R Notebook

Introduction

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

This output was generated using version xx (dd-dd-dddd) of the DDI assessment R script.

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
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

Table 2: Compound parameters for M1

parameter	value	source
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
F_a	NA	
F_g	NA	
k_a (1/min)	NA	

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 (µM)
I_{gut}	1800000.0	3654.080
$I_{max,ss,u}$	81.2	0.165
$I_{max,inlet,u}$	95.0	0.193
$I_{max,intestinal,u}$	74.6	0.151

Table 4: Key perpetrator concentrations for M1

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

Basic modeling as per the FDA guideline results in the following risk assessment for direct CYP inhibition by xxx.

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

CYP	K_i	$K_{i,u}$	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	$K_{i,u}$	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.

Modeling of CYP induction

Basic/fold-change method

The basic (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 drug concentrations, 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:

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 the current implementation of this tool (and listed in the table below), only reversible inhibition and induction (as reflected in the A- and C-terms of the AUCR formula, see Appendix) is included. In general, the FDA guidelines advises to investigate mechanistic static models of inhibition (reversible and mechanism-dependent) and induction separately.

Table 7: Mechanistic static modeling of CYP inhibition risk for examplinib

CYP	substrate	$K_{i,u}$	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	C_g	C_h	AUCR	risk
CYP1A2	tizanidine	NA	1.00	0.95	0.98	NA	NA	1.00	1.00	NA	NA
CYP2B6	NA	NA	NA	NA	NA	NA	NA	1.00	1.00	NA	NA
CYP2C8	repaglinide	11.0	1.00	1.00	0.61	0.986	0.983	1.00	1.00	1.011	FALSE
CYP2C9	S-warfarin	13.5	1.00	1.00	0.91	0.989	0.986	1.00	1.00	1.013	FALSE
CYP2C19	omeprazole	15.0	1.00	1.00	0.87	0.990	0.987	1.00	1.00	1.011	FALSE
CYP2D6	NA	NA	NA	NA	NA	NA	NA	1.00	1.00	NA	NA
CYP3A4	midazolam	12.5	0.57	0.96	1.00	0.988	0.985	1.62	1.77	0.463	TRUE

Table 8: Mechanistic static modeling of CYP inhibition risk for M1

CYP	substrate	$K_{i,u}$	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	C_g	C_h	AUCR	risk
CYP2C9	S-warfarin	4.4	1	1	0.91	0.994	0.994	1	1	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 9: Risk for UGT inhibition by examplinib (basic model)

UGT	$K_{i,u}$	R_1	risk
UGT1A1	7.50	1.021976	TRUE
UGT1A3	7.50	1.021976	TRUE
UGT1A4	7.50	1.021976	TRUE
UGT1A6	7.50	1.021976	TRUE
UGT1A9	1.90	1.086747	TRUE
UGT2B7	7.50	1.021976	TRUE
UGT2B15	7.50	1.021976	TRUE
UGT2B17	3.05	1.054039	TRUE

Table 10: Risk for UGT inhibition by M1 (basic model)

UGT	$K_{i,u}$	R_1	risk
UGT1A1	0.55	1.044708	TRUE
UGT1A3	2.90	1.008479	FALSE
UGT1A4	3.10	1.007932	FALSE
UGT1A6	7.50	1.003279	FALSE
UGT1A9	1.80	1.013661	FALSE
UGT2B7	7.50	1.003279	FALSE
UGT2B15	4.80	1.005123	FALSE
UGT2B17	1.10	1.022354	TRUE

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 11: 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

transporter	IC_{50}	source	R	thld FDA	risk FDA	thld EMA	risk EMA
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