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1  $PROBLEM ONE COMPARTMENT ORAL MIXED ORDER ABSORPTION          ;DATE = 6/2/04 PROGRAMMER=XXXX
2                                                                    ;Units: Time=hr,
3                                                                    ;Concentration=ug/ml,
4                                                                    ;Dose = 100mg and 250mg
5
6  $DATA KAKOEST_CRSO.CSV IGNORE=C
7
8  $INPUT ID TIME CONC=DV AMT CMT RATE EVID OCC MDV
9  ;RATE = -2 in the data file means that the duration for zero order input will be mentioned
10 ;in the controlstream and hence NONMEM calculates the RATE
11
12 $SUBROUTINE ADVAN2 TRANS2
13
14 $PK
15   OC1=0
16   IF(OCC.EQ.1)OC1=1
17   OC2=0
18   IF(OCC.EQ.2)OC2=1
19
20   BOVCL = ETA(7)*OC1+ETA(8)*OC2
21   BOVV  = ETA(9)*OC1+ETA(10)*OC2
22
23   POPCL = THETA(1)
24   POPV  = THETA(2)
25   POPKA = THETA(3)
26   POPDUR = THETA(4)
27   POPLAG = THETA(5)
28   POPFKA = THETA(6)
29
30   CL    = POPCL*EXP(ETA(1)+BOVCL)      ;CL/F in L/hr
31   V     = POPV*EXP(ETA(2)+BOVV)       ;V/F in L
32   KA    = POPKA*EXP(ETA(3))           ;Absorption rate constant
33   D2    = POPDUR*EXP(ETA(4))          ;Duration of zero order input
34   ALAG2 = POPLAG*EXP(ETA(5))         ;Lag time after which zero order absorption starts
35   F1    = POPFKA*EXP(ETA(6))         ;Fraction of dose absorbed by first order process
36   F2    = 1-F1
37
38   S2 = V                               ;Scaling factor
39
40
41 $ERROR
42   IPRED=F
43   Y=F+F*ERRCV+ERRSD
44                                       ;Additive and proportional residual error model
45
46 $THETA (0.01,1)           ;POPCL/F
47 $THETA (0.1,10)          ;POPV/F
48 $THETA (0.1,3)           ;POPKA
49 $THETA (0.1,1)           ;POPDUR
50 $THETA (0.1,2)           ;POPLAG
51 $THETA (0.01,0.4,1)      ;POPFka
52
53 $OMEGA 0.09              ;BSVCL
54 $OMEGA 0.09              ;BSVV
55 $OMEGA 0.09              ;BSVKA
56 $OMEGA 0.04              ;BSVDUR
57 $OMEGA 0.04              ;BSVLAG
58 $OMEGA 0.04              ;BSVFKA
59 $OMEGA BLOCK(1) 0.09     ;BOVCL occ=1
60 $OMEGA BLOCK(1) SAME     ;BOVCL occ=2
61 $OMEGA BLOCK(1) 0.09     ;BOVV occ=1
62 $OMEGA BLOCK(1) SAME     ;BOVV occ=2
63
64
65 $SIGMA
66   0.5                    ;ERRCV
67   10                     ;ERRSD
68
69 $ESTIMATION METHOD=0 MAXEVAL=9999 PRINT=5 POSTHOC
70 $COVARIANCE
71

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```
72 $TABLE ID TIME DV IPRED
73 NOPRINT ONEHEADER FILE=KAKOEST_crso.fit
74
75
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