Matrix (covariate; 1 = capillary, 2 = venous)  OCC ; Dose occasion (1 = first dose, 2 = second dose , 3 = third dose)  $DATA  dataset.csv IGNORE = #  $SUBROUTINE  ADVAN5 TRANS1  $MODEL  COMP = (1) ; Dose  COMP = (2) ; Central compartment  COMP = (3) ; First peripheral compartment  COMP = (4) ; Second peripheral compartment  COMP = (5) ; Transit compartment 1  COMP = (6) ; Transit compartment 2  $PK  ;------------------------------------Dose occasion covariate----------------------------------------------------------------------  F1COVD = (1 + THETA(10) \* (OCC - 1)) ; Linear covariate relationship for dose occasion  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------Age covariate-----------------------------------------------------------------------------------  EM50 = THETA(11) ; Age to reach 50% of full maturation  HILL = THETA(12) ; Hill coefficient  MF = ((AGE)\*\*HILL) / (((EM50)\*\*HILL) + ((AGE)\*\*HILL) ) ; Age-maturation relationship  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ Scaling factor for venous to capillary concentration ----------------------------------  IF(MAT.EQ.2) SCALEVC = 1 ; Capillary concentration  IF(MAT.EQ.1) SCALEVC = 1 + THETA(9) ; Scaling for venous concentration  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ Inter-dose occasion variability (IOV) ----------------------------------------------------  OC1 = 0 ; Initial value, first dose occasion  OC2 = 0 ; Initial value, second dose occasion  OC3 = 0 ; Initial value, third dose occasion  IF(OCC.EQ.1) OC1 = 1 ; First dose occasion  IF(OCC.EQ.2) OC2 = 1 ; Second dose occasion  IF(OCC.EQ.3) OC3 = 1 ; Third dose occasion  IOV1 = ETA(9) \* OC1 + ETA(10) \* OC2 + ETA(11) \* OC3 ; IOV for relative bioavailability  IOV2 = ETA(12) \* OC1 + ETA(13) \* OC2 + ETA(14) \* OC3 ; IOV for mean transit time  ;----------------------------------------------------------------------------------------------------------------------------------------  TVCL = THETA(1) \* MF \* ((WT / 54)\*\*0.75) ; Population clearance  CL = TVCL \* EXP(ETA(1)) ; Individual  TVV2 = THETA(2) \* ((WT / 54)\*\*1) ; Population central volume  V2 = TVV2 \* EXP(ETA(2)) ; Individual central volume  TVQ1 = THETA(3) \* ((WT / 54)\*\*0.75) ; Population inter-compartment clearance 1  Q1 = TVQ1 \* EXP(ETA(3)) ; Individual inter-compartment clearance 1  TVV3 = THETA(4) \* ((WT / 54)\*\*1) ; Population peripheral volume 1  V3 = TVV3 \* EXP(ETA(4)) ; Individual peripheral volume 1  TVQ2 = THETA(5) \* ((WT / 54)\*\*0.75) ; Population inter-compartment clearance 2  Q2 = TVQ2\* EXP(ETA(5)) ; Individual inter-compartment clearance 2  TVV4 = THETA(6) \* ((WT / 54)\*\*1) ; Population peripheral volume 2  V4 = TVV4 \* EXP(ETA(6)) ; Individual peripheral volume 2  TVMT = THETA(7) ; Population mean transit time  MT = TVMT \* EXP(ETA(7) + IOV2) ; Individual mean transit time  TVF1 = THETA(8) \* F1COVD ; Population relative bioavailability  F1 = TVF1 \* EXP(ETA(8) + IOV1) ; Individual relative bioavailability  NN = 2 ; Number of transit compartments  KTR = (NN + 1) / MT ; Transit rate constant  K15 = KTR ; Transit rate constant (COMP 1 --> 5)  K56 = KTR ; Transit rate constant (COMP 5 --> 6)  K62 = KTR ; Transit rate constant (COMP 6 --> 2)  K20 = CL / V2 ; Elimination rate constant (COMP 2 --> 0)  K23 = Q1 / V2 ; Distribution rate constant (COMP 2 --> 3)  K32 = Q1 / V3 ; Distribution rate constant (COMP 3 --> 2)  K24 = Q2 / V2 ; Distribution rate constant (COMP 2 --> 4)  K42 = Q2 / V4 ; Distribution rate constant (COMP 4 --> 2)  S2 = V2 /1000 ; Scaling for central volume  $ERROR  IPRED = A(2) / S2 ; Predicted plasma concentration  IPRED = IPRED \* SCALEVC ; Scaling factor (venous to capillary)  IF(IPRED.GT.0) IPRED = LOG(IPRED) ; Natural logarithm of predictions  W = SQRT(SIGMA(1,1)) ; Residual error  IRES = IPRED – DV ; Individual residual error  IWRES = IRES / W ; Individually weighted residual error  Y = IPRED + EPS(1) ; Additive residual error  $THETA ; Initial estimates of theta  (0, 55.4) ; 1. Clearance  (0, 2910) ; 2. Central volume of distribution  (0, 310) ; 3. Inter-compartment clearance 1  (0, 4910) ; 4. Peripheral volume of distribution 1  (0, 105) ; 5. Inter-compartment clearance 2  (0, 30900) ; 6. Peripheral volume of distribution 2  (0, 2.11) ; 7. Mean transit time  (1 FIX) ; 8. Relative bioavailability  (0, 1.06) ; 9. Scaling factor (venous to capillary)  (-1, 0.237) ; 10. Dose occasion on relative bioavailability  (0, 0.575) ; 11. Age to reach 50% of full maturation  (0, 5.51) ; 12. Hill coefficient  $OMEGA ; Initial estimates for omega  (0.075) ; 1. IIV clearance  (0.371) ; 2. IIV central volume of distribution  (0 FIX) ; 3. IIV Inter-compartment clearance 1  (0.056) ; 4. IIV peripheral volume of distribution 1  (0.054) ; 5. IIV inter-compartment clearance 2  (0.114) ; 6. IIV peripheral volume of distribution 2  (0.135) ; 7. IIV mean transit time  (0.158) ; 8. IIV relative bioavailability  $OMEGA BLOCK(1) 0.252 ; 9. IOV relative bioavailability  $OMEGA BLOCK(1) SAME ;10. IOV relative bioavailability  $OMEGA BLOCK(1) SAME ;11. IOV relative bioavailability  $OMEGA BLOCK(1) 0.195 ; 12. IOV mean transit time  $OMEGA BLOCK(1) SAME ; 13. IOV mean transit time  $OMEGA BLOCK(1) SAME ; 14. IOV mean transit time  $SIGMA ; Initial estimates of sigma  (0.115) ; Residual variability  $ESTIMATION POSTHOC MAXEVAL = 9999 METHOD = 1 INTER |