

## Comment on: “Enzalutamide: A Step Towards Pharmacokinetic-Based Dosing in Men with Metastatic Castration-Resistant Prostate Cancer”

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Dear Editors,

We thank Dr. Paul Hutson for his thorough commentary [1] on our recent article entitled ‘Enzalutamide: a step towards pharmacokinetic-based dosing in men with metastatic castration-resistant prostate cancer’ [2]. We would like to provide an important correction to Dr. Hutson’s commentary, regarding the following statements:

Gibbons et al. do not report the renal clearance or the effect of renal failure on the clearance of enzalutamide or its active *N*-desmethyl metabolite, and to date no other reports of enzalutamide renal clearance are available to guide dosing. The mass-balance studies in the present study demonstrate that approximately 60 % of the dose was recovered in the urine, suggesting that dosing of the drug may need to be reduced in patients with kidney dysfunction.

While not emphasized, the article does describe renal clearance on page 1050 (paragraph 2):

The major route of excretion of <sup>14</sup>C-radioactivity was urine (71.0 % of dose), primarily as metabolites. The remainder of the radioactivity was excreted in feces (13.6 % of dose). Based on LC–MS/MS analysis, the main component in urine was the carboxylic acid metabolite, which accounted for 62.7 % of the dose. A trace amount of unchanged parent enzalutamide was excreted in urine. *N*-Desmethyl enzalutamide

was too low to quantitate in urine by LC–MS/MS. Based on this information, renal excretion is a minor elimination pathway for unchanged parent enzalutamide and *N*-desmethyl enzalutamide.

As indicated in this excerpt, 62.7 % of the dose was recovered in urine as the inactive carboxylic acid metabolite, and the remainder was additional minor metabolites; enzalutamide and *N*-desmethyl enzalutamide (active metabolite) were present in urine at only trace amounts. These data indicate that renal excretion is a minor elimination pathway for unchanged parent enzalutamide and *N*-desmethyl enzalutamide. Further details are captured in the US prescribing information for XTANDI® (enzalutamide) capsules (product label), which states the following:

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment [30 mL/min ≤ creatinine clearance (CrCL) ≤ 89 mL/min] compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed [see Clinical Pharmacology (12.3)].

In summary, data presented in our original research article [2], as well as results in the XTANDI® product

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label, indicate that starting dose reductions are not required in patients with mild to moderate renal impairment. There are no data to assess the effects of severe renal impairment (CrCL <30 mL/min). As Dr. Hutson's commentary misstates dosing recommendations for XTANDI<sup>®</sup>, we request that you kindly publish a supplementary response to Dr. Hutson's commentary in *Clinical Pharmacokinetics*.

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## References

1. Hutson P. Enzalutamide: A step towards pharmacokinetic-based dosing in men with metastatic castration-resistant prostate cancer. *Clin Pharmacokinet*. 2015;54:989–91.
2. Gibbons JA, Ouatas T, Krauwinkel W, Ohtsu Y, van der Walt JS, Beddo V, et al. Clinical pharmacokinetics of enzalutamide. *Clin Pharmacokinet*. 2015;54:1043–55.