Pharmacokinetics of etravirine (ETR; TMC125) are not affected by sex, age, race, use of enfuvirtide (ENF) or treatment duration in HIV-1-infected subjects

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Abstract

Introduction

ETR is a highly potent, non-nucleoside reverse transcriptase inhibitor (NNRTI) that is indicated for the treatment of HIV-1 infection in adults and adolescents. Steady-state pharmacokinetics were estimated in 575 subjects. Mean (standard deviation [SD]) ETR area under the curve (AUC) 12h was 6,027 (3,591) ng h/mL, respectively (p=0.23). ETR exposure (AUC 12h) was slightly higher with decreasing weight or increasing adherence. No dose adjustments for ETR are necessary for these covariates. There was no apparent treatment duration-dependent clearance in ETR pharmacokinetics.

Subjects with viral load <50 copies/mL at Week 48 (ITT-TLOVR) 4,5

Subjects with viral load <50 copies/mL at Week 48 from two identical, ongoing Phase III, double-blind, randomized trials (DUET-1 and DUET-2) in treatment-experienced HIV-1-infected subjects achieving viral load <500 copies/mL at baseline were included. Steady-state pharmacokinetics were estimated in 575 subjects. Mean (SD) ETR AUC 12h by weight, age and adherence (p=0.0187) or decreasing weight (p=0.0490). Use of ENF had no effect on ETR AUC 12h.

ETR pharmacokinetics do not vary by sex, race, age, use of ENF, or treatment duration. ETR exposure, whereas hepatitis B and/or C coinfection was associated with higher ETR exposure. ETR exposure were higher in subjects with lower weight and greater adherence. No doseadjustments for ETR are necessary for these covariates. There was no apparent treatment duration-dependent clearance in ETR pharmacokinetics.

Discussion and conclusions

ETR has moderate to high rate and intersubject variability – drug–drug interactions probably due to metabolism via multiple CYP isozymes (i.e. CYP3A, 2C9 and 2C19), adherence, concomitant medications (e.g. TDF) and/or hepatitis coinfection status – parental variability probably due to CYP3A5*3A1 and/or CYP2C9*2 allelic variants – consistent with interaction studies in healthy volunteers – no obvious difference in concomitant medications or baseline demographics – mechanism unclear: effect of ENF on CYP3A4/5

References