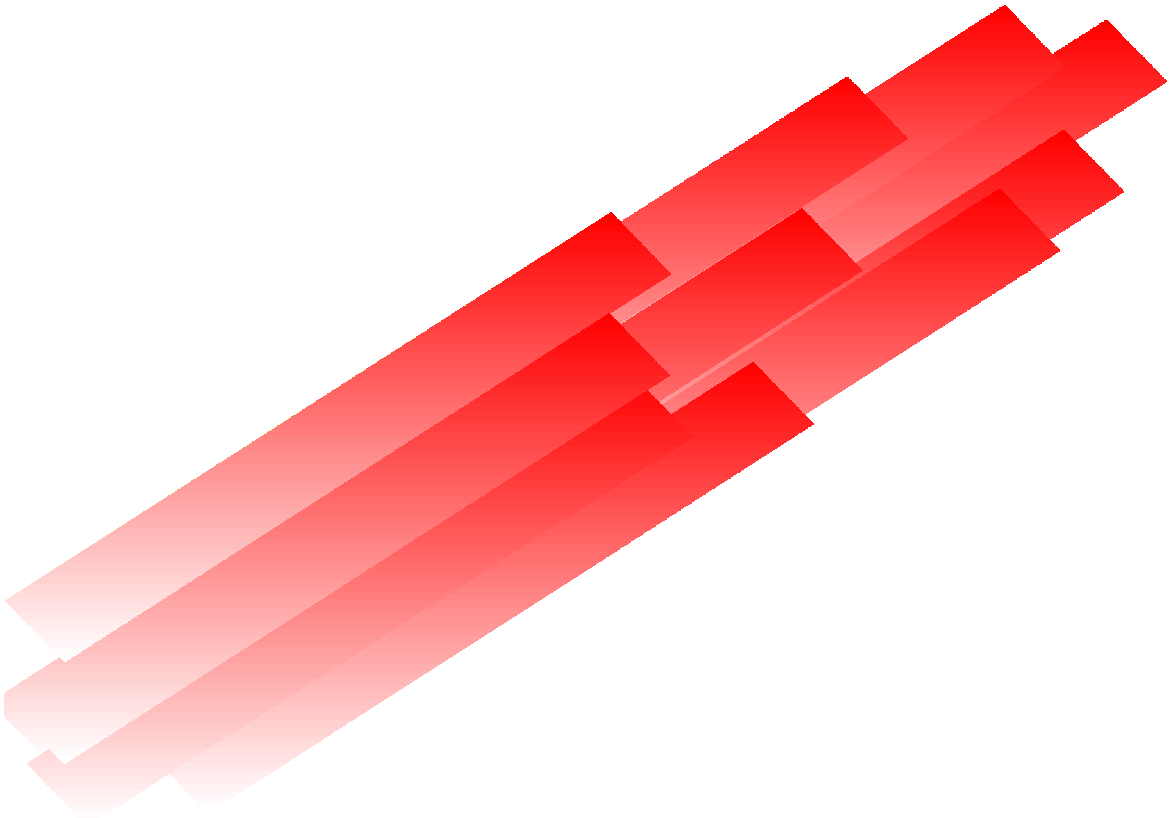
Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
BP 3

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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance is intended for sponsors who, during the investigational phase of drug development, plan to conduct studies to assess the influence of renal impairment on the pharmacokinetics of an investigational drug.

II. BACKGROUND

After entering the body, a drug is eliminated either by excretion or by metabolism. Although elimination can occur via any of several routes, most drugs are cleared by elimination of unchanged drug by the kidney and/or by metabolism in the liver. For a drug eliminated primarily via renal excretory mechanisms, impaired renal function may alter its pharmacokinetics (PK) and pharmacodynamics (PD) to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function. Although the most obvious type of change arising from renal impairment is a decrease in renal excretion, or possibly renal metabolism, of a drug or its metabolites, renal impairment has also been associated with other changes, such as changes in absorption, hepatic metabolism, plasma protein binding, and drug distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. Thus, for most drugs that are likely to be administered to patients with renal impairment, PK characterization should be assessed in patients with renal impairment to provide rational dosing recommendations.

[1] This guidance has been prepared by the Renal Impairment Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER), with input from the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on this subject. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance makes recommendations regarding:

- When studies of PK in patients with impaired renal function should be performed—and conversely, when they may be unnecessary;
- The design and conduct of PK studies in patients with impaired renal function;
- The design and conduct of PK studies in end-stage renal disease (ESRD) patients treated with dialysis (hemodialysis or peritoneal dialysis);
- The analysis and reporting of the results of such studies;
- Representation of these results in approved product labeling.

III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED RENAL FUNCTION

A. When Studies May Be Important

A PK study in patients with impaired renal function is recommended when the drug is likely to be used in these patients and (1) renal impairment is likely to significantly alter the PK of a drug and/or its active/toxic metabolites and (2) a dosage adjustment is likely to be necessary for safe and effective use in such patients. In particular, a study in patients with impaired renal function is recommended when the drug or its active metabolites exhibit a narrow therapeutic index[2] and when excretion and/or metabolism occurs primarily via renal mechanisms (excretion or metabolism). A study also should be considered when a drug or an active metabolite exhibits a combination of high hepatic clearance (relative to hepatic blood flow) and significant plasma protein binding. In this setting, renal impairment could induce a significant increase in the unbound concentrations after parenteral administration due to a decreased plasma protein binding coupled with little or no change in the total clearance (decrease in unbound clearance).

B. When Studies May Not Be Important

For some drugs, renal impairment is not likely to alter PK enough to justify dosage adjustment. In such cases, a study to confirm that prediction may be helpful but is not necessary. If a study is not conducted, the labeling should indicate that the impact of renal

[2] The therapeutic index may be derived from the concentration- or dose-response data existing in the safety/efficacy database.

impairment was not studied, but that an effect requiring dosage adjustment is unlikely to be present. Current knowledge suggests that the following drug properties may justify this approach:

- Drug and active metabolites with a relatively wide therapeutic index and that are primarily eliminated via hepatic metabolism or biliary excretion;

- Gaseous or volatile drug and active metabolites that are primarily eliminated via the lungs;

- Drugs intended only for single-dose administration unless clinical concerns dictate otherwise.

Controversy exists regarding the impact of severe renal impairment on hepatic metabolism. For this reason, a renal impairment study is still considered desirable for a drug eliminated primarily via hepatic metabolism unless it also has a relatively wide therapeutic index.

Even when renal impairment is likely to have little or no effect on a drug's PK, the impact of dialysis on the PK of a drug should be considered. Patients on dialysis may require greater doses of certain drugs than patients with normal renal function. This is discussed further in the following section.

IV. STUDY DESIGN

The safety and efficacy of a drug generally are established for a particular dosage regimen (or range of dosage regimens) in late phase (phase 3) clinical trials involving relatively typical representatives from the target patient population. More often than not, individuals with significantly impaired renal function are explicitly ***excluded*** from participation in these studies, although there may be a sufficient range of function to obtain an initial estimate of the effects of decreased renal function. The primary goal of the recommended study in patients with impaired renal function is to determine if the PK is altered to such an extent that the dosage should be adjusted from that established in the phase 3 trials.

Thus, the study should reasonably focus on comparing patients with renal impairment to patients with renal function that is typical of the usual patient population — ***not necessarily to normal healthy young volunteers***.

The strategy used in this section describes the basic "full" study design that could be applied to most drugs whose pharmacodynamics (i.e., concentration-response relationship) are known to be unaffected by renal impairment or whose therapeutic indices are sufficiently large to preclude safety concerns. Then, cases are identified for which some elements of the full study design may

be simplified or excluded depending on the properties of the drug and its anticipated use in the target patient population.

A. Basic "Full" Study Design

1. Study Participants

The control renal function group in this study should optimally be representative of a typical patient population for the drug to be studied. In particular, it should not consist of normal healthy young male volunteers if the typical patient population is made up of older people, including women. However, enrollment of enough individuals with varying degrees of renal impairment who are also patients with the condition for which the drug is indicated may be difficult. An acceptable alternative would be to use volunteers who are comparable to the typical patient population with respect to renal function and other factors such as age, gender, and weight. For example, an acceptable control group for a drug intended for treatment of Alzheimer's disease would be otherwise healthy elderly male and female patients whose baseline renal function would clearly not be comparable to young healthy male volunteers.

The study could also include a group of subjects with greater renal function than the control renal function group (e.g., a group of healthy young volunteers). The resulting wider range of renal function enhances the ability to detect and characterize the effect of renal function on PK. It also allows for the possibility that the actual patient population may include some people with greater renal function than the control group. However, recommendations about dosage adjustments should be based on comparison to the patients with renal function that is typical of the usual patient population — not necessarily to normal healthy young volunteers.

To ensure adequate representation of patients with various degrees of renal impairment, recruitment of approximately equal numbers of patients from each of the following groups is suggested:

Group	Description	Estimated Creatinine Clearance (milliliters/ minutes)
1	Normal renal function	> 80 mL/min
2	Mild renal impairment	50-80 mL/min
3	Moderate renal impairment	30-50 mL/min
4	Severe renal impairment	<30 mL/min
5	ESRD	Requiring dialysis

The renal function groups should be comparable to each other with respect to age, gender, and weight. Other factors with significant potential to affect the PK of a drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity) should be considered depending on the drug.

The number of patients enrolled in the study should be sufficient to detect PK differences large enough to warrant dosage adjustments. The PK variability of the drug as well as the PK/PD relationships for both therapeutic and adverse responses (therapeutic index) will affect this decision.

2. Drug Administration

A single-dose study is satisfactory for cases where there is clear prior evidence that the multiple-dose PK is accurately predictable from single-dose data for all chemical species of interest (drug and potentially active metabolites). A multiple-dose PK is predictable from a single-dose PK when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time-dependent PK.

In single-dose studies, the same dose can usually be administered to all patients in the study regardless of renal function because the peak concentration generally is not greatly affected by renal function. For multiple-dose studies, lower or less frequent doses as renal function decreases may be important to prevent accumulation of drug and

metabolites to unsafe levels. The dosage regimen may be adjusted based on the best available prestudy estimates of the PK of the drug and its active metabolites in patients with impaired renal function. Alternatively, a concentration-controlled study design could be employed. Specifically, the study could be conducted to achieve a specific target concentration using therapeutic drug monitoring procedures. In multiple-dose studies, the dosing should usually be continued for a sufficiently long duration to achieve steady state. A loading dose strategy may be desirable to facilitate this, particularly if the elimination half-life is greatly prolonged in patients with renal impairment.

3. Sample Collection and Analysis

Plasma or whole blood, if appropriate, (and optionally urine) samples should be analyzed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). This is particularly important in patients with impaired renal function since renally excreted metabolites can accumulate to a much higher degree in such patients. The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent drug and its active metabolites (see section V. on Data Analysis).

Plasma protein binding is often altered in patients with impaired renal function. For systemically active drugs and metabolites, the unbound concentrations are generally believed to determine the rate and extent of delivery to the sites of action. This leads to the recommendation that the PK should be described and analyzed with respect to the unbound concentrations of the drug and active metabolites. Although unbound concentrations should be measured in each plasma sample, if the binding is concentration-independent and is unaffected by metabolites or other time-varying factors, the fraction unbound may be determined using a limited number of samples or even a single sample from each patient. The unbound concentration in each sample is then estimated by multiplying the total concentration by the fraction unbound for the individual patient. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations in binding due to impaired renal function are small in relative terms. In such cases, description and analysis of the PK in terms of total concentrations should be sufficient.

4. Measures of Renal Function

Currently, creatinine clearance is used widely in patient care settings as a measure of renal function. Consequently, it is more practical than most other alternatives as a criterion for adjusting dosage in outpatient and inpatient settings. The Cockroft-Gault formula is one way of estimating creatinine clearance based on serum creatinine levels.

Using other measures of renal function that can characterize differentially glomerular filtration or renal tubular secretion may provide an additional mechanistic understanding of the effect of renal impairment on PK. Such methods are encouraged as useful additions, but not as alternatives to methods that are more readily available in patient care settings, such as using creatinine clearance or serum creatinine concentration.

The basic full study design should be structured to characterize comprehensively the effect of renal impairment on PK. This approach presumes that the drug's PK is likely to change as renal function decreases. The full study then provides the information needed to rationally adjust doses for patients with impaired renal function.

B. Reduced/Staged Study Design

If there is good reason to believe that renal impairment does not affect PK to a degree sufficient to warrant dosage adjustment, then a full study may be larger and more complex than necessary. An acceptable alternative is an adaptive two-stage approach. Stage 1 consists of studying only patients at the extremes of renal function (i.e., patients with normal [Group 1] and severely impaired [Group 4] renal function). If the results confirm that renal impairment does not alter PK to an extent that warrants dosage adjustment, no further study is warranted. If the results do not strongly support such a conclusion, in stage 2, the intermediate renal function groups (mild and moderate renal impairment) should also be studied. The results of both stages should be combined for all subsequent data analyses.

C. Population PK Studies [3]

A population PK screen of patients participating in phase 2/phase 3 clinical trials may be used to assess the impact of various covariates on the PK of a drug. Typically, each patient is only sparsely sampled to obtain plasma drug concentration data.

Techniques such as nonlinear mixed effects modeling may be used to model the relationship between the various covariates and PK parameters. A measure of renal function such as creatinine clearance may be one of the covariates. Therefore, it may be possible to model the relationship between creatinine clearance and PK parameters, such as the apparent clearance of the drug (CL/F). In principle, such a population PK study design and analysis can be an acceptable alternative if it retains some of the critical components of the more conventional studies described in previous sections:

[3] A draft guidance for industry, "Population Pharmacokinetics," (September 1997) is available on the internet (http://www.fda.gov/cder/guidance/index.htm)

- A sufficient number of patients and a sufficient representation of a range of renal function that the study could detect PK differences large enough to warrant dosage adjustment;

- Measurement of unbound concentrations when appropriate;

- Measurement of parent drug and potentially active metabolites.

Such features are particularly critical if the sponsor intends to use the results to support a claim that no dosage adjustment is required for patients with impaired renal function.

Patients with severe renal impairment often are excluded or poorly represented in population PK studies. When that occurs for a drug that is likely to be administered to such patients, a separate study should be conducted to assess PK in patients with severe renal impairment (i.e., a study such as the reduced/staged study design described in the previous section). The data from both sources should be combined to construct an overall assessment of the effect of renal impairment.

D. Effect of Dialysis on Pharmacokinetics

Dialysis may significantly affect the PK of a drug to an extent that dosage adjustment is appropriate. The need for dosage adjustment results when a significant fraction of the drug or active metabolites in the body is removed by the dialysis process. In such cases, a change in the dosage regimen, such as a supplemental dose following the dialysis procedure, may be required.

For drugs that are likely to be administered to end stage renal disease (ESRD) patients treated with dialysis, PK should be studied in such patients under both dialysis and nondialysis conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites. Primary questions to be addressed are whether the dosage should be adjusted as a consequence of dialysis and, if so, by how much. The results of the study also provide valuable insight regarding the value of dialysis for treatment of overdose. The assessment of PK in dialysis may be integrated with the PK in renal impairment study, as described above, or it may be conducted as a separate study.

As it is most commonly used in ESRD patients, intermittent hemodialysis is usually the most important method to be evaluated. PK studies in patients treated with peritoneal dialysis may also be desirable (e.g., CAPD, continuous ambulatory peritoneal dialysis, which is the next most common form of dialysis). A study in CAPD patients is recommended if the drug is likely to be used in such patients and CAPD is likely to significantly affect PK.

In general, a study of the effect of dialysis on PK may be omitted if the dialysis procedure is unlikely to result in significant elimination of drug or active metabolites. This is arguable for drugs and active metabolites that have a large unbound volume of distribution (V_u) or a large unbound nonrenal clearance ($CL_{NR,u}$).

If the drug and metabolites have a large unbound volume of distribution (V_u), only a small fraction of the amounts in the body will be removed by dialysis. For example, if V_u were greater than 360 L, less than 10 percent of the amount initially in the body could be removed by 3 hours of high flux hemodialysis with an unbound dialysis clearance of 200 mL/min.

If the drug and metabolites have a large unbound nonrenal clearance ($CL_{NR,u}$), dialysis contributes a relatively small amount to the overall unbound clearance. For example, if $CL_{NR,u}$ were greater than 125 mL/min, 3 hours of high-flux hemodialysis with an unbound dialysis clearance of 200 mL/min administered every 2 days would contribute less than 10 percent to the overall clearance.

E. Pharmacodynamic Assessments

Whenever appropriate, pharmacodynamic assessment should be included in the studies of renal impairment. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff and should be based on the pharmacological characteristics of the drug and metabolites (e.g., extent of protein binding, therapeutic index, and the behavior of other drugs in the same class in patients with renal impairment).

V. DATA ANALYSIS

The primary intent of the data analysis is to assess whether dosage adjustment is required for patients with impaired renal function, and, if so, to develop dosing recommendations for such patients based on measures of renal function. The data analysis typically consists of the following steps:

- Estimation of PK parameters;
- Mathematical modeling of the relationship between measures of renal function and the PK parameters;
- Development of dosing recommendations including an assessment of whether dosage adjustment is warranted in patients with impaired renal function.

A. Parameter Estimation

Plasma concentration data (and urinary excretion data if collected) should be analyzed to estimate various parameters describing the PK of the drug and its active metabolites. The PK parameters of a drug can include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), apparent clearance (CL/F), renal clearance (CL_R), apparent volume of distribution (V_z/F or V_{ss}/F), terminal half-life ($t_{1/2}$). The PK parameters of active metabolites can include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), renal clearance (CL_R), terminal half-life ($t_{1/2}$). If possible, parameters are preferably expressed in terms of unbound concentrations; for example, apparent clearance relative to the unbound drug concentrations ($CL_u/F = D/AUC_u$) where the subscript 'u' indicates unbound drug. Noncompartmental and/or compartmental modeling approaches to parameter estimation can be employed.

B. Modeling the Relationship Between Renal Function and PK

The objective of this step is to construct mathematical models for the relationships between the RF, the measures of renal function, particularly creatinine clearance (CLcr) and relevant PK parameters. The PK parameters of greatest interest are usually the apparent unbound clearance (CL_u/F), or the dose-normalized area under the unbound concentration curve (AUC_u/D), and the dose-normalized peak unbound concentration ($C_{max,u}$/D) for the drug and active metabolites. The intended result is a model that can successfully predict PK behavior given information about renal function. Generally, this involves a regression approach in which RF and the PK parameters are treated as continuous variables. This is usually preferred to an analysis in which RF is treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment groups. One commonly used model is a linear relationship between CLcr and the total or renal clearance of the drug. Other models can be used if adequately supported by the data and/or mechanistic arguments.

The intent of the modeling exercise is to provide a rational quantitative basis for dosage recommendations in the drug's labeling. The model itself may be described in the clinical pharmacology section of the labeling.

The reported modeling results should include estimates of the parameters of the chosen model as well as measures of their precision (standard errors or confidence intervals). Prediction error estimates are also desirable (e.g., confidence bounds for prediction of AUC_u/D for the drug and its active metabolites over a range of RF).

C. Development of Dosing Recommendations

Specific dosing recommendations should be constructed based on the study results using the aforementioned model for the relationships between RF and relevant PK parameters. Typically the dose is adjusted to produce a comparable range of unbound plasma concentrations of drug or active metabolites in both normal patients and patients with

impaired renal function. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal for patients with different levels of renal function.

For some drugs, even severe renal impairment may not alter PK sufficiently to warrant dosage adjustment. A sponsor could make this claim by providing an analysis of the study data to show that the PK measurements most relevant to therapeutic outcome in patients with severe renal impairment are similar, or equivalent, to those in patients with normal renal function.

One approach would be for the sponsor to recommend, prior to the conduct of the studies, specific "no effect" boundaries for the ratio of a PK measurement from patients with severe and normal renal functions respectively, such as (AUCu,severe / AUCu,normal) (Dnormal/Dsevere). If the 90% confidence interval for the ratio of PK measurements fell within these boundaries, the sponsor could claim "no effect" of severe renal impairment on PK, and it would be reasonable to conclude that no dosage adjustment is required for renal impairment. The sponsor could determine "no effect" boundaries from population (or individual) PK-PD relationships, dose-finding studies and/or dose-response studies which are conducted as part of drug development.

Another approach would be for the sponsor to assume, a priori, "no effect" boundaries of 70-143% for Cmax and 80-125% for AUC without further justification, recognizing that the limitation for small clinical sample sizes in renal impairment studies coupled with high inter-subject variability may preclude meeting these “no-effect” boundaries.

VI. LABELING

The labeling should reflect the data pertaining to the effect of renal function on the pharmacokinetics and pharmacodynamics (if known) obtained from studies conducted. The various permutations of intrinsic drug characteristics and the effect of renal impairment on drug performance preclude precise specification of how such drugs should be labeled. The following comments offer general suggestions on which sections of the labeling should include standardized information and how such information should be structured.

A. Clinical Pharmacology

1. The pharmacokinetics subsection should include information on the:

- Mechanism of renal elimination (e.g., filtration, secretion, active reabsorption)

- Percentage of drug that is eliminated by renal excretion and whether it is eliminated unchanged or as metabolites;

- Disposition of metabolites in patients with impaired renal function (if applicable);

- Effects of renal impairment on protein binding of parent drug and metabolites (if applicable);

- Effects of changes in urinary pH or other special situations that should be mentioned (e.g., tubular secretion inhibited by probenecid);

- If applicable, the effects of impaired renal function on stereospecific disposition of enantiomers of a racemic drug product should be described if there is evidence of differential stereoisomeric activity or toxicity

2. Special Populations Subsection

This section should recapitulate, in brief, the pharmacokinetic changes found in various degrees of renal impairment and, if necessary, dosing adjustments for patients with varying degrees of renal impairment. This information should be based on the studies performed as described in this guidance. Reference should be made to the PRECAUTIONS/WARNINGS and the DOSAGE AND ADMINISTRATION sections. The following text provides examples of appropriate wording for these sections.

The simplest situation involves drugs for which impaired renal function has little or no effect on PK:

Impaired renal function has little or no influence on _____ pharmacokinetics and no dosing adjustment is required.

Similarly, for drugs whose PK is influenced by renal impairment, the following statement may be modified as appropriate and in accordance with what is known about the drug (e.g., racemate with different activity of stereoisomers, active or toxic metabolite) and from the studies performed in accordance with this guidance:

The disposition of _____ was studied in patients with varying degrees of renal function. Elimination of the drug (and metabolite, if applicable) is significantly correlated with the creatinine clearance. Total body clearance of (unbound, if applicable) _____/metabolite was reduced in patients with impaired renal function by --- % in mild (CLcr = __-__ mL/min), --- % in moderate (CLcr = __-__ mL/min) and --- % in severe renal impairment (CLcr = __-__ mL/min), and --- % in patients under dialysis compared to normal subjects (CLcr > ___mL/min). The terminal half-life of _____/metabolite is prolonged by ---, ---, and --- fold in mild, moderate, and severe renal impairment, respectively. [Alternatively, the relationship between renal function and the PK parameters may be described in terms of equations, e.g., a linear equation relating unbound clearance and CLcr.] *Protein binding of _____/metabolite is/is not affected by decreasing renal function. The drug/metabolite accumulates in patients with impaired renal function on chronic administration. The pharmacologic response is/is not affected by renal function. Approximately --- % of the drug/metabolite in the body was cleared from the body during a standard 4-hour hemodialysis procedure. The dosage should be reduced in patients with impaired renal function receiving _____ and supplemental doses should/should not be given to patients after dialysis. (See DOSAGE AND ADMINISTRATION).*

B. Precautions/Warnings

Use in Patients with Impaired Renal Function: If the effects of renal impairment result in clinically important changes in drug pharmacokinetics, this should be included in the PRECAUTIONS/WARNINGS section with reference to DOSAGE AND ADMINISTRATION section.

C. Dosage and Administration

As appropriate, the following statement may be considered:

The influence of impaired renal function on _____ pharmacokinetics is sufficiently small that no dosing adjustment is required.

However, for many drugs, impaired renal function may require dosing adjustments. In such cases, the following information should be included:

1. A statement describing the relationship between _____ clearance and endogenous creatinine clearance.

2. If there is a need for dosage adjustment, the following statement may be adapted as appropriate:

   _____ *dosing must be individualized according to the patient's renal function status. Refer to the following table for recommended doses and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is required. CLcr in mL/min may be estimated from a spot serum creatinine (mg/dL) determination using the following formula:*

$$CLcr \approx \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)}\ \{\times 0.85\ for\ female\ patients\}$$

   The serum creatinine should represent a steady-state of renal function. The following formulas are preferable for children (to be included if the drug has a pediatric indication):

   Infants less than one year:

$$CLcr \approx \frac{0.45 \times length\ (cm)}{serum\ creatinine\ (mg/dL)}$$

   Children 1–12 years:

$$CLcr \approx \frac{0.55 \times length\ (cm)}{serum\ creatinine\ (mg/dL)}$$

3. The dosing adjustment regimen should be represented in tabular format (see example below).

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> __	x	Every x hours
Mild	__–__		
Moderate	__–__		
Severe	< __		
ESRD patients using dialysis			Supplemental dose should be given after dialysis.

4. Special consideration should be given to combination drug products.

Dosing adjustment should be recommended according to the degree of renal impairment, provided there is sufficient information to indicate that the pharmacokinetics/pharmacodynamics of the individual components of the combination product are comparably affected by impaired renal function. In situations in which this does not apply, the following statement should be adapted:

Because the doses of this fixed combination product cannot be individually titrated and impaired renal function results in a reduced clearance of component A to a much greater extent than component B, combination drug should generally be avoided in patients with suspected or documented renal impairment (see PRECAUTIONS/WARNINGS).

D. Overdosage

Although the primary objective of a hemodialysis study is to evaluate the need for dosing adjustments in ESRD, additional information regarding the value of hemodialysis in overdose situations may reasonably be garnered from such studies (if performed). In situations in which this information is known, the following wording may be adapted as appropriate:

_____ *is not eliminated to a therapeutically significant degree by hemodialysis.*

or

Standard hemodialysis procedures result in significant clearance of _____ *and should be considered in cases of life-threatening overdose.*