**Table S1a.** Key input parameters for the PBPK model of erlotinib

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Method/Reference** |
| Mol Weight (g/mol) | 393.4 | EMA, FDA |
| log P | 2.7 | EMA, (Gruber et al., 2018)1 |
| Compound Type | Monoprotic Base |  |
| pKa 1 | 5.42 | EMA, (Gruber et al., 2018)1 |
| B/P | 0.55 | (Rakhit et al., 2008)2 |
| fu | 0.05 | (Scheffler et al., 2011)3, (Gruber et al., 2018)1 |
| Main plasma binding protein | HSA | FDA |
|  |  |  |
| **Absorption Model** | ADAM |  |
| fugut | 0.017 | Predicted |
| Peff,man (10-4 cm/s) | 3.576 | (Schwenger et al., 2018)4 |
| Permeability Assay | Caco-2 |  |
| Apical pH : Basolateral pH | 7.4 : 7.4 | (Schwenger et al., 2018)4 |
| Activity | Passive |
| PCaco-2(10-6 cm/s) | 33.600 |
| Reference Compound | Midazolam |
| Reference Compound Value (10-6 cm/s) | 70.100 |
| Scalar | 0.997 |
| Input Form | Solid Formulation |  |
| Formulation | Immediate Release (IR) |  |
| Dissolution Type | Solubility |  |
| Solubility Type | Solubility-pH profile | (Dodd et al., 2019)5 |
| **Absorption Model** | First Order |  |
| fa | 0.77 | Obtained via simulations using the ADAM model |
| ka (1/h) | 0.467 | Via parameter estimation |
| fugut | 1.23E-05 | Predicted in Simcyp |
| Qgut (L/h) | 8.69 | Predicted in Simcyp |
|  |  |  |
| **Distribution Model** | Full PBPK Model |  |
| Vss input type | Predicted |  |
| Vss (L/kg) | 1.998 | (Lu et al., 2006)6 |
| Prediction Method | Method 2 |  |
|  |  |  |
| Kp Scalar | 1.930 |  |
|  |  |  |
| **Elimination Model** |  |  |
| CLiv (L/h)  fm,CYP1A2  fm,CYP3A4 | 4  0.3  0.7 | (Lu et al., 2006)6  (Gruber et al., 2018)1 |
| Enzyme | CYP1A2 |  |
| Pathway | Pathway 1 |  |
| CLint (µL/min/pmol) | 0.193 | Predicted in Simcyp using the retrograde calculator |
| fumic | 1.000 |  |
|  |  |  |
| Enzyme | CYP3A4 |  |
| Pathway | Pathway 1 |  |
| CLint (µL/min/pmol) | 0.198 | Predicted in Simcyp using the retrograde calculator |
| fumic | 1.000 |  |
| **Inhibition Model** |  |  |
| Enzyme | CYP3A4 |  |
| *Ki* (µM) | 10.12 | Determined experimentally |
| fumic | 0.92 | (Burns et al., 2015)7 |
| *KI* (µM) | 10.98 | Determined experimentally |
| *kinact* (h-1) | 2.283 | Determined experimentally |
| fumic | 0.92 | (Burns et al., 2015)7 |
|  |  |  |
| Enzyme | CYP2J2 |  |
| *Ki* (µM) | 0.758 | Determined experimentally |
| fumic | 0.92 | (Burns et al., 2015)7 |
| *KI* (µM) | 1.308 | Determined experimentally |
| *kinact* (h-1) | 1.062 | Determined experimentally |
| fumic | 0.92 | (Burns et al., 2015)7 |

B/P, blood to plasma partition ratio; CLint, *in vitro* intrinsic clearance; CLiv, intravenous clearance; fa,fraction available from dosage form; fm,fraction metabolized by a given enzymatic pathway; fu, fraction unbound in plasma; fugut, fraction unbound in the enterocytes; fumic, fraction unbound in the microsomal incubation; ka,first order absorption rate constant; *KI,* concentration of mechanism-based inactivator associated with half maximal inhibition;*kinact,* inactivation rate of the enzyme;*Ki,* concentration of reversible inhibitor that supports half maximal inhibition; log P, common logarithm of the octanol:water partition coefficient; Peff,man, Human jejunum effective permeability; Qgut, Nominal flow in gut model; Vss, volume of distribution at steady state

**Table S1b.** Key input parameters for the PBPK model of nilotinib

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Method/Reference** |
| Molecular Weight (g/mol) | 529.53 |  |
| log P | 5.844 | (Heimbach et al., 2019)8 |
| Compound Type | Diprotic Base |  |
| pKa 1 | 5.4 | (Heimbach et al., 2019)8 |
| pKa 2 | 3.9 |
| B/P | 0.68 | (Xia et al., 2012)9 |
| fu | 0.016 |
| Main plasma binding protein | HSA |  |
|  |  |  |
| **Absorption Model** | 1st order absorption |  |
| Input type | User |  |
| fa | 0.3 | (Heimbach et al., 2019)8 |
| ka (1/h) | 0.3 |
| fugut | 1.23E-05 | Predicted in Simcyp |
| Qgut (L/h) | 8.69 | Predicted in Simcyp |
| Peff,man (10-4 cm/s) | 1.56 | (Heimbach et al., 2019)8 |
| Permeability Assay | Caco-2 |
| Apical pH:Basolateral pH | 7.4:7.4 |
| Activity | Passive |
| PCaco-2(10-6 cm/s) | 5.33 |
| Reference Compound | Propranolol |
| Reference Compound Value (10-6 cm/s) | 16.5 |
| Scalar | 2.606 |
|  |  |  |
| **Distribution Model** | Minimal PBPK Model |  |
| Q (L/h) | 52.5 | (Heimbach et al., 2019)8 |
| Vsac (L/kg) | 1.46 |
| Vss (L/kg) | 1.67 | (Heimbach et al., 2019)8 |
| Prediction Method | Method 2 |  |
|  |  |  |
| **Elimination** |  |  |
| CL/F (L/h)  fm,CYP1A2  fm,CYP2C8  fm,CYP3A4 | 27.6  0.04  0.16  0.8 | (Giles et al., 2013)10 |
| Enzyme | CYP3A4 |  |
| Pathway | Pathway 1 |  |
| CLint (µL/min/pmol) | 1.694 | Predicted in Simcyp using the retrograde calculator |
| fumic | 1.000 |  |
|  |  |  |
| Enzyme | CYP1A2 |  |
| Pathway | Pathway 1 |  |
| CLint (µL/min/pmol) | 0.248 | Predicted in Simcyp using the retrograde calculator |
| fumic | 1.000 |  |
|  |  |  |
| Enzyme | CYP2C8 |  |
| Pathway | Pathway 1 |  |
| CLint (µL/min/pmol) | 2.225 | Predicted in Simcyp using the retrograde calculator |
| fumic | 1.000 |  |
|  |  |  |
| **Inhibition Model** |  |  |
| Enzyme | CYP3A4 | Internal Data |
| *Ki* (µM) | 3.025 | Determined experimentally |
| fumic | 0.43  1 | (Burns et al., 2015)7  Optimized value |
| *KI* (µM) | 4.44 | Determined experimentally |
| *kinact* (h-1) | 2 | Determined experimentally |
| fumic | 0.43  1 | (Burns et al., 2015)7  Optimized value |
|  |  |  |
| Enzyme | CYP2J2 |  |
| *Ki* (µM) | 0.758 | Determined experimentally |
| fumic | 0.43  1 | (Burns et al., 2015)7  Optimized value |

B/P, blood to plasma partition ratio; CLint, *in vitro* intrinsic clearance; CL/F, apparent oral clearance; fa,fraction available from dosage form; fm,fraction metabolized by a given enzymatic pathway; fu, fraction unbound in plasma; fugut, fraction unbound in the enterocytes; fumic, fraction unbound in the microsomal incubation; *KI,* concentration of mechanism-based inactivator associated with half maximal inhibition;*kinact,* inactivation rate of the enzyme;*Ki,* concentration of reversible inhibitor that supports half maximal inhibition; log P, common logarithm of the octanol:water partition coefficient; Peff,man, Human jejunum effective permeability; Q, intercompartmental clearance in the Minimal PBPK model; Vsac, volume of the single adjusting compartment representing a lump of all tissues excluding the liver and portal vein in the Simcyp Minimal PBPK model; Qgut, Nominal flow in gut model; Vss, volume of distribution at steady state

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