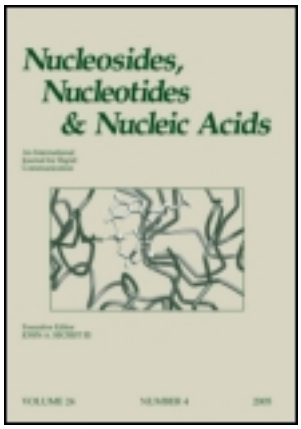

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PK/PD and Safety of a Single Dose of TMX-67 (Febuxostat) in Subjects with Mild and Moderate Renal Impairment

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ABSTRACT

A single oral dose of 20 mg febuxostat was administered to subjects with normal, mild or moderate impairment in renal function. There was less than a 2-fold difference in AUC of plasma unchanged febuxostat among the renal function groups, and changes in plasma urate levels from pre-dose levels were not significant. A total of five adverse events were reported with all mild in severity. The results indicate that renal impairment will have little clinical impact on the pharmacokinetics (PK), pharmacodynamics (PD) and safety of the study drug.

Key Words: Febuxostat; XOD/XDH inhibitor; Hyperuricemia; Renal impairment; TMX-67.

INTRODUCTION

Febuxostat (TMX-67, 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid), a novel non-purine, selective inhibitor of xanthine oxidase and xanthine dehydrogenase (NPSIXO), is currently in clinical development for the treatment of hyperuricemia or gout.[1,2] In healthy subjects, the renal clearance of febuxostat was estimated as

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approximately 2% of oral clearance. This study was conducted to investigate the effects of renal impairment on PK, PD and safety of febuxostat prior to a multiple-dose study in renally impaired subjects.

SUBJECTS AND METHODS

Fifteen subjects (13 males, 2 females) were enrolled and assigned to three renal function groups of 5 subjects based on creatinine clearance (Ccr); Normal: Ccr > or = 80, Mild impairment: 50 = or < Ccr < 80, Moderate impairment: 30 = or < Ccr < 50 mL/min, respectively. Twenty (20) mg of the study drug was administered orally within 30 min after breakfast. Serial blood sampling and urine collection were performed, and followed by determination of febuxostat, its metabolites, and uric acid in plasma or urine with validated HPLC or LC-MS/MS. Safety evaluation was based on adverse events (including clinical laboratory tests, 12-lead electrocardiogram, and vital signs).

RESULTS

The mean (SD) AUCs of plasma unchanged febuxostat were 2644.08 (593.04), 2338.62 (290.36), and 4005.26 (1467.40) ng · h/mL for subjects with normal, mild or moderate impairment in renal function, respectively. The mean (SD) delta AUCs ($C_{pre\text{-}dose} \times 48 - AUC_{48h}$) of plasma uric acid were 25.881 (12.850), 42.920 (28.690), and 40.621 (18.260) mg·h/100 mL for subjects with normal, mild or moderate impairment in renal function, respectively. A total of five adverse events (AEs), gastric ulcer, constipation, headache, nausea, and upper respiratory tract infection, were reported. All AEs were mild in severity with only nausea ''possibly related'' to the study drug.

DISCUSSION

The results indicate that renal impairment will have little clinical impact on PK, PD and safety of febuxostat. It is considered that the study drug was well tolerated and there were no safety concerns following a single oral dose of 20 mg febuxostat in subjects with mild or moderate renal impairment.

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