

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 exemplinib

| 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 (μ M) |
|------------------------|---------------|------------------|
| 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 (μ M) |
|------------------------|---------------|------------------|
| 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 exemplinib

| 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, usually 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 examplininb (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 usually kept very low in relation to K_m in order to minimize passive permeation, $K_i = IC_{50}$ can be assumed.

The relevant perpetrator concentrations $[I]$ are: I_{gut} for intestinal P-gp and BCRP, $I_{max,inlet,u}$ 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 examplininb

| 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 |