ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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May 21, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2010–D–0133: Revised Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling; Availability

Dear Ladies and Gentlemen,

On behalf of the American Society of Nephrology, thank you for the opportunity to provide comment on the 'Revised Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling; Availability." ASN was pleased to recently submit comments from the society on this document to FDA.

In addition, ASN has reviewed and is in full support of the comment letter on this topic prepared by Kidney Disease: Improving Global Outcomes (KDIGO). Please accept this letter of notification that ASN endorses the comments submitted by KDIGO.

Again, thank you for your time and consideration of comments from the renal community on this important issue. To discuss ASN's endorsement of the KDIGO letter, please contact ASN Director of Policy and Public Affairs Paul C. Smedberg at psmedberg@asn-online.org or at (202) 416-0646.

Sincerely,

Sharon Anderson, MD, FASN
President

May 16, 2010

Division of Dockets Management (HFA-305)
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Room 1061
Rockville, MD 20852

Re: Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

Docket Number: FDA–2010–D–0133

This letter is to provide public comment on the recently released draft "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling." KDIGO (Kidney Disease Improving Global Outcomes) is a global foundation dedicated to improving the care and outcomes of kidney disease patients worldwide. Established in 2003 as an independently incorporated non-profit foundation governed by an international board, KDIGO is managed by the National Kidney Foundation, a U.S. foundation with more than a decade of experience in developing and implementing guidelines for patient evaluation and care. KDIGO sponsored an international conference to examine what is known, what can be done with what is known, and what needs to be known about drug prescribing in kidney disease. This conference brought together an international group of experts to delineate current practice recommendations and identify clinical questions that might be used to steer the evidence review process for the development of clinical practice guidelines. Specifically, the purpose of the conference was to explore our understanding of drug disposition in patients with chronic kidney disease and acute kidney injury, and to develop rational approaches to pharmacotherapy with practical recommendation for individualized drug dosing. The group of attendees included a wide range of participants from the United States, Europe, and Asia. It included clinicians, researchers, representatives of the pharmaceutical industry, the United States Food and Drug Administration, and the European Medicines Agency (Appendix 1). The conference was held in Baltimore, Maryland, May 14-15, 2010. The following are comments and recommendations from the conference, which we believe are pertinent to the draft "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling."

Measurement of kidney function

There remains controversy regarding the best measurements of kidney function across diverse patient groups. Because of advances in the standardization of serum creatinine measurements, more accurate and reproducible estimates of glomerular filtration rate (GFR) have been established. A recommendation from the conference is that in drug development, GFR should be measured directly with an inert tracer (e.g. inulin, iohexol, iothalamate, etc) to determine pharmacokinetic or pharmacodynamic alterations due to kidney dysfunction. In clinical practice, the most accurate estimate of GFR can be used for drug dosing. If GFR is measured directly during pharmacokinetic and pharmacodynamic studies, then whatever method of GFR estimation that is used clinically for drug dosing will always be referenced to the same values, that is, a measured GFR. Drug labels should refer to measured or estimated GFR without specifying the methodology to be used for drug dosing.

Pre-marketing studies

The conference recommends that a reduced pharmacokinetic study be performed in patients with reduced kidney function for all drugs. The study population should consist of patients requiring regular hemodialysis treatments on interdialytic (non-dialysis) days or peritoneal dialysis patients. Although this group may not exhibit the greatest changes in pharmacokinetic or pharmacodynamic parameters compared to patients with end stage renal disease not yet on dialysis, they are a more available patient population and should exhibit sufficient pharmacokinetic differences from patients with normal kidney function to establish whether full pharmacokinetic studies are warranted. Full pharmacokinetic studies in patients with impaired kidney function should be performed for all drugs where:

1) The reduced pharmacokinetic study indicated a change in pharmacokinetics in the study population.
2) Thirty percent or more of the drug or its active or toxic metabolites are excreted by the kidneys.
3) The drug has a narrow therapeutic index and is likely to be used in patients with reduced kidney function, including critically ill patients with potential development of multiple organ dysfunction syndrome.

Full pharmacokinetic studies should ensure inclusion of patients across the entire range of GFR and GFR should be measured directly with an inert tracer (e.g. inulin, iohexol, iothalamate, etc) to determine the relationship between kidney function and pharmacokinetic or pharmacodynamic parameters. Drug labels should state strength of evidence for dosing modifications for reduced kidney function.

The conference recommends the co-development of practical assays of drug levels concurrent to drug development to facilitate the use of therapeutic drug monitoring for drugs with a

narrow therapeutic window and under circumstances where it is unclear whether adequate drug levels are achieved.

Post-marketing studies

Post-marketing studies should be performed to further evaluate drugs in populations not sufficiently represented in pre-marketing studies. Depending on drug indication and target group it may be acceptable to postpone pharmacokinetic studies in patients with kidney disease to the post-marketing phase.

Hemodialysis

The conference suggested that hemodialysis treatments used for pharmacokinetic studies be standardized to a Kt/Vurea of 1.2-1.5 and that contemporary dialyzers be used. The conference also recommended that an effort be made to do studies in children.

All studies in hemodialysis dependent chronic kidney disease patients (HDD-CKD) should:

1) Assess and report residual kidney function by urea clearance, volume status by reporting the interdialytic weight gain and the ultrafilitration during the pharmacokinetic study dialysis treatment.
2) Asses body composition and nutritional status by reporting lean body mass, adiposity, and serum albumin.
3) Report co-morbidities, concomitant medications, and relevant pharmacogenetics.
4) Record and report dialysis blood flow, dialysate flow rate, treatment duration, measurement of recirculation and of dialysis solute removal as Kt/Vurea.

Each drug should have measures of plasma protein binding and rbc/plasma partitioning (both before and after the study HD treatment).

In order to assess both dialytic and interdialytic periods, either one or two studies should be required, depending on the drug's elimination half-life, with the understanding that clearances may change over the interdialytic interval.

Drugs should be administered intravenously whenever possible. If only oral forms are available, then the drug should be given before the dialysis treatment.

All studies of hemodialysis drug clearance should include dialysate collection, that is should report recovery clearances. Afferent and efferent blood samples should be collected every 30 min during hemodialysis and their ratio reported as an index of clearance and stability throughout the treatment. The use of either plasma or blood drug concentrations is acceptable, but should be consistent for each with pharmacokinetic studies in non- HDD-CKD patients.

Studies need to be continued after the hemodialysis treatment to fully characterize the post-dialytic rebound and possible changes in elimination clearance, assessment of changes in slow inter-compartmental clearance, and effective volume of distribution.

Acute Kidney Injury (AKI) and Continuous Renal Replacement Therapies (CRRT)

The conference suggested the addition of guidance for pharmacokinetic analysis and therapeutic drug monitoring for life-saving drugs in patients with unstable kidney function to include patients with *de novo* AKI, or AKI superimposed on CKD, including those requiring acute renal replacement therapy. AKI should be defined by the RIFLE, AKIN or pRIFLE criteria. This recommendation includes an expectation for pharmacokinetic analysis of life-saving medications used commonly in critically ill adults and children at-risk (control group) for and with AKI (study group). Studies should be encouraged and guidance provided for the effect of renal replacement modalities on the pharmacokinetics of life-saving medications used commonly in critically ill adults and children.

The consensus conference agreed that *in vitro* data can serve as practical surrogates in place of full CRRT pharmacokinetic studies when developing initial drug dosing recommendations. Specifically, *in vitro* data might be useful for initial characterization of flow rate and filter properties and performance to assist in establishing estimates of CRRT drug clearance and establish a starting point for clinical studies. However, the conference did not agree that such studies are adequate to determine the disposition (including extracorporeal removal) and effect of life-saving medications in critically-ill patients, for which studies should be required, likely in the post-marketing phase.

The conference suggested that CRRT used for pharmacokinetic study be standardized to an ultrafiltration rate of 25-35 mL/hr/kg and that contemporary dialyzers be used. An effort should be made to include children in the studies where the drugs are likely to be used in that population. Studies with sustained, low efficiency dialysis (SLED) should also be standardized. Pharmacokinetic studies of drug disposition during CRRT should be done in critically ill patients with acute kidney injury, because drug kinetics are likely to be different in that population compared to stable patients with chronic kidney failure.

The conference agreed that PK-PD studies in critically ill patients receiving CRRT should report details of RRT prescription and delivery in a standard format, including: membrane type, surface area, method of CRRT, pre- and post-filter replacement fluid, sieving and saturation coefficients, dialysate and ultrafiltration rates, and blood flow rate. Concurrent measured clearances of endogenous markers such as urea and/or beta-2 microglobulin should be reported.

Specific parameters for assessing kidney and liver function exist and have been evaluated extensively in non-critically ill patients. Although there is limited evidence for their applicability in critically ill patients, the conference suggests that standard techniques of

measured organ function be used for drug development and post-marketing studies in patients with acute kidney injury and those with multiple organ dysfunction syndrome (MODS). Drug label information should state what techniques were used for measurement and time points of estimation of organ function. Post-marketing pharmacokinetic, pharmacodynamic, and drug interaction surveillance studies should be required in patients with MODS for drugs with a narrow therapeutic index. Drugs anticipated to be used in critically ill should have focused post-marketing assessments in this population, and drug development should include provision of therapeutic drug monitoring measurements to individualize dosing in patients with MODS, if a drug is likely to be used in this setting. Drug labels should state the level of evidence for use in MODS and should describe the measurement techniques used to establish drug clearance. Post-marketing studies should be encouraged to validate drug clearance in the setting of MODS with quantification of measured drug clearance.

Thank you for the opportunity to share the recommendations of the KDIGO conference on "Drug Prescribing in Kidney Disease" as public comment on the draft "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling."

Sincerely,

George R. Aronoff, MD
Conference Co-Chair

Patrick Murray, MD
Conference Co-Chair

Bertram Kasiske, MD
KDIGO Co-Chair

Kai-Uwe Eckardt, MD
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Appendix 1: Conference Attendees

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