

**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>