

SUPPLEMENTAL DATA

Authors: Mikael O. W. Piha, Kristiina Cajanus, Marica T. Engström, Mikko Neuvonen, Troels K. Bergmann, Mikko Niemi, Janne T. Backman, Anne M. Filppula, Aleksi Tornio

Title: Candesartan Has No Clinically Meaningful Effect on the Plasma Concentrations of CYP2C8 Substrate Repaglinide in Humans

Drug Metabolism and Disposition: DMD-AR-2024-001798

Supplemental Methods

The liver-to-plasma ratios of candesartan and candesartan acyl- β -D-glucuronide in humans were predicted using Simcyp version 23 release 1 (Certara UK Limited, Sheffield, UK). The relevant input values, derived from either the literature or the present study, and the predicted liver-to-plasma ratios are presented in Supplemental Table 1.

The static interaction predictions (described in the main manuscript) were based either on the assumption that the liver-to-plasma ratios of candesartan and candesartan acyl- β -D-glucuronide were equal to 1, or on a worst-case scenario. Assuming a worst-case scenario, the predicted liver-to-plasma ratio (3.88; Supp. Table 1) was used for candesartan. For candesartan acyl- β -D-glucuronide, however, the predicted liver-to-plasma ratio was lower than 1 (Supp. Table 1). To avoid any underestimation of the drug-drug interaction risk, a ratio of 1 was used for candesartan acyl- β -D-glucuronide also in the worst-case static drug-drug interaction predictions.

SUPPLEMENTAL TABLE 1

Biochemical input parameters, and predicted liver-to-blood ratios of candesartan and
candesartan acyl- β -D-glucuronide.

Parameter	Value	Reference/Comment
<i>Candesartan</i>		
molar mass (g/mol)	440.463	Chemicalize
$\log P$	4.1	PubChem
pK_a	3.51 (acid)	Chemicalize
$f_{u,p}$	0.01	FDA, 1998
R_L^a	3.8793	Predicted
<i>Candesartan acyl-β-D-glucuronide</i>		
molar mass (g/mol)	616	Chemicalize
$\log P$	2.5	PubChem
pK_a	3.21 (acid)	Chemicalize
$f_{u,p}$	0.01	Present study
R_L^a	0.53574	Predicted

a liver-to-plasma ratio

References

Chemicalize, <https://chemicalize.com/> (Accessed: August 20, 2024)

National Center for Biotechnology Information (2024) PubChem Compound Summary for CID 2541, Candesartan. Retrieved August 20, 2024 from <https://pubchem.ncbi.nlm.nih.gov/compound/Candesartan>.

National Center for Biotechnology Information (2024) PubChem Compound Summary for CID 131769984, Candesartan O-glucuronide. Retrieved August 20, 2024 from <https://pubchem.ncbi.nlm.nih.gov/compound/Candesartan-O-glucuronide>.

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