

## Supplemental Digital Content 1: NONMEM Code for the Pharmacokinetic Model

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1: $PROBLEM PARE/VALDECOXIB IN CHILDREN
2:
3: $INPUT ID TIME AMT RATE DV CMT MDV TYPE AGE WT SEX PROP MRPH PRCT FENT ATCR ONDN DEXA ABIO
4:
5: $DATA PAREBLQDATA.CSV IGNORE=#
6:
7: $SUBROUTINE ADVAN5 TRANS1
8:
9: $PRIOR NWPRI NTHETA=14 NETA=4 NEPS=2 NTHP=2 NETP=0 NPEXP=1
10:
11: $MODEL COMP=PAREN ;1
12: COMP=META ;2
13: COMP=PAR2 ;3
14: COMP=PAR3 ;4
15:
16: $PK
17: ;TYPICAL(POPULATION) ESTIMATES FOR PARECOXIB
18: TVCL1=THETA(3)*((WT/70)**0.75)*(1+THETA(10)*(AGE-6.9))
19: TVV1 =THETA(4)*WT/70
20: TVQ3=THETA(5)*((WT/70)**0.75)
21: TVV3=THETA(6)*WT/70
22: TVQ4=THETA(7)*((WT/70)**0.75)
23: TVV4=THETA(8)*WT/70
24:
25: ;ERROR(%) ESTIMATE FOR PARECOXIB
26: SIG=THETA(9)
27:
28: ;TYPICAL(POPULATION) ESTIMATES FOR VALDECOXIB PARAMETERS INCORPORATING MATURATION
29: TVHILL=THETA(1)
30: HILL=TVHILL
31: TVMA50=THETA(2)
32: MA50=TVMA50
33: FCL=((AGE+.74615)**HILL)/(((AGE+.74615)**HILL)+MA50**HILL)
34: TVCL2=THETA(11)*FCL*((WT/70)**0.75)
35:
36: TVHIL2=THETA(13)
37: HILL2=TVHIL2
38: TVMA52=THETA(14)
39: MA502=TVMA52
40: FCL2=((AGE+.74615)**HILL2)/(((AGE+.74615)**HILL2)+MA502**HILL2)
41: TVV2=THETA(12)*FCL2*WT/70
42:
43: ;INDIVIDUAL ESTIMATES FOR PARECOXIB RELATED PARAMETERS
44: CL1=TVCL1*EXP(ETA(3))
45: V1=TVV1
46: Q3=TVQ3
47: V3=TVV3*EXP(ETA(4))
48: Q4=TVQ4
49: V4=TVV4
50: ;INDIVIDUAL ESTIMATES FOR VALDECOXIB RELATED PARAMETERS INCORPORATING MOLECULAR RATIO
51: CL2=TVCL2*(314.36/370.42)*EXP(ETA(1))
52: V2=TVV2*(314.36/370.42)*EXP(ETA(2))
53:
54: ;CUSTOM RATES BETWEEN COMAPARTMENTS
55: K12=CL1/V1
56: K31=Q3/V3
57: K13=Q3/V1
58: K41=Q4/V4
59: K14=Q4/V1
60: K20=CL2/V2
61:
62: ;SCALE TERMS FOR COMAPARTMENTS
63: S1=V1
64: S2=V2
65: S3=V3
66: S4=V4
67:
68: $ERROR
69: ; ERROR MODEL FOR PARECOXIB INCORPORATING BLQ DATA
70: IF(CMT.EQ.1) THEN
71: LOQ=LOG(10)
72: IPRED=LOG(F+0.001)
73: IRES=DV-IPRED
74: IWRES=IRES/1
75: DUM=(LOQ-IPRED)/SIG
76: CUMD=PHI(DUM)
77: ENDF
78: IF(TYPE.EQ.1.AND.CMT.EQ.1) THEN
79: F_FLAG=0
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80: Y=LOG(F)+SIG*ERR(1)
81: ENDIF
82: IF(TYPE.EQ.2.AND.CMT.EQ.1) THEN
83: F_FLAG=1
84: Y=CUMD
85: ENDIF
86:
87: ; ERROR MODEL FOR VALDECOXIB
88: IF(CMT.EQ.2) THEN
89: IPRE =LOG(F+0.001)
90: IRES=DV-IPRE
91: IWRE=IRES/1
92: Y=LOG(F)+ERR(2)
93: ENDIF
94:
95: ;INITIAL ESTIMATES OF THETA
96: $THETA
97: (0,2.4,100) ; HILL-CL(VALDECOXIB)/F*
98: (-1,1.0,4) ; MA50-CL(VALDECOXIB)/F*
99: (0,21) ; CL(PARECOXIB)
100: (0,5.4) ; VC(PARECOXIB)
101: (0,7.0) ; Q1(PARECOXIB)
102: (0,83) ; VP1(PARECOXIB)
103: (0,2.7) ; Q2(PARECOXIB)
104: (0,4.9) ; VP2(PARECOXIB)
105: (0,0.31) ; ERROR(%) ESTIMATE FOR PARECOXIB
106: (0,0.021,.3) ; MATURATION SLOPE (%) CL(PARECOXIB)
107: (0,11) ; CL(VALDECOXIB)/F*
108: (0,87) ; V(VALDECOXIB)/F*
109: (0,2.6,100) ; HILL-V(VALDECOXIB)/F*
110: (-1,0.71,4) ; MA50-V(VALDECOXIB)/F*
111:
112: ; PRIOR DATA FOR THETA(1)&(2)
113: $THETA
114: 3 FIX ; HILL-CL(VALDECOXIB)/F*
115: 1.4115 FIX ; MA50-CL(VALDECOXIB)/F*
116:
117: ;INITIAL ESTIMATES FOR ETAS AND COVARIANCES
118: $OMEGA BLOCK(4)
119: 0.1 ; CL2
120: 0.05 0.1 ; V2
121: 0 0.05 0.1 ; CL1
122: 0 0 0.05 0.1 ; V3
123:
124: ;PRIOR DATA FOR THETA(1)&(2)
125: $OMEGA BLOCK(2) FIX
126: 0.011207 ; HILL-CL(VALDECOXIB)/F*
127: 0 0.338724 ; MA50-CL(VALDECOXIB)/F*
128:
129: ;INITIAL ESTIMATES FOR ERR TERMS
130: $SIGMA
131: 1 FIX ; PARECOXIB
132: 0.0360 ; VALDECOXIB
133:
134: $ESTIMATION MAX=9999 SIG=2 METHOD=COND INTER LAPLACIAN NUMERICAL POSTHOC PRINT=1 MSFO=MSF1
135:
136: $COVARIANCE PRINT=E MATRIX=R
137:

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