DDI precipitant risk assessment for examplinib and M1

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# Introduction

This drug-drug interaction (DDI) precipitant risks assessment report for examplinib and M1 is based on the [ICH M12 guidance document](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf).

All calculations were done using the [ddir](https://github.com/rstrotmann/ddir) package, version 0.15.1.

# Drug properties

The following physico-chemical, ADME and clinical exposure data were used for the calculation of the relevant precipitant drug concentrations:

Compound parameters for examplinib

| parameter | value | source |
| --- | --- | --- |
| oral | TRUE |  |
| (g/mol) | 492.6 |  |
| (mg) | 450 | clinical dose |
| (ng/ml) | 3530 | study 001 |
|  | 0.023 | study 002 |
|  | 1 | default |
|  | 1 | study 003 |
|  | 0.81 | study 003 |
|  | 1 | default |
| (1/min) | 0.00267 | unknown |
| (mg/l) | Inf | default |

Compound parameters for M1

| parameter | value | source |
| --- | --- | --- |
| oral | FALSE |  |
| (g/mol) | 506.56 |  |
| (mg) | NA |  |
| (ng/ml) | 1038 | study 001 |
|  | 0.012 | study 002 |
|  | 1 | default |
|  | 1 | study 002 |
| (mg/l) | Inf | default |

# Key perpetrator concentrations

The following perpetrator concentrations were calculated as described in Appendix 1:

Key perpetrator concentrations for examplinib

| parameter | value (ng/ml) | value (uM) |
| --- | --- | --- |
|  | 1800000.0 | 3654.080 |
|  | 81.2 | 0.165 |
|  | 95.0 | 0.193 |
|  | 3244.1 | 6.586 |

Key perpetrator concentrations for M1

| parameter | value (ng/ml) | value (uM) |
| --- | --- | --- |
|  | 0.0 | 0.0000 |
|  | 12.5 | 0.0246 |
|  | 12.5 | 0.0246 |
|  | 12.5 | 0.0246 |

# DDI risk as inhibitor or inducer of drug-metabolizing enzymes

## Basic modeling of CYP inhibition

### Reversible inhibition

Following the basic modeling approach (refer to Section 2.1.2.1 of the [ICH M12 guideline](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf)), the relevant metric for the assessment of the direct CYP inhibition risk is with the inhibitor concentration being for hepatic CYP enzymes and for intestinal CYP enzymes.

R values of and for hepatic and intestinal enzymes are considered to indicate a potential clinical risk.

Risk for direct CYP inhibition by examplinib, basic model

| CYP | () | () |  | risk (hepatic) |  | risk (intestinal) |
| --- | --- | --- | --- | --- | --- | --- |
| CYP1A2 | NA | NA | NA |  |  |  |
| CYP2B6 | NA | NA | NA |  |  |  |
| CYP2C8 | 11.0 | 11.0 | 0.015 | No |  |  |
| CYP2C9 | 13.5 | 13.5 | 0.012 | No |  |  |
| CYP2C19 | 15.0 | 15.0 | 0.011 | No |  |  |
| CYP2D6 | NA | NA | NA |  |  |  |
| CYP3A4 | 12.5 | 12.5 | 0.013 | No | 292.3 | Yes |

Risk for direct CYP inhibition by M1, basic model

| CYP | () | () |  | risk (hepatic) |  | risk (intestinal) |
| --- | --- | --- | --- | --- | --- | --- |
| CYP2C9 | 4.4 | 4.4 | 0.006 | No |  |  |

### Time-dependent inhibition

As per the ICH M12 guideline, the risk for time-dependent inhibition (TDI) of CYP enzymes is assessed based on the formula given in Appendix 1, where suggest a clinically relevant DDI potential that requires further investigation.

Risk for CYP TDI by examplinib, basic model

| CYP | () |  | (1/h) | (1/h) | source |  | risk |
| --- | --- | --- | --- | --- | --- | --- | --- |
| CYP3A4 | 0.17 | 0.02 | 0.04 | 0.02 | study 001 | 3.06 | Yes |

## Modeling of CYP induction

### Basic ‘fold-change’ method

The basic ‘fold-change’ approach evaluates whether the maximal change in CYP mRNA expression is > 2-fold at concentrations up to 50-fold of the expected unbound systemic concentration of the drug (refer to Section 2.1.4.1 of the [ICH M12 guidance document](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf)).

Basic modeling as per the FDA guideline results in the following risk assessment:

Risk for hepatic CYP induction by examplinib, basic static model

| CYP |  | () | source |  | risk | notes |
| --- | --- | --- | --- | --- | --- | --- |
| CYP1A2 | 1.00 | 5 | study 007 | 30.3 | No | Low maxc |
| CYP2B6 | 1.00 | 5 | study 007 | 30.3 | No | Low maxc |
| CYP3A4 | 7.35 | 3 | study 007 | 18.2 | Yes | Low maxc |

Risk for hepatic CYP induction by M1, basic static model

| CYP |  | () | source |  | risk | notes |
| --- | --- | --- | --- | --- | --- | --- |
| CYP1A2 | 1.00 | 5 | study 007 | 203.3 | No |  |
| CYP2B6 | 6.98 | 5 | study 007 | 203.3 | Yes |  |
| CYP3A4 | 22.70 | 5 | study 007 | 203.3 | Yes |  |

### Basic kinetic method

The basic kinetic method for the assessment of CYP induction is based on the and parameters derived from in vitro studies (refer to Section ‘[Basic kinetic modeling of CYP induction](#basic-kinetic-modeling-of-cyp-induction)’ in Appendix 1). For , an in vivo induction risk cannot be excluded:

Risk for CYP induction by examplinib, basic kinetic model

| CYP |  | () | source |  | risk |
| --- | --- | --- | --- | --- | --- |
| CYP1A2 | 1.00 | NA | study 007 | NA |  |
| CYP2B6 | 1.00 | NA | study 007 | NA |  |
| CYP3A4 | 7.35 | 1.64 | study 007 | 0.21 | Yes |

Risk for CYP induction by M1, basic kinetic model

| CYP |  | () | source |  | risk |
| --- | --- | --- | --- | --- | --- |
| CYP1A2 | 1.00 | NA | study 007 | NA |  |
| CYP2B6 | 6.98 | 1.86 | study 007 | 0.55 | Yes |
| CYP3A4 | 22.70 | 1.10 | study 007 | 0.19 | Yes |

## Mechanistic static modeling

Using the mechanistic static modeling approach (refer to Section 7.5.1.2 of the [ICH M12 guideline](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf), AUC ratios for specific sensitive CYP substrates are calculated, considering the available in vitro data for both direct and time-dependent inhibition, and mRNA induction (refer to Section ‘[Mechanistic static modeling of CYP modulation](#X9513131ca0815418b816faa96cb17e9f06d1f0d)’ in Appendix 1).

Mechanistic static modeling may be used to investigate CYP inhibition alone, or both inhibition and induction effects.

### CYP inhibition only

Mechanistic static modeling of the CYP inhibition risk for examplinib

| CYP | substrate |  |  |  |  |  |  |  |  |  | AUCR | risk |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CYP1A2 | tizanidine | 1.00 | 0.95 | 0.98 | 1.00 | 1.00 | 1.00 | 1.00 | 1 | 1 | 1.00 | No |
| CYP2B6 | NA | NA | NA | NA | 1.00 | 1.00 | 1.00 | 1.00 | 1 | 1 | NA |  |
| CYP2C8 | repaglinide | 1.00 | 1.00 | 0.61 | 0.63 | 0.98 | 1.00 | 1.00 | 1 | 1 | 1.01 | No |
| CYP2C9 | S-warfarin | 1.00 | 1.00 | 0.91 | 0.67 | 0.99 | 1.00 | 1.00 | 1 | 1 | 1.01 | No |
| CYP2C19 | omeprazole | 1.00 | 1.00 | 0.87 | 0.69 | 0.99 | 1.00 | 1.00 | 1 | 1 | 1.01 | No |
| CYP2D6 | desipramine | 1.00 | 1.00 | 0.85 | 1.00 | 1.00 | 1.00 | 1.00 | 1 | 1 | 1.00 | No |
| CYP3A4 | midazolam | 0.57 | 0.96 | 1.00 | 0.65 | 0.98 | 0.43 | 0.48 | 1 | 1 | 2.95 | Yes |

Mechanistic static modeling of the CYP inhibition risk for M1

| CYP | substrate |  |  |  |  |  |  |  |  |  | AUCR | risk |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CYP2C9 | S-warfarin | 1 | 1 | 0.91 | 0.99 | 0.99 | 1 | 1 | 1 | 1 | 1.01 | No |

### CYP inhibition and induction

Mechanistic static modeling of the CYP inhibition risk for examplinib

| CYP | substrate |  |  |  |  |  |  |  |  |  | AUCR | risk |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CYP1A2 | tizanidine | 1.00 | 0.95 | 0.98 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.000 | No |
| CYP2B6 | NA | NA | NA | NA | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | NA |  |
| CYP2C8 | repaglinide | 1.00 | 1.00 | 0.61 | 0.63 | 0.98 | 1.00 | 1.00 | 1.00 | 1.00 | 1.011 | No |
| CYP2C9 | S-warfarin | 1.00 | 1.00 | 0.91 | 0.67 | 0.99 | 1.00 | 1.00 | 1.00 | 1.00 | 1.013 | No |
| CYP2C19 | omeprazole | 1.00 | 1.00 | 0.87 | 0.69 | 0.99 | 1.00 | 1.00 | 1.00 | 1.00 | 1.011 | No |
| CYP2D6 | desipramine | 1.00 | 1.00 | 0.85 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.000 | No |
| CYP3A4 | midazolam | 0.57 | 0.96 | 1.00 | 0.65 | 0.98 | 0.43 | 0.48 | 6.88 | 1.77 | 0.845 | No |

Mechanistic static modeling of the CYP inhibition risk for M1

| CYP | substrate |  |  |  |  |  |  |  |  |  | AUCR | risk |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CYP2C9 | S-warfarin | 1 | 1 | 0.91 | 0.99 | 0.99 | 1 | 1 | 1 | 1 | 1.01 | No |

## Basic modeling of UGT inhibition

The relevant metric for basic modeling of the UGT inhibition risk is (refer to Section 2.1.2.1 of the [ICH M12 guidance document](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf)) for details.

is considered to indicate a potential UGT inhibition risk.

Note that in in vitro UGT inhibition studies, often rather than values are reported. Assuming that substrate concentrations close to are used, is calculated as (refer to Cheng, Prusoff 1973).

Basic modeling of UGT inhibition results in the following risk assessment:

Risk for UGT inhibition by examplinib, basic model

| UGT |  |  | risk |
| --- | --- | --- | --- |
| UGT1A1 | 7.50 | 0.022 | Yes |
| UGT1A3 | 7.50 | 0.022 | Yes |
| UGT1A4 | 7.50 | 0.022 | Yes |
| UGT1A6 | 7.50 | 0.022 | Yes |
| UGT1A9 | 1.90 | 0.087 | Yes |
| UGT2B7 | 7.50 | 0.022 | Yes |
| UGT2B15 | 7.50 | 0.022 | Yes |
| UGT2B17 | 3.05 | 0.054 | Yes |

Risk for UGT inhibition by M1, basic model

| UGT |  |  | risk |
| --- | --- | --- | --- |
| UGT1A1 | 0.55 | 0.045 | Yes |
| UGT1A3 | 2.90 | 0.008 | No |
| UGT1A4 | 3.10 | 0.008 | No |
| UGT1A6 | 7.50 | 0.003 | No |
| UGT1A9 | 1.80 | 0.014 | No |
| UGT2B7 | 7.50 | 0.003 | No |
| UGT2B15 | 4.80 | 0.005 | No |

## DDI risk as inhibitor of drug transporters

The metric for the assessment of the drug transporter inhibition risk is . For the relevant perpetrator concentrations, refer to Appendix 1, Section ‘[Inhibition of drug transporters](#inhibition-of-drug-transporters)’.

Note that OCT1 is currently not covered by the M12 guideline.

Risk for drug transporter inhibition by examplinib

| transporter |  | source |  | threshold | risk |
| --- | --- | --- | --- | --- | --- |
| Pgp\_int | 0.41 | study 005 | 8912.39 | 10.00 | Yes |
| Pgp\_sys | 0.41 | study 005 | 0.40 | 0.02 | Yes |
| BCRP\_int | 1.90 | study 005 | 1923.20 | 10.00 | Yes |
| BCRP\_sys | 1.90 | study 005 | 0.09 | 0.02 | Yes |
| OATP1B1 | 177.00 | study 006 | 0.00 | 0.10 | No |
| OATP1B3 | 35.00 | study 006 | 0.01 | 0.10 | No |
| OAT1 | 271.00 |  | 0.00 | 0.10 | No |
| OAT3 | 300.00 |  | 0.00 | 0.10 | No |
| BSEP | 12.80 |  | 0.01 | 0.10 | No |
| OCT1 | 2.30 | study 006 | NA | NA |  |
| OCT2 | 67.00 | study 006 | 0.00 | 0.10 | No |
| MATE1 | 3.60 | study 006 | 0.05 | 0.02 | Yes |
| MATE2k | 1.10 | study 006 | 0.15 | 0.02 | Yes |

# Appendix 1: Calculations and formulae

## Relevant precipitant drug concentrations

### Gut concentration

The maximal gut concentration () for the orally administered compounds is the administered dose dissolved in 250 ml.

### Systemic concentration

The unbound systemic () concentration is considered the relevant precipitant concentration for hepatic enzyme inhibition and induction:

### Hepatic inlet concentration

The hepatic inlet concentration is considered the relevant perpetrator concentration for inhibition of the hepatic uptake transporters OATPB1B1 and OATP1B3, and for the hepatic terms in the mechanistic static modeling equation (refer to Section ‘[Mechanistic static modeling of CYP inhibition/induction]’).

The hepatic inlet concentration is composed of the systemic concentration and the portal contribution. For orally administered drugs, the portal term is calculated as:

with

* the administered dose in mg
* the fraction absorbed after oral administration
* the fraction available after gut metabolism
* the absorption rate
* the hepatic blood flow
* the blood-to-plasma ratio.

The standard hepatic blood flow is assumed as 97 l/h/70 kg or 1.61 l/min/70 kg.

The relevant hepatic inlet (, also called in the mechanistic static modeling equations) concentration is the sum of the maximal systemic plasma concentration and the portal contribution:

### Enteric concentration

For the parent compound, the villous concentration in the gut (, also called in the mechanistic static modeling equations) is calculated as:

with

* the fraction absorbed after oral administration
* the absorption rate constant
* the enteric villous blood flow

Note that as per the ICH M12 guideline and [Rostami-Hodjegan and Tucker, 2004](https://doi.org/10.1016/j.ddtec.2004.10.002) the blood-to-plasma distribution ratio and the plasma binding of the drug are not applicable for the calculation of the villous concentration.

The standard villous blood flow is assumed as 18 l/h/70 kg or 0.3 l/min/70 kg.

## Basic modeling of enzyme inhibition

### Reversible inhibition

For the basic modeling of direct (reversible) enzyme inhibition, the ratios of the relevant inhibitor concentration to the are considered (refer to Section 2.1.2.1 of the [ICH M12 guidance document](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m12-guideline-drug-interaction-studies-step-5_en.pdf)).

For in vitro studies conducted using human liver microsomes, the microsomal unbound fraction, is used to calculate . If unknown, a default of 1 is assumed.

values larger than 0.02 (liver) or 10 (gut), are considered to indicate a potential clinical enzyme inhibition risk using this method.

#### Liver

#### Gut wall

### Time-dependent CYP inhibition

For the basic modeling of the potential for time-dependent CYP inhibition (TDI), the following metric is considered:

with

The CYP degradation constant, is a physiological constant that should be derived from the scientific literature. In this DDI assessment report, standard values are used unless otherwise indicated.

Values of is considered to indicate a clinically relevant TDI potential and suggest the need for further investigation.

## Basic kinetic modeling of CYP induction

For the basic kinetic modeling of the CYP induction potential, the following metric is considered:

with a scaling factor that has a standard value of 1. A different value can be used if warranted by prior experience with the experimental conditions.

suggest a relevant in vivo CYP induction potential.

## Mechanistic static modeling of CYP modulation

In this approach, AUC ratios for specific DDI object substrates are projected based on their known intestinal and hepatic metabolism. Both direct (competitive) and time-dependent inhibition, as well as enzyme induction are considered. AUC ratios are calculated according to the below formula (refer to Section 7.5.1.2 of the ICH M12 guideline):

This calculation is applied for typical probe substrates for which , i.e., the fraction escaping gut metabolism and , i.e., the fraction metabolized are known.

Note that the is composed of the overall fraction metabolized for the respective probe substrate, and the fraction metabolized by the CYP enzyme in questions:

The individual terms in the AUC calculation are:

### Reversible inhibition

### Time-dependent inhibition

### Induction

with the hepatic inlet concentration and the intestinal concentration (see above). is an induction scaling factor (assumed to be 1 but can be adjusted based on the experimental conditions).

## Inhibition of drug transporters

As per the M12 guideline, the metric for the assessment of the drug transporter inhibition risk is:

In the respective in vitro studies, the substrate concentration is usually very low, so that can be assumed. Under common assay conditions, no protein is added to the medium so that the fraction unbound can be assumed 1, i.e. .

The following relevant precitipant concentrations and regulatory thresholds of concern apply for the transporters:

|  | transporter | threshold |
| --- | --- | --- |
|  | P-gp and BRCR when drugs are orally administered | 10 |
|  | P-gp and BRCR when drugs are administered parenterally or for drug metabolites | 0.02 |
|  | hepatic basolateral transporters OCT1, OATP1B1 and OATP1B3 | 0.1 |
|  | renal basolateral transporters OAT1, OAT3 and OCT2 | 0.1 |
|  | apical transporters MATE1 and MATE2-K | 0.02 |

Refer to Section ‘[Relevant precipitant drug concentrations](#relevant-precipitant-drug-concentrations)’ for the calculation of the relevant precipitant concentrations.

# Appendix 2: R Session Info

This document was created using R version 4.4.1 (2024-06-14) and the following packages:

| name | version |
| --- | --- |
| ddir | 0.15.1 |
| knitrdata | 0.6.1 |
| knitr | 1.48 |
| lubridate | 1.9.3 |
| forcats | 1.0.0 |
| stringr | 1.5.1 |
| dplyr | 1.1.4 |
| purrr | 1.0.2 |
| readr | 2.1.5 |
| tidyr | 1.3.1 |
| tibble | 3.2.1 |
| ggplot2 | 3.5.1 |
| tidyverse | 2.0.0 |