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Clinical pharmacology of axitinib.

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Abstract

Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3 that is approved in the US and several other countries for treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy. The recommended clinical starting dose of axitinib is 5 mg twice daily, taken with or without food. Dose increase (up to a maximum of 10 mg twice daily) or reduction is permitted based on individual tolerability. Axitinib pharmacokinetics are dose-proportional within 1-20 mg twice daily, which includes the clinical dose range. Axitinib has a short effective plasma half-life (range 2.5-6.1 h), and the plasma accumulation of axitinib is in agreement with what is expected based on the plasma half-life of the drug. Axitinib is absorbed relatively rapidly, reaching maximum observed plasma concentrations (C max) within 4 h of oral administration. The mean absolute bioavailability of axitinib is 58 %. Axitinib is highly (>99 %) bound to human plasma proteins with preferential binding to albumin and moderate binding to α1-acid glycoprotein. In patients with advanced renal cell carcinoma, at the 5-mg twice-daily dose in the fed state, the geometric mean (% coefficient of variation) C max and area under the plasma concentration-time curve (AUC) from time 0-24 h (AUC24) were 27.8 ng/mL (79 %) and 265 ng·h/mL (77 %), respectively. Axitinib is metabolized primarily in the liver by cytochrome P450 (CYP) 3A4/5 and, to a lesser extent (<10 % each), by CYP1A2, CYP2C19, and uridine diphosphate glucuronosyltransferase (UGT) 1A1. The two major human plasma metabolites, M12 (sulfoxide product) and M7 (glucuronide product), are considered pharmacologically inactive. Axitinib is eliminated via hepatobiliary excretion with negligible urinary excretion. Although mild hepatic impairment does not affect axitinib plasma exposures compared with subjects with normal hepatic function, there was a 2-fold increase in AUC from time zero to infinity (AUC∞) following a single 5-mg dose in subjects with moderate hepatic impairment. In the presence of ketoconazole, a strong CYP3A4/5 inhibitor, axitinib C max and AUC∞ increased by 1.5- and 2-fold, respectively, whereas co-administration of rifampin, a strong CYP3A4/5 inducer, resulted in a 71 and 79 % decrease in the C max and AUC∞, respectively. Axitinib does not inhibit CYP3A4/5, CYP1A2, CYP2C8, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or UGT1A1 at concentrations obtained with the clinical doses and is not expected to have major interactions with drugs that are metabolized by these enzymes. Axitinib is an inhibitor of the efflux transporter P-glycoprotein (P-gp) in vitro, but is not expected to inhibit P-gp at therapeutic plasma concentrations. A two-compartment population pharmacokinetic model with first-order absorption and lag time was used to describe axitinib pharmacokinetics. No clinically relevant effects of age, sex, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 inferred phenotype on the clearance of axitinib were identified.

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