

**PHARMACOKINETIC REPORT**

**Model development of Warfarin following   
a Single Oral Dose**

**Run:** %project\_fileName%

**Dataset:** %data\_fileName%

**Date:** %reportGenerationDateTime(MM-dd-yyyy)%

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# List of Abbreviations

|  |  |
| --- | --- |
| AUC | Area under the concentration-time curve |
| AUCinf | Area under the concentration-time curve from zero to infinity |
| AUClast | Area under the concentration-time curve from zero to the last timepoint |
| AUCextra | Percentage of Extrapolated Area Under the Curve |
| Cmax | Maximum observed drug concentration |
| CV | Coefficient of variation |
| (L)LOQ | (Lower) Limit of quantification |
| NCA | Noncompartmental analysis |
| PK | Pharmacokinetic(s) |
| SD | Standard deviation |
| SE | Standard error |
| Tmax | Time to reach maximum observed concentration |
| T1/2 | Half-life |

# Executive Summary

**Objective and study design**

Warfarin is an anticoagulant normally used in the prevention of thrombosis and thromboembolism, the formation of blood clots in the blood vessels and their migration elsewhere in the body, respectively. The data set provides set of plasma warfarin concentrations and Prothrombin Complex Response in thirty normal subjects after a single loading dose. A single large loading dose of warfarin sodium, 1.5 mg/kg of body weight, was administered orally to all subjects. Measurements were made each 12 or 24h.

The objective of this study is to develop a PK model that describes the population behaviour as well as variability between individuals.

**Method**

Model development is performed using Monolix version %version%.

# Methods

## Data analysis

The data set provides set of plasma warfarin concentrations and Prothrombin Complex Response in thirty normal subjects after a single loading dose. A single large loading dose of warfarin sodium, 1.5 mg/kg of body weight, was administered orally to all subjects. Measurements were made each 12 or 24h.

Observed data plot in linear scale shows no outliers.

<lixoftPLH>

plot: outputplot

widthCm: 16

heightCm: 12.6

zoom: 100

caption: Observed data

captionAbove: false

settings:

fixedNbBins: 20

isNumberOfBinsFixed: true

obsErrorMethod: standardError

legend: true

obsLines: false

obsMean: true

xLabel: time

yEqualDomains: false

yLabel: y1

legendPosition: ne

preferences:

observationStatisticsStrokeDasharray: '10'

observationStatisticsWidth: 2

stratification:

state: {split: [age], color: [age], mergedSplits: true}

</lixoftPLH>

Plot with the logarithmic scale on the y-axis suggests that the elimination follows a one compartment model.

## Covariate data analysis

Covariate data includes weight, sex and age.

<lixoftPLH>

plot: covariateviewer

widthCm: 16

heightCm: 12.6

zoom: 100

caption: Covariate viewer

captionAbove: false

settings:

colSelection: [age, wt, sex]

rowSelection: [age, wt, sex]

baseline: false

quartile: false

</lixoftPLH>

# Results

## Model fit

The final model is a one compartment model with linear elimination. The absorption is of first order with a delay Tlag. The model uses the combined 2 error model. Part of the variability between individuals in the values of volume and clearance has been explained with individual weight.

<lixoftPLH>

data:

task: populationParameters

methods: all

metrics: all

types: all

display:

significantDigits: 3

fitToContent: true

colored: false

caption: "Estimated population parameters"

captionAbove: true

</lixoftPLH>

## Pharmacokinetic individual parameters

Calculated PK individual parameters for each subject.

<lixoftPLH>

data:

task: individualParameters

method: mode

metrics: [ID]

parameters: all

covariates: all

covariatesAfterParameters: true

display:

significantDigits: 1

fitToContent: true

metricsDirection: vertical

caption: "Estimated individual parameters (EBEs)"

captionAbove: true

</lixoftPLH>

## Diagnostic plots

The VPC plot shows a good correspondence between empirical percentiles and prediction intervals obtained from 500 simulations.

<lixoftPLH>

plot: vpc

widthCm: 16

heightCm: 12.6

zoom: 100

caption: Visual predictive check

captionAbove: false

settings:

useCensoredData: false

observations: true

xLabel: time

yInterval: [0.1, 20]

yLabel: y1

yLog: true

areaOutliers: false

</lixoftPLH>