DDI perpetrator risk assessment for examplinib and M1

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Introduction

This assessment of the perpetrator risks for examplinib and M1 is based on the relevant FDA and EMA guidance documents (refer to FDA 2020 and EMA 2012).

This output was generated using the `ddir` package.

Drug properties

The following physico-chemical, ADME and clinical exposure data were used for the calculation of the maximal gut and portal vein concentrations, and the unbound systemic concentrations.

Table 1: Compound parameters for examplinib

parameter	value	source
oral	TRUE	
MW (g/mol)	492.6	
dose (mg)	450	clinical dose
$C_{max,ss}$ (ng/ml)	3530	study 001
f_u	0.023	study 002
$f_{u,mic}$	1	default
R_B	1	study 003
F_a	0.81	study 003
F_g	1	default
k_a (1/min)	0.00267	unknown
solubility (mg/l)	Inf	default

Table 2: Compound parameters for M1

parameter	value	source
oral	FALSE	
MW (g/mol)	506.56	
dose (mg)	NA	
$C_{max,ss}$ (ng/ml)	1038	study 001
f_u	0.012	study 002
$f_{u,mic}$	1	default
R_B	1	study 002
solubility (mg/l)	Inf	default

Key perpetrator concentrations

The relevant perpetrator concentrations are calculated as outlined in the Appendix:

Table 3: Key perpetrator concentrations for examplinib

parameter	value (ng/ml)	value (uM)
I_{gut}	1800000.0	3654.080
$I_{max,ss,u}$	81.2	0.165
$I_{max,inlet,u}$	95.0	0.193
$I_{max,intestinal}$	3244.1	6.586

Table 4: Key perpetrator concentrations for M1

parameter	value (ng/ml)	value (uM)
I_{gut}	0.0	0.0000
$I_{max,ss,u}$	12.5	0.0246
$I_{max,inlet,u}$	12.5	0.0246
$I_{max,intestinal}$	12.5	0.0246

DDI perpetrator risk assessment

Basic modeling of CYP inhibition

Reversible inhibition

As per the FDA guideline (FDA, 2020), the relevant metric for the basic modeling of the direct CYP inhibition risk is $R = 1 + [I]/K_{i,u}$ with the relevant inhibitor concentration $[I]$ being $I_{max,ss,u}$ for hepatic CYP enzymes and I_{gut} for intestinal CYP enzymes.

Thresholds of $R < 1.02$ and $R < 11$ apply for hepatic and intestinal enzymes, respectively. Note that intestinal CYP inhibition is only evaluated for CYP3A4.

Table 5: Risk for direct CYP inhibition by examplinib (basic model)

CYP	K_i (µM)	$K_{i,u}$ (µM)	R_1	risk (hepatic)	$R_{1,gut}$	risk (intestinal)
CYP1A2	NA	NA	NA	NA	NA	NA
CYP2B6	NA	NA	NA	NA	NA	NA
CYP2C8	11.0	11.0	1.015	FALSE	NA	NA
CYP2C9	13.5	13.5	1.012	FALSE	NA	NA
CYP2C19	15.0	15.0	1.011	FALSE	NA	NA
CYP2D6	NA	NA	NA	NA	NA	NA
CYP3A4	12.5	12.5	1.013	FALSE	293.3	TRUE

Table 6: Risk for direct CYP inhibition by M1 (basic model)

CYP	K_i (µM)	$K_{i,u}$ (µM)	R_1	risk (hepatic)	$R_{1,gut}$	risk (intestinal)
CYP2C9	4.4	4.4	1.006	FALSE	NA	NA

Note that the ratios used in the EMA guidance correspond to the FDA ratios listed above minus 1.

Time-dependent inhibition

As per the FDA guideline, the risk for time-dependent inhbition (TDI) of CYP enzymes is assessed based on R_2 (see appendix), where $R_2 \geq 1.25$ suggest a clinically relevant DDI potential that requires further investigation.

Table 7: Risk for CYP TDI by examplinib (basic model)

CYP	K_I(ţM)	f_u	k_{inact} (1/h)	k_{deg} (1/h)	source	R_2	risk
CYP3A4	0.17	0.02	0.04	0.02	study 001	3.07	TRUE

Modeling of CYP induction

Basic static/fold-change method

The basic static (EMA) or fold-change (FDA) methods evaluate whether the maximal fold-change in mRNA expression is > 2-fold at the expected unbound hepatic concentration of the drug.

For the relevant maximal drug concentrations to be tested in vitro ($maxc$), the FDA guidance suggests considering $30 * I_{max,ss,u}$ while the EMA guidance considers $50 * I_{max,ss,u}$ for hepatic and $0.1 * I_{gut}$ for intestinal induction. It is expected that the concentrations in the respective in vitro assays cover these concentrations.

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

Table 8: Risk for hepatic CYP induction by examplinib (basic static model)

CYP	E_{max}	$maxc$ (µM)	source	$maxc/I_{max,ss,u}$	risk	notes
CYP1A2	1.00	5	study 007	30.3	FALSE	Maximal tested concentration is below FDA expectations
CYP2B6	1.00	5	study 007	30.3	FALSE	Maximal tested concentration is below FDA expectations
CYP3A4	7.35	3	study 007	18.2	TRUE	Maximal tested concentration is below EMA/FDA expectations

Table 9: Risk for hepatic CYP induction by M1 (basic static model)

CYP	E_{max}	$maxc$ (µM)	source	$maxc/I_{max,ss,u}$	risk	notes
CYP1A2	1.00	5	study 007	203.3	FALSE	
CYP2B6	6.98	5	study 007	203.3	TRUE	
CYP3A4	22.70	5	study 007	203.3	TRUE	

Basic kinetic method

In the basic kinetic method, R_3 is calculated according to the equation given in the appendix. For $R_3 > 0.8$, a potential in vivo induction risk is assumed that needs furher investigation

Table 10: Risk for CYP induction by examplinib (basic kinetic model)

CYP	E_{max}	EC_{50} (µM)	$maxc$ (µM)	source	R_3	risk
CYP1A2	1.00	NA	5	study 007	NA	NA
CYP2B6	1.00	NA	5	study 007	NA	NA
CYP3A4	7.35	1.64	3	study 007	0.213	TRUE

Table 11: Risk for CYP induction by M1 (basic kinetic model)

CYP	E_{max}	EC_{50} (µM)	$maxc$ (µM)	source	R_3	risk
CYP1A2	1.00	NA	5	study 007	NA	NA
CYP2B6	6.98	1.86	5	study 007	0.551	TRUE
CYP3A4	22.70	1.10	5	study 007	0.194	TRUE

Mechanistic static modeling of CYP modulation

As per the FDA guideline (FDA 2020), the relevant metric for mechanistic static modeling of the CYP inhibition potential is the predicted AUC ratio ($AUCR$) for specific probe substrates. A cut-off of $R < 1.25$ applies.

In general, the FDA guidelines advises to investigate mechanistic static models of inhibition (reversible and mechanism-dependent) and induction separately.

CYP inhibition only

Table 12: Mechanistic static modeling of CYP inhibition risk for examplinib

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP1A2	NA	tizanidine	1.00	0.95	0.98	1.000	1.000	1.000	1.000	1.000	1.000	1.00	FALSE
CYP2B6	NA	NA	NA	NA	NA	1.000	1.000	1.000	1.000	1.000	1.000	NA	NA
CYP2C8	11.0	repaglinide	1.00	1.00	0.61	0.626	0.983	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2C9	13.5	S-warfarin	1.00	1.00	0.91	0.672	0.986	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2C19	15.0	omeprazole	1.00	1.00	0.87	0.695	0.987	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2D6	NA	NA	NA	NA	NA	1.000	1.000	1.000	1.000	1.000	1.000	NA	NA
CYP3A4	12.5	midazolam	0.57	0.96	1.00	0.655	0.985	0.435	0.476	1.000	1.000	2.95	TRUE

Table 13: Mechanistic static modeling of CYP inhibition risk for M1

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP2C9	4.4	S-warfarin	1	1	0.91	0.994	0.994	1.000	1.000	1.000	1.000	1.01	FALSE

CYP inhibition and induction

Table 14: Mechanistic static modeling of CYP inhibition risk for examplinib

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP1A2	NA	tizanidine	1.00	0.95	0.98	1.000	1.000	1.000	1.000	1.000	1.000	1.000	FALSE
CYP2C8	11.0	repaglinide	1.00	1.00	0.61	0.626	0.983	1.000	1.000	1.000	1.000	1.011	FALSE
CYP2C9	13.5	S-warfarin	1.00	1.00	0.91	0.672	0.986	1.000	1.000	1.000	1.000	1.013	FALSE
CYP2C19	15.0	omeprazole	1.00	1.00	0.87	0.695	0.987	1.000	1.000	1.000	1.000	1.011	FALSE
CYP3A4	12.5	midazolam	0.57	0.96	1.00	0.655	0.985	0.435	0.476	6.885	1.774	0.845	FALSE

Table 15: Mechanistic static modeling of CYP inhibition risk for M1

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP2C9	4.4	S-warfarin	1	1	0.91	0.994	0.994	1.000	1.000	1.000	1.000	1.01	FALSE

Basic modeling of UGT inhibition

The relevant metric for basic modeling of the UGT inhibition risk is $R_1 = I_{max,ss,u}/K_{i,u}$. For the clinical risk assessment, a cut-off of $R < 1.02$ applies.

In in vitro UGT inhibition studies, ususally IC_{50} rather than k_i values are determined. Assuming that a substrate concentration close to K_m is used, K_i is calculated as $K_i = IC_{50}/2$ (refer to Cheng, Prusoff 1973).

Basic modeling as per the FDA guideline (FDA 2020) results in the following risk assessment:

Table 16: Risk for UGT inhibition by examplinib (basic model)

UGT	$K_{i,u}$	R_1	risk
UGT1A1	7.50	1.022	TRUE
UGT1A3	7.50	1.022	TRUE
UGT1A4	7.50	1.022	TRUE
UGT1A6	7.50	1.022	TRUE
UGT1A9	1.90	1.087	TRUE
UGT2B7	7.50	1.022	TRUE
UGT2B15	7.50	1.022	TRUE
UGT2B17	3.05	1.054	TRUE

Table 17: Risk for UGT inhibition by M1 (basic model)

UGT	$K_{i,u}$	R_1	risk
UGT1A1	0.55	1.045	TRUE
UGT1A3	2.90	1.008	FALSE
UGT1A4	3.10	1.008	FALSE
UGT1A6	7.50	1.003	FALSE
UGT1A9	1.80	1.014	FALSE
UGT2B7	7.50	1.003	FALSE
UGT2B15	4.80	1.005	FALSE

UGT	$K_{i,u}$	R_1	risk

Inhibition of drug transporters

The relevant metric for the assessment of transporter interactions is $R = [I]/K_i$. In in vitro transporter inhibition studies, IC_{50} values are experimentally determined. Since the transporter substrate concentration is ususally kept very low in relation to K_m in order to minimze passive permeation, $K_i = IC_{50}$ can be assumed.

The relevant perpetrator concentrations $[I]$ are: I_{gut} for intestinal P-gp and BRCR, $I_{max,inlet,u}$ for the hepatic basolateral transporters OCT1, OATP1B1 and OATP1B3, and $I_{max,ss,u}$ for the renal basolateral transporters OAT1, OAT3 and OCT2, as well as the apical transporters outside the intestinal mucosa, i.e., hepatic P-gp and BCRP, and MATE1, MATE2-k.

The FDA and EMA guidelines differ in their threshold definitions. The risk assessments according to both guidelines are presented below:

Table 18: Risk for drug transporter inhibition by examplinib

transporter	IC_{50}	source	R	thld FDA	risk FDA	thld EMA	risk EMA
Pgp_int	0.41	study 005	8912.391	10.0	TRUE	10.00	TRUE
Pgp_sys	0.41	study 005	0.402	0.1	TRUE	0.02	TRUE
BCRP_int	1.90	study 005	1923.200	10.0	TRUE	10.00	TRUE
BCRP_sys	1.90	study 005	0.087	0.1	FALSE	0.02	TRUE
OCT1	2.30	study 006	0.084	NA	NA	0.04	TRUE
OATP1B1	177.00	study 006	0.001	0.1	FALSE	0.04	FALSE
OATP1B3	35.00	study 006	0.006	0.1	FALSE	0.04	FALSE
OAT1	271.00		0.001	0.1	FALSE	0.04	FALSE
OAT3	300.00		0.001	0.1	FALSE	0.04	FALSE
BSEP	12.80		0.013	0.1	FALSE	0.02	FALSE
OCT2	67.00	study 006	0.002	0.1	FALSE	0.02	FALSE
MATE1	3.60	study 006	0.046	0.1	FALSE	0.02	TRUE
MATE2k	1.10	study 006	0.150	0.1	TRUE	0.02	TRUE

Appendix 1: Calculations and formulae

Perpetrator concentrations

Gut concentration

As per the FDA guideline, the maximal gut concentration (I_{gut}) for the parent compound is to be assumed the administered dose dissolved in 250 ml.

$$I_{gut} = \frac{D}{250}$$

Systemic concentration

The unbound systemic ($I_{max,ss,u}$) concentrations of the parent compound and the metabolites that are relevant for the DDI potential are derived from the total maximal plasma concentration and the respective unbound fractions:

$$I_{max,ss,u} = I_{max,ss} * f_u$$

Hepatic inlet concentration

For the parent compound, the portal contribution to the hepatic inlet concentration is calculated as:

$$portal\ term = D * \frac{F_a * F_g * k_a}{Q_h * R_B} * 1000\ ng/ml$$

With D the administered dose in mg, F_a the fraction absorbed after oral administration, F_g the fraction available after gut metabolism, k_a the absorption rate, Q_h the hepatic blood flow and R_B the blood-to-plasma ratio.

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

The relevant hepatic inlet ($I_{max,inlet,u}$, also called I_h in the mechanistic static modeling equations) concentration is the sum of the maximal systemic plasma concentration and the portal contribution:

$$I_{max,inlet,u} = (I_{max,ss} + portal\ term) * f_u$$

Enteric concentration

For the parent compound, the villous concentration in the gut ($I_{enteric}$, also called I_g in the mechanistic static modeling equations) is calculated as:

$$I_{enteric,u} = D * \frac{F_a * k_a}{Q_{ent}} * 1000\ ng/ml$$

with F_a the fraction absorbed after oral administration, k_a the absorption rate, and Q_{ent} the enteric villous blood flow.

Note that as per the FDA and EMA guidelines and Rostami-Hodjegan and Tucker, 2004 the blood-to-plasma ratio and the plasma binding of the drug are not applicable for the villous concentration.

The standard villous blood flow is 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 K_i are considered (refer to the FDA guidance, FDA 2020, Fig. 1). A cut-off of 1.02 applies.

Liver

$$R_1 = 1 + \frac{I_{max,ss,u}}{K_{i,u}}$$

Gut wall

$$R_{1,gut} = 1 + \frac{I_{gut}}{K_{i,u}}$$

Time-dependent CYP inhibition

For the basic modeling of the potential for time-dependent CYP inhibition (TDI), R_2 is considered with:

$$R_2 = \frac{k_{obs} + k_{deg}}{k_{deg}}$$

and

$$k_{obs} = \frac{50 * k_{inact} * I_{max,u}}{K_{I,u} + 50 * I_{max,u}}$$

The CYP degradation constant, $k_{deg} 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 $R_2 \geq 1.25$ may indicate a relevant TDI potential and need further investigation.

Basic kinetic modeling of CYP induction

$$R_3 = \frac{1}{1 + d * \frac{E_{max} * 10 * I_{max,u}}{EC_{50} + 10 * I_{max,u}}}$$

Static mechanistic modeling of CYP inhibition/induction

In this approach, AUC ratios for probe substrates are calculated based on their known intestinal and hepatic metabolism. Both direct (competitive) and time-dependent inhibition are considered. The below formula given by the FDA guideline (refer to FDA 2020, Fig. 7) also includes intestinal and hepatic enzyme induction terms (C_g and C_h, respectively). At the same time, the guideline states that both inhibition and induction should be considered separately.

$$AUCR = \frac{1}{A_g * B_g * C_g * (1 - F_g) + F_g} * \frac{1}{A_h * B_h * C_h * f_m + (1 - f_m)}$$

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

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

$$f_m = f_{m,overall} * f_{m,CYP}$$

The individual terms in the AUC calculation are:

Reversible inhibition

$$A_g = \frac{1}{1 + \frac{I_g}{K_i}}$$

$$A_h = \frac{1}{1 + \frac{I_h}{K_i}}$$

Time-dependent inhibition

$$B_g = \frac{k_{deg,g}}{k_{deg,g} + \frac{I_g * k_{inact}}{I_g + K_I}}$$

$$B_h = \frac{k_{deg,h}}{k_{deg,h} + \frac{I_h * k_{inact}}{I_h + K_I}}$$

Induction

$$C_g = 1 + \frac{d * E_{max} * I_g}{I_g + EC_{50}}$$

$$C_h = 1 + \frac{d * E_{max} * I_h}{I_h + EC_{50}}$$

with the hepatic inlet concentration $I_h = I_{max,inlet,u}$ and the intestinal concentration $I_g = I_{enteric}$ (see above). d is an induction scaling factor (assumed to be 1 but can be adjusted).

Appendix 2: R Session Info

This document was created using R version 4.3.2 (2023-10-31) and the following packages:

name	version
ddir	0.13.0
knitrdata	0.6.1
knitr	1.45
lubridate	1.9.3
forcats	1.0.0
stringr	1.5.1
dplyr	1.1.4
purrr	1.0.2
readr	2.1.4
tidyr	1.3.0
tibble	3.2.1
ggplot2	3.4.4
tidyverse	2.0.0