

CYP4F2 is the Major Cytochrome P450 Enzyme Involved in CMX001 Metabolism

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CMX001 is a novel, broad spectrum, orally administered, lipid acyclic nucleotide phosphonate in development for prevention and/or treatment of diseases caused by double-stranded DNA viruses, including cytomegalovirus, BK virus and adenovirus. Previous in vitro studies identified CYP3A4, 2C8, 2C19 and 2E1 as the cytochrome P450 (CYP) enzymes responsible for CMX001 metabolism. The objective of this study was to quantify the percentage of CMX001 metabolized by each CYP, and to explore potential metabolic pathways for CMX001 via less traditional CYPs known to metabolize endogenous long chain fatty acids. Pooled human liver microsomes, recombinant human CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2J2, 3A4, 4A11, 4F2, 4F3a, 4F3b and 4F12) and specific CYP inhibitors were used for this study.

Incubations with recombinant human CYP enzymes suggested that only CYP4F2 metabolizes CMX001. The complete inhibition of CMX001 metabolism in human liver microsomes by N-hydroxy-N'-(4-n-butyl-2-methylphenyl)formamidine (HET0016), a specific CYP4F2/3 inhibitor, and the partial inhibition by ketoconazole, a dual CYP3A and CYP4F2 inhibitor, confirmed the recombinant CYP results. The near complete inhibition of CMX001 metabolism by quercetin (CYP2C8 inhibitor), disulfiram (CYP2E1 inhibitor) and tranilcypromine (CYP2C19 inhibitor) was also observed in human liver microsomes; however, subsequent experiments performed with recombinant CYP4F2 alone indicated that these chemicals also inhibit CYP4F2-mediated metabolism of CMX001. Thus, inhibition of microsomal metabolism of CMX001 by these inhibitors is likely due to inhibition of CYP4F2 rather than inhibition of CYP2C8, CYP2C19, CYP2E1, or CYP3A4. Posaconazole, fluconazole and voriconazole, which, like ketoconazole, are known to inhibit CYP3A, did not inhibit metabolism of CMX001, indicating their CYP inhibitory activity does not extend to CYP4F2.

In conclusion, these data indicate that CYP-mediated metabolism of CMX001 is primarily by CYP4F2, and that other CYP enzymes previously identified as having a potential role in CMX001 metabolism, namely 3A4, 2C8, 2C19 and 2E1, likely do not contribute significantly to the metabolism of CMX001. The results from this study confirm the dual inhibition of CYP3A and CYP4F2 by ketoconazole, and extend the list of compounds known to inhibit CYP4F2 to include quercetin, tranilcypromine, and disulfiram. By contrast, voriconazole, fluconazole and posaconazole were not observed to inhibit CYP4F2 at concentrations below or up to 2x above the reported peak human plasma concentration for each drug; therefore, no clinically relevant interaction is expected between CMX001 and these azoles.

